Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, September 26, 2013 1:00-5:00 PM
Hewlett-Packard Building
4070 27th Ct. SE
Salem, OR 97302

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

I. CALL TO ORDER
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)
- d. Department Update — T. Douglass (DMAP)

II. HCMB Subcommittee Approval — R. Citron (OSU)

III. DUR OLD BUSINESS
- a. Kuvan® (sapropterin) — M. Herink (OSU)
  1. Definition Phe levels and adults treatment
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA
- b. Juxtapid® (lomitapide) & Kynamro® (mipomersen) — K. Ketchum (OSU)
  1. Maximal Lipid Lowering Definition
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA

IV. DUR NEW BUSINESS
- a. Metabolic Monitoring of Antipsychotics in Children — T. Williams (OSU)
  1. Proposed RetroDUR Initiatives
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA
- b. Follow Up for Children Prescribed Their First ADHD Medication — T. Williams (OSU)
  1. Drug Use Evaluation
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA
- c. RetroDUR for the Use of Psychotropic Medications in Children — T. Williams (OSU)
  1. Proposed RetroDUR Initiatives
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA

d. Synagis® (palivizumab) Policy Evaluation K. Ketchum (OSU)

1. Policy Evaluation
2. Public Comment
3. Discussion of Clinical recommendations to OHA

V. PREFERRED DRUG LIST (PDL classes will be reviewed for annual pricing update)

a. Diabetes Class Update K. Sentena (OSU)

1. Drugs included at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf
2. New Drug Evaluations
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

b. Other Lipotropics M. Herink (OSU)

1. Drugs included at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf
2. Vascepa® (icosapent ethyl) New Drug Evaluation
3. Class Review
4. Public Comment
5. Discussion of Clinical Recommendations to OHA

c. Parkinson's Disease B. Liang (OSU)

1. Drugs included at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf
2. Class Update
3. Public Comment
4. Discussion of Clinical recommendations to OHA

d. Multiple Sclerosis M. Herink (OSU)

1. Drugs included at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf
2. Tecfidera® (dimethyl fumurate) New Drug Evaluation
3. Class Update
4. Public Comment
5. Discussion of Clinical recommendations to OHA

e. Long Acting Opioids K. Ketchum (OSU)

1. Drugs included at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf
2. Abbreviated Class Update
3. Public comment
4. Discussion of Clinical recommendations to OHA

f. Hepatitis C Agents M. Herink (OSU)

1. Drugs included at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf
2. Abbreviated Class Update
3. Public comment
4. Discussion of Clinical recommendations to OHA

g. Drug Class Scans M. Herink (OSU)

1. Topical Androgens http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf

2. Topical Antiparasitics
http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf
3. Chronic Obstructive Pulmonary Disease (COPD)
http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf
4. Growth Hormones
http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf
5. Alzheimer's Agents
http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meetings/meetingdocs/2013_09_26/finals.pdf
6. Public Comment
7. Discussion of Clinical Recommendations to OHA

h. Classes Under Consideration for Annual PDL Pricing Review R. Citron (OSU)
1. TIMS
2. Antiepileptic Medications
3. Ulcerative Colitis
4. Public Comment
5. Discussion of clinical recommendations to OHA

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, July 25, 2013 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to coverage, PDL composition, or utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff.

Members Present: Cathy Zehrung, RPh; David Pass, MD; Phillip Levine, PhD; Stacy Ramirez, PharmD; William Origer, MD, James Slater, PharmD,
Members Present by Phone: Joshua Bishop, PharmD; William Nunley, MD
Staff Present: Kathy Ketchum, RPh, MPA:HA; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD, BCPS; Trevor Douglass, DC, MPH; Shannon Jasper,
Staff Present by Phone: Kathy Sentena, PharmD, Bing Bing Liang, PharmD, Sherry Argyres, PharmD,
Audience: Carol Choutka (Natl. MS Society); Barry Benson (Merck); Deborah Crawford (Acorda); Shane Hall (Purdue); Bruce Smith (GSK); Paul Barham (NovoNordisk); Bruce Howard (Acorda); Shannon Beatty (Med Immune); Gina Guinasso (Acorda); Kayla Berkey (OHSU Pharmacy student); Barbara Felt (GSK); Lisa Valaika (Genzyme); Steve Fuldon (Otsuka); Karen Ward (Aegerion); Chris DeSimone (Aegerion); Tom Burns (Government Task Force); David Barba (Forest); Richard McLeod (Pfizer); Jim Hoover (Bayer); Nate Miles (Lilly); Molly Meeking (Hypercon); Chelsea Arakawa (Pacific University student); John Mcilveen, Ph.D, LMHC; Dean Haxby, PharmD,

I. CALL TO ORDER
a. The meeting was called to order at approximately 1pm.
b. Mr. Citron reported there are no new conflicts of interest to declare.
c. The May 30, 2013 meeting minutes were reviewed.

ACTION: Approved as is.

II. DUR ACTIVITIES
a. Mr. Citron presented the 2nd Quarterly Utilization Reports.
b. Mr. Holsapple presented the ProDUR Report. Same reports presented last meeting.
c. Dr. Williams presented the RetroDUR Report. Presented the proposed layout of new reporting, projected availability 1st quarter for next fiscal year.
d. Mr. Citron stated within packet was copies of screen shots for the CMS Annual report submitted.
e. Dr. Sentena presented the Oregon State Drug Review "Updates and Future Perspectives in Chronic Obstructive Pulmonary Disease".

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

III. DUR OLD BUSINESS

a. Juxtapid® (lomitapide)
   Testimony given by Karen Ward, PharmD., from Aegerion.
b. Kynamro® (mipomersen)
   The Committee considered information from specialist on reliability of genetic testing and definition of apheresis failure. PA criteria approved to limit use to confirmed adult HoFH patients that have failed or are unable to tolerate maximum lipid lowering thereapy and LDL-C apheresis. Due to unreliability of the HoFH genetic testing and potential patients who will get missed through genetic testing, the Committee recommended to not restrict diagnosis by genetic testing only, but to require patients either have OHSU consult or be seen at an apheresis center.

ACTION: All in favor

c. Ampyra® (dalfampridine)
   The Committee recommended requiring physician reassessment after a 12-week trial to include demonstration of a ≥20% improvement in walking speed as assessed by the T25FW and to revise prior authorization criteria to allow for use in patients with moderate ambulatory dysfunction who do not require a walking aid. The Committee also recommended dalfampridine be considered by the HCMB subcommittee.
   Testimony given by Deborah Crawford, DVM, from Acorda.
   Testimony given by Carol Chowtka.

ACTION: After Executive Session, all in favor.

IV: DUR NEW BUSINESS

a. Kuvan® (sapropterin)
   The Committee recommended implementation of the amended saproterin prior authorization criteria and to require it be prescribed by a specialist due to lack of long term data and clinical significance outcomes data to support decreased blood Phe level associated with improved neurocognitive and/or psychosocial functions. The Committee recommended that renewal criteria require the Phe level goal of the trial having been met and compliance with the Phe-restricted diet. In light of lack of national treatment consensus, the Committee recommended working with metabolic clinic providers in the region to formulate a uniform and practical treatment protocol for managing patients with PKU including the use of saproterin for patients who are likely to respond. The Committee also recommended saproterin be considered for the HCMB subcommittee.

ACTION: All in favor.

V: PREFERRED DRUG LIST

a. Suboxone® and Opioid Addiction Therapies
   The Committee recommended continuing to require PA for all buprenorphine and buprenorphine/naltrexone products approved for opioid addition to ensure the diagnosis is for the treatment of opioid dependence. After executive session, the Committee recommended making both buprenorphine and buprenorphine/naloxone products preferred on the PMPDP. The Committee deferred taking action on naltrexone and directed staff to bring back additional information ad a future meeting.
   Testimony given by John Mcilveen, PhD., LMHC, from OHA Addictions and Mental Health.

ACTION: After Executive Session, all in favor.

b. Long Acting Opioids
   The Committee recommended removing methadone from preferred status on the PMPDP due to safety concerns, but to maintain a form of morphine ER as a preferred option and to review relative cost of the different formulations in executive session. After executive session, the recommendation was no changes to PMPDP

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

status. The Committee also recommended adding Tramadol ER and Conzip to the LAO class.
Testimony given by Tom Burns, Glaxo Smith Kline.

ACTION: After Executive Session, all in favor.

c. Drug Class Scans

1. ADHD Scan
The Committee found that there was insufficient evidence that the new methylphenidate formulation (Quillivant XR®) has improved efficacy or safety or other formulations and that there was no new clinical evidence necessitating changes to current DL status. The Committee recommended that no further research was needed at this time and to evaluate costs in executive session.
Testimony given by Richard McLeod from Pfizer.
After executive session, the Committee recommended accepting Focalin, Focalin XR, Vyvanse SRs and keep preferred; accepting the Daytrana SR and make preferred; accept the Adderall XR SR and make non-preferred on but preferred over its generic equivalent; add Metadate CD brand only; monitor quarterly and add generic Concerta when AAC drops below $2/day; keep Provigil non-preferred but preferred over its generic equivalent and monitor price quarerly; and make dextroamphetamine IR non-preferred.

ACTION: After Executive Session, all in favor.

2. Controller Medicaitons for Asthma
The Committee recommended that no further research was needed at this time and to evaluate costs in executive session.
After executive session, the Committee recommended making Alvesco, safirlukast and montelukast granules non-preferred due to their high price and low use; accept Lovent, Qvar and Advair SRs and keep preferred; accept Pulmicort and make preferred; make Symbicort preferred IF they accept our clinical edit.

ACTION: After Executive Session, all in favor.

3. Triptans
The Committee recommended that no further research was needed at this time and to evaluate costs in executive session.
After executive session, the Committee recommended making Zomig Spray non-preferred and making generic sumatriptan SQ preferred as it now has price parity with the brand.

ACTION: After Executive Session, all in favor.

4. Short Acting Opioids
The Committee recommended updating the PA criteria to include new spray formulations of fentanyl to current PA criteria. The Committee deferred taking action on high dose APAP containing combinations (>325mg/unit) at this time. Also recommended no further research was needed at this time and to evaluate costs in executive session.
After executive session, the Committee recommended making Subsys non-preferred due to high cost; making hydrocodone/ APAP solution non-preferred as it is PA'd for cough; and to make butorphanol tartrate preferred on the PMPDP.

ACTION: After Executive Session, all in favor.

VI: EXECUTIVE SESSION

VII: RECONVENED FOR PUBLIC RECOMMENDATIONS

VIII. ADJOURN

The meeting was adjourned at approximately 5:10 pm.

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

Saproterin (Kuvan)

Goal(s):

- Promote safe and cost effective therapy for the treatment of phenylketonuria.

Length of Authorization: Initial – 2 months; Renewal – one year

Covered Alternatives: NA

Approval Criteria - Initial		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the drug prescribed by or in consultation with a specialist in metabolic disorders?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the diagnosis tetrahydrobiopterin- (BH4-) responsive phenylketonuria?	**Yes:** Go to #4	**No:** Pass to RPh, Deny (medical appropriateness).
4. Is member currently participating in a Phe-restricted diet and unable to achieve target blood phenylalanine level?	**Yes:** Go to #5	**No:** Deny and recommend Phe-restricted diet.
5. Is member's baseline blood phenylalanine level provided in the request?	**Yes:** Approve for 2 months.	**No:** Request information from provider.
Approval Criteria – Renewal		
1) Did the patient meet the target phenylalanine level set by the specialist? AND **2)** Is the patient remaining compliant with the Phe-restricted diet?	**Yes:** Approve for 12 months.	**No:** Deny for lack of treatment response.

Mipomersen (Kynamro®) and Lomitapide (Juxtapid®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which mipomersen has been shown to be effective and safe.

Length of Authorization: 6 months

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the drug prescribed by or in consultation with a specialist in lipid disorders?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the diagnosis homozygous familial hypercholesterolemia?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Has the patient tried and failed or does the patient have a medical contraindication to maximum lipid lowering therapy with a combination of traditional drugs?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny (medical appropriateness)
5. Has the patient failed or are they not appropriate for LDL-C apheresis OR Is LDL-C apheresis not available to them?	**Yes:** Approve for 6 months.	**No:** Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

Mipomersen and lomitapide are approved only for HoFH, a rare but serious disorder associated with premature cardiovascular morbidity and mortality with few effective treatment options. Both are proven effective in reducing LDL-C levels, but there is uncertainty about whether this equates to reduced cardiovascular morbidity and mortality. It is not feasible to do an outcomes study due to the low prevalence of the disease. However, the current safety data does not support the use of mipomersen in patients with lower CHD risk.[1, 2]

1. FDA Summary Review. Reference ID 3252189. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203568Orig1s000SumR.pdf. Accessed April 1, 2013.

2. FDA. Lomitapide Summary Review - Reference ID 3236195. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203858Orig1s000SumR.pdf. Accessed April 3, 2013.

P&T Action: *5/30/2013 (KK/MH)*
Revision(s):
Initiated:

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Metabolic Monitoring of Antipsychotics in Children

Recommendations

- Fax quarterly reports to providers addressing the absence of glucose monitoring in children receiving antipsychotics
- Reports to contain:
  - Dashboard comparing the target provider to other Medicaid providers and providers within their specialty
  - Educational materials highlighting recommendations for monitoring and management of metabolic abnormalities in children
  - Provide list of patient without claims for glucose monitoring within the past 12 months
  - Form indicating the status of metabolic monitoring for each patient for the provider to complete and return to the Medical Assistance Program

Background

Awareness of mental health disorders in children has increased in recent years, with an estimated 15-25% of children in the United States having a diagnosable mental health disorder.[1] Data from 2001-2002 showed 13.5% of all child welfare patients were receiving psychotropics.[2] As of January 2013, 18.5% of children in the Oregon Child Welfare Program received at least one psychotropic. Of these, 48% received at least one antipsychotic. In the entire Medicaid program, 29% (3,115 of 10588) of children receiving any psychotropic received at least one antipsychotic. Although the use of antipsychotics in children is controversial, based on available claims data, it is not uncommon for the children covered by the Oregon Medicaid program to receive antipsychotics. In light of the prevalence of antipsychotic use in children, an understanding of appropriate use and adequate monitoring practices are essential for all prescribers.

The metabolic risks of antipsychotic medications are well documented in three systematic reviews, including a 2012 report from Agency for Healthcare Research and Quality (AHRQ).[3–5] Second generation antipsychotics (SGAs) have an FDA warning about the risk of metabolic abnormalities but First Generation Antipsychotics (FGAs) also are associated with metabolic effects. SGAs described as "weight neutral" are neutral when compared to a FGA (typically lower dose haloperidol).[3,4] However, both SGAs and FGAs have been demonstrated to have some amount of weight gain upon initiation of therapy.[6–8] Children may be particularly susceptible to the metabolic effects of antipsychotics.[9] Despite FDA

Metric	Medication	Mean	(95% CI)	p Value
Weight (kg)				
	Aripiprazole	4.44	(3.71 to 5.18)	<.001
	Olanzapine	8.54	(7.38 to 9.69)	<.001
	Quetiapine	6.06	(4.90 to 7.21)	<.001
	Risperidone	5.34	(4.81 to 5.87)	<.001
	Untreated	0.19	(−1.04 to 1.43)	0.77
Waist, cm				
	Aripiprazole	5.4	(2.87 to 7.93)	<.001
	Olanzapine	8.55	(7.43 to 9.67)	<.001
	Quetiapine	5.27	(4.07 to 6.47)	<.001
	Risperidone	5.1	(4.49 to 5.71)	<.001
	Untreated	0.7	(−0.87 to 2.27)	0.4
Glucose, mg/dL				
	Aripiprazole	0.54	(−2.85 to 3.93)	0.76
	Olanzapine	3.14	(0.69 to 5.59)	0.02
	Quetiapine	2.64	(−0.65 to 5.93)	0.12
	Risperidone	1.14	(−0.84 to 3.12)	0.26
	Untreated	0.69	(−4.84 to 6.22)	0.81

Table 1. Changes in metabolic parameters in antipsychotic naïve children and adolescents.[8]

recommendations, consensus guidelines, and primary literature highlighting the importance of monitoring for metabolic abnormalities, two recent, well designed retrospective cohort studies suggested that glucose and lipid monitoring rates continue to be low in adults and children.[10,11] The annual glucose monitoring rates for children receiving antipsychotics were 59% and 60% for the first two quarters of the 2012-2013 Federal Fiscal Year (FFY) in the Oregon Medicaid program.

Recommended schedules for monitoring of glucose and lipids have been proposed by multiple groups including the American Diabetes Association (ADA), American Psychiatric Association, and American Association of Clinical Endocrinologists.[12,13] The ADA recommends monitoring of blood glucose, blood pressure and waist circumference at initiation of therapy, 12 weeks, and annually thereafter. Body Mass Index (BMI) monitoring is recommended at baseline and every four weeks for 12 weeks and quarterly for the first year. Lipids checks are recommended at baseline, 12 weeks and every 5 years. More frequent monitoring may be indicated based on patient-specific factors. Patient specific factors include a personal or family history of diabetes, metabolic syndrome, or cardiovascular disease.

There is a lack of long term clinical data to define metrics and risk thresholds predicting development of diabetes and cardiovascular disease on which to base diagnostic criteria for metabolic syndrome in children.[14] In 2007, the International Diabetes Federation (IDF) developed consensus guidelines for the diagnosis of metabolic syndrome in children.[14] These guidelines synthesized recommendations from the ADA, the World Health Organization, and National Cholesterol Education Program. The IDF guidelines use waist circumference plus two other risk factors as diagnostic criteria. Waist circumference has been show to predict metabolic syndrome with similar accuracy to BMI when gender, age and ethnic group have been considered.[14] The IDF Guidelines define three age groups: 6-9 years, 10-15 years, and 16 and older. The IDF concluded diagnosis of metabolic syndrome in children under 10 years was determined unreliable. Monitoring of children less than 10 years with waist circumferences greater that the 90th percentile may be warranted in patients with a family history of diabetes or cardiovascular disease.

Critera for Metabolic Syndrome in Children and Adolescents

Age group (years)	Obesity Waist Circumference‡		Triglycerides	HDL-C	Blood pressure	Fasting Plasma Glucose
6–<10	>=90th percentile	Plus two or more of the following	Metabolic Syndrome cannot be diagnosed in this age group, but additional testing may be warranted for patients with a family history of risk factors			
10–<16	>=90th percentile or adult cut-off whichever is lower		>=150 mg/dL	<40 mg/dL	Systolic >=130mmHg or Diastolic >=85mm Hg	>=100 mg/dL or T2DM
16+ (Adult criteria)	Male >= 90 cm* Female >=80 cm¥		>=150 mg/dL	Male <40 mg/dL Female <50 mg/dL	Systolic >=130mmHg or Diastolic >=85mm Hg	>=100 mg/dL
			Or Active Lipid Treatment		Or Active Treatment	Or T2DM

Table 2 International Diabetes Federation criteria for metabolic syndrome. Adapted from *Diabetes*. 2007;8(5):299–306 and *Diabetes Voice*. 2005;50(3):31–33.[14,15]

Several national and state agencies have proposed standard metrics for the monitoring of antipsychotics. The National Committee for Quality Assurance (NCQA) added four antipsychotic-

related measures to the Healthcare Effectiveness Data and Information Set (HEDIS®) 2013 specification, including two specifically addressing glucose abnormalities associated with antipsychotics.[16] In April 2013, NCQA also posted draft measures for the monitoring metabolic abnormalities of antipsychotics in children.[17] The Oregon Health Authority (OHA) was awarded a technical assistance grant from the Center for Health Care Strategies (CHCS) to improve the use of psychotropics in foster children.[18] Part of the work under this grant has been the development of standard quality metrics for psychotropic use, which includes monitoring of glucose abnormalities for children receiving antipsychotic therapy. These quality metrics are now being reported to the Coordinated Care Organizations (CCO) along with detailed provider and patient information with the goal of improving rates of metabolic monitoring across all of Medicaid. The following RetroDUR intervention is proposed with the goal of improving the frequency of glucose monitoring for children receiving antipsychotics in the Fee For Service (FFS) program.

RetroDUR Intervention

Reminders to perform annual glucose monitoring in children receiving antipsychotics were sent to prescribers via fax in October and November of 2012. The results as reported by providers appear in Table 3. The overall response rate was 30%, with providers indicating that 57% of patients listed were scheduled for testing based on this notification. This program will be modified and expanded with reports sent to providers quarterly (see Appendix A for proposed provider report format). An expanded educational message explaining the importance of metabolic monitoring will be included along with a list of patients without a claims history indicating metabolic monitoring within the last 12 months.

Results by Patient Count	#	%
No Response	1,716	70
Response Received	746	30
Already Tested	240	32
Newly Scheduled Test	425	57
Not my patient	140	19

Table 3. Responses to Fall 2012 metabolic monitoring fax campaign.

Counts represent unique patient counts. More than one response sub-type (already tested, newly scheduled test, etc.) was allowed for each patient.

Providers will be notified of a particular patient only once every 12 months. Delays in claim submission, combined with the day-to-day constraints on contacting patients and scheduling tests suggests more frequent notifications may include patients for which testing has already been performed.

The notification report will include a request that providers respond with the status of monitoring (e.g. already tested, newly scheduled, testing unnecessary, etc.). Messages will only be sent for FFS patients. Providers can request a report for all of their FFS and CCO patients.

A report card allows providers to compare their monitoring practices to other providers. Current metabolic monitoring rates by provider specialty appear in Table 4. These values are based on the CHCS data specification (Appendix B) and reflect total Medicaid monitoring rates, not just FFS.

	Provider Type			Medicaid		
Provider	**Numerator**	**Denominator**	**%**	**Numerator**	**Denominator**	**%**
NURSE PRACTITIONER - FAMILY	27	42	64%	1,320	2,453	54%
NURSE PRACTITIONER - PEDIATRICS: PEDIATRICS	41	64	64%			
NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH	196	438	45%			
PHYSICIAN ASSISTANT	10	25	40%			
PHYSICIAN ASSISTANT - MEDICAL	8	17	47%			
PHYSICIAN-FAMILY MEDICINE	107	163	66%			
PHYSICIAN-PEDIATRICS	247	356	69%			
PHYSICIAN-PEDIATRICS-ADOLESCENT MEDICINE	23	36	64%			
PHYSICIAN-PEDIATRICS-DEVELOPMENTAL BEHAVORIAL PEDIATRICS	37	56	66%			
PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY	305	614	50%			
PHYSICIAN-PSYCHIATRY&NEUROLOGY-FORENSIC PSYCHIATRY	15	61	25%			
PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY	197	369	53%			
REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH	6	22	27%			
SPECIALIST	23	37	62%			
STUDENT IN AN ORGANIZED HEALTH CARE EDUCATION/TRAINING PROGRAM	25	51	49%			
Sub-specialties are based on NPI Registry primary taxonomy and related codes and descriptions						
Lower than the Overall Medicaid Rate						
Higher than the Overall Medicaid Rate						

Table 4 – Rates of children receiving antipsychotic medications without annual blood glucose screening

The following metrics will be monitored quarterly as part of the RetroDUR activity report:

- Member Profiles Sent
- Member With Responses
- Members With Newly Scheduled Monitoring
- New Onset Diabetes Identified
- Response Rate (members)
- Providers Contacted
- Provider Responses
- Response Rate (providers)
- Provider Agree With Recommendation

Using the same CHCS data specification, changes in monitoring rates will also be presented as part of the quarterly RetroDUR reports (Table 5). These data have been presented to the P & T Committee in the past in a different format. The new format includes several metrics not directly related to this metabolic monitoring program, but are part of the Psychotropic Use in Children program.[19]

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Pediatric Psychotropic Quarterly Report

Fee For Service

Fiscal Year 2012 - 2013

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar		
	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	367	622	59%	344	577	60%
Five or more concurrent psychotropics	30	2,163	1%	29	2,152	1%
Three or more concurrent psychotropics	354	2,163	16%	350	2,152	16%
Two or More Concurrent Antipsychotics	28	2,163	1%	21	2,152	1%
Under 18 years old on any antipsychotic	623	2,163	29%	578	2,152	27%
Youth five years and younger on psychotropics	49	2,017	2%	54	2,152	3%

Table 5. RetroDUR Pediatric Psychotropic Quarterly Report

References

1. Briggs-Gowan M, Horowitz S, Schwab-Stone M, Leventhal J, Leaf P. Mental Health in Pediatric Settings: Distribution of Disorders and Factors Related to Service Use. *J Am Acad Child Adolesc Psychiatry*. 2000;39(7):841–849. doi:10.1097/00004583-200007000-00012.

2. Raghavan R, Zima BT, Andersen RM, Leibowitz AA, Schuster MA, Landsverk J. Psychotropic medication use in a national probability sample of children in the child welfare system. *J Child Adolesc Psychopharmacol*. 2005;15(1):97–106. Available at: http://online.liebertpub.com/doi/abs/10.1089/cap.2005.15.97. Accessed July 30, 2013.

3. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *The Lancet*. 3;373(9657):31–41. doi:10.1016/S0140-6736(08)61764-X.

4. Almandil NB, Liu Y, Murray ML, Besag FMC, Aitchison KJ, Wong ICK. Weight Gain and Other Metabolic Adverse Effects Associated with Atypical Antipsychotic Treatment of Children and Adolescents: A Systematic Review and Meta-analysis. *Pediatr Drugs*. 2013. doi:10.1007/s40272-013-0016-6.

5. Seida JC, Schouten JR, Mousavi SS, et al. First- and Second- Generation Antipsychotics for Children and Young Adults. *Agency Healthc Res Qual*. 2012;39. Available at: http://www.ncbi.nlm.nih.gov/books/NBK84643/. Accessed July 30, 2013.

6. Seida JC, Schouten JR, Boylan K, et al. Antipsychotics for Children and Young Adults: A Comparative Effectiveness Review. *Pediatrics*. 2012;129(3):e771–e784. doi:10.1542/peds.2011-2158.

7. Lieberman JA, Phillips M, Gu H, et al. Atypical and Conventional Antipsychotic Drugs in Treatment-Naive First-Episode Schizophrenia: A 52-Week Randomized Trial of Clozapine Vs Chlorpromazine. *Neuropsychopharmacology*. 2003;28(5):995–1003. doi:10.1038/sj.npp.1300157.

8. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA J Am Med Assoc*. 2009;302(16):1765–1773. Available at: http://jama.ama-assn.org/content/302/16/1765.short. Accessed May 9, 2013.

9. Correl C, Carlson HE. Endocrine and Metabolic Adverse Effects of Psychotropic Medications in Children and Adolescents. *Am Acad Child Adolesc Psychiatry*. 2006;45(7):771–791.

10. Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, Cuffel B. Metabolic Screening After the American Diabetes Association's Consensus Statement on Antipsychotic Drugs and Diabetes. *Diabetes Care*. 2009;32(6):1037–1042. Available at: http://care.diabetesjournals.org/content/32/6/1037.abstract.

11. Morrato EH, Nicol GE, Maahs D, et al. Metabolic screening in children receiving antipsychotic drug treatment. *Arch Pediatr Adolesc Med*. 2010;164(4):344. Available at: http://archpedi.ama-assn.org/cgi/reprint/164/4/344.pdf. Accessed March 27, 2013.

12. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care*. 2004;27(2):596 –601. doi:10.2337/diacare.27.2.596.

13. Pringsheim T, Panagiotopoulos C, Davidson J, Ho J. Evidence-Based Recommendations for Monitoring Safety of Second Generation Antipsychotics in Children and Youth. *J Can Acad Child Adolesc Psychiatry*. 2011;20(3):218–233. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3143700/. Accessed March 27, 2013.

14. Zimmet P, Alberti KGM, Kaufman F, et al. The metabolic syndrome in children and adolescents – an IDF consensus report. *Pediatr Diabetes*. 2007;8(5):299–306. doi:10.1111/j.1399-5448.2007.00271.x.

15. George A, Shaw J, Zimmet P. A new IDF worldwide definition of the metabolic syndrome: the rationale and the results | International Diabetes Federation. *Diabetes Voice*. 2005;50(3):31–33. Available at: http://www.idf.org/diabetesvoice/articles/a-new-idf-worldwide-definition-of-the-metabolic-syndrome-the-rationale-and-the-results. Accessed March 25, 2013.

16. HEDIS 2013. *Natl Comm Qual Assur - HEDIS Qual Meas*. Available at: http://www.ncqa.org/HEDISQualityMeasurement/HEDISMeasures/HEDIS2013.aspx. Accessed July 29, 2013.

17. Public Invited to Help Shape New Antipsychotic Medication Use Measures for Medicaid and CHIP. *NCQA Newsroom*. 2013. Available at: http://www.ncqa.org/Newsroom/2013NewsArchives/NewsReleaseApril292013.aspx. Accessed May 9, 2013.

18. Oregon selected for a national pilot project to improve the use of psychotropic medications among children in foster care.

19. *Oregon Administrative Rules 410-121-0100 Drug Use Review*. Available at: http://arcweb.sos.state.or.us/pages/rules/access/numerically.html. Accessed January 11, 2013.

20. *Warning about Hyperglycemia and Atypical Antipsychotic Drugs.*; 2004. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/printer.cfm?id=229. Accessed April 23, 2013.

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

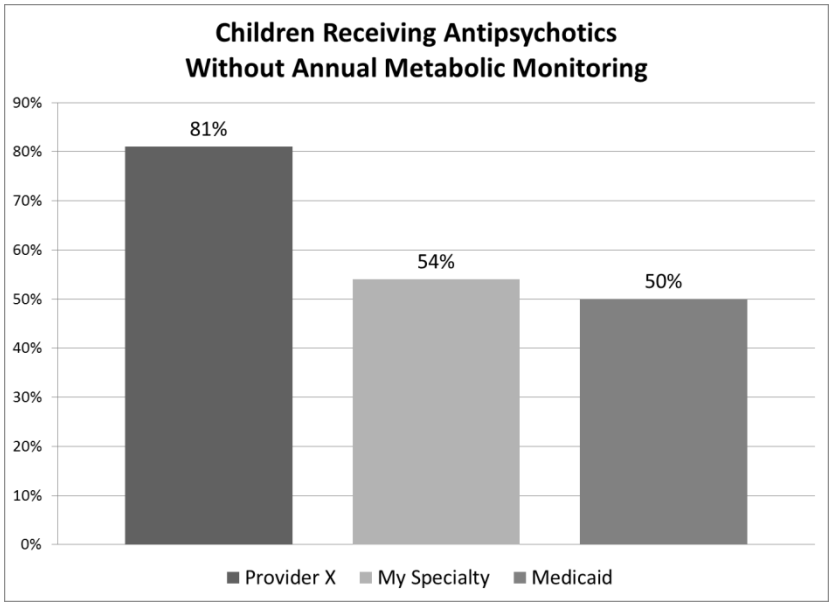
Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Appendix A: Antipsychotic Metabolic Monitoring Provider Report

Date: mm/dd/yyyy

Attention: Provider X
Fax: 541-123-4567

Re: Your pediatric patients receiving antipsychotics without claims for routine glucose monitoring



The FDA issued a safety warning for all second generation antipsychotics recommending monitoring of blood glucose.[20] Careful monitoring for metabolic abnormalities (body composition, lipids, glucose, blood pressure) is the standard of care when prescribing antipsychotics.

The following pages contain a list of Fee-For-Service (FFS) Medicaid patients that you are identified by the pharmacy claim as the most recent prescriber of an antipsychotic and who do not have annual glucose screening claims. We understand claims data do not always reflect actual testing, that laboratory claims may be delayed and errors are made in prescriber identification.

The chart above reflects the proportion of patients **without** annual glucose screening who recently filled an antipsychotic prescription indicating you are the prescriber. Overall Medicaid rates and rates for your specialty are included for reference.

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (2004) Diabetes Care, 27(2), 596-601

	Baseline	4 wks	8 wks	12 wks	Quarterly	Annually	Q 5 Yr
Personal/ Family History	X					X	
Weight	X	X	X	X	X		
Waist Circumference	X			X		X	
Blood Pressure	X			X		X	
Fasting Blood Glucose	X			X		X	
Lipids	X			X			X

Use the following form to indicate the status of glucose testing. Please fax this report within 30 days to the Medical Assistance Program at 503-947-2596.

If you have any questions, or would like a complete list of all of your Medicaid patients (FFS and Coordinated Care Organization), please fax your request to 503-947-2596 or call at 503-945-6513.

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor
Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Metabolic Syndrome Detection and Management

The 2007 International Diabetes Federation[1] consensus guidelines for the diagnosis of metabolic syndrome in children synthesized recommendations from the ADA, the World Health Organization, and National Cholesterol Education Program (see table below).

- Weight is not a reliable surrogate marker for glucose and lipid irregularities. Waist circumference predicts metabolic syndrome similarly to body mass index when gender, age and ethnic group have been considered.[1]
- The metabolic effect profiles vary from one antipsychotic to another thus changing antipsychotics is an option to manage metabolic abnormalities for some patients.[2]
- A meta-analysis found individual and group non-pharmacological interventions such as cognitive behavioral therapy and diet and exercise counseling reduce mean body weight (-2.56kg) and BMI (-0.91kg/m^2) in adults, but studies in children are lacking.[3]
- Pharmacologic strategies to mitigate weight gain include:[4]
  - Metformin may prevent new weight gain in antipsychotic-naïve patients and patients who have gained weight due to antipsychotic therapy.[5,6]
  - A recent meta-analysis found only metformin, d-fenfluramine, and topiramate superior to placebo at reducing weight gain.[7]
  - Methylphenidate, dextroamphetamine, amantadine, orlistat, famotidine and rosiglitazone **all failed to show significant advantages** compared to placebo.[7,8]

Changes in metabolic parameters in antipsychotic naïve children and adolescents after 12 weeks

Metric	Medication	Mean	(95% CI)	p Value
Weight (kg)				
	Aripiprazole	4.44	(3.71 to 5.18)	<.001
	Olanzapine	8.54	(7.38 to 9.69)	<.001
	Quetiapine	6.06	(4.90 to 7.21)	<.001
	Risperidone	5.34	(4.81 to 5.87)	<.001
	Untreated	0.19	(−1.04 to 1.43)	0.77
Waist, cm				
	Aripiprazole	5.4	(2.87 to 7.93)	<.001
	Olanzapine	8.55	(7.43 to 9.67)	<.001
	Quetiapine	5.27	(4.07 to 6.47)	<.001
	Risperidone	5.1	(4.49 to 5.71)	<.001
	Untreated	0.7	(−0.87 to 2.27)	0.4
Glucose, mg/dL				
	Aripiprazole	0.54	(−2.85 to 3.93)	0.76
	Olanzapine	3.14	(0.69 to 5.59)	0.02
	Quetiapine	2.64	(−0.65 to 5.93)	0.12
	Risperidone	1.14	(−0.84 to 3.12)	0.26
	Untreated	0.69	(−4.84 to 6.22)	0.81

Critera for Metabolic Syndrome in Children and Adolescents

Age group (years)	Obesity Waist Circumference‡		Triglycerides	HDL-C	Blood pressure	Fasting Plasma Glucose
6–<10	>=90th percentile	Plus two or more of the following	Metabolic Syndrome cannot be diagnosed in this age group, but additional testing may be warranted for patients with a family history of risk factors			
10–<16	>=90th percentile or adult cut-off whichever is lower		>=150 mg/dL	<40 mg/dL	Systolic >=130mmHg or Diastolic >=85mm Hg	>=100 mg/dL or T2DM
16+ (Adult criteria)	Male >= 90 cm* Female >=80 cm¥		>=150 mg/dL	Male <40 mg/dL Female <50 mg/dL	Systolic >=130mmHg or Diastolic >=85mm Hg	>=100 mg/dL
			Or Active Lipid Treatment		Or Active Treatment	Or T2DM

HDL-C, high-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus
*Male Europids >=94cm, Male Japanese >=85cm, ¥ Female Japanese >=90cm, ‡Tables for waist Circumference Percentiles for American children by age, gender, and ethnic backgroup available at: http://www.idf.org/webdata/docs/Mets_definition_children.pdf

1. Zimmet P, Alberti KGM, Kaufman F, et al. The metabolic syndrome in children and adolescents – an IDF consensus report. Pediatr Diabetes. 2007;8(5):299–306.
2. Correl C, Carlson HE. Endocrine and Metabolic Adverse Effects of Psychotropic Medications in Children and Adolescents. Am Acad Child Adolesc Psychiatry. 2006;45(7):771–791
3. Alvarez-Jimenez M, Hetrick SE, Gonzalez-Blanch C, Gleeson JF, McGorry PD. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. Br J Psychiatry. 2008;193(2):101–107.
4. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of Medications Used to Attenuate Antipsychotic-Related Weight Gain and Metabolic Abnormalities: A Systematic Review and Meta-Analysis. Neuropsychopharmacology. 2010;35(7):1520–1530.
5. Klein DJ, Cottingham EM, Sorter M, Barton B, Morrison JA. A Randomized, Double-Blind, Placebo-Controlled Trial of Metformin Treatment of Weight Gain Associated with Initiation of Atypical Antipsychotic Therapy in Children and Adolescents. Am J Psychiatry. 2006;163(12):2072–2079.
6. Arman S, Sadramely MR, Nadi M, Koleini N. A randomized, double-bline, placebo-controlled trial of metformin treatment for weight gain associated with initiation of risperidone in children and adolescents. Saudi Med J. 2008;29(8):1130–1134.
7. Maayan L, Correll CU. Weight gain and metabolic risks associated with antipsychotic medications in children & adolescents. J Child Adolesc Psychopharmacol. 2011;21(6):517–535.
8. Penzner JB, Dudas M, Saito E, et al. Lack of effect of stimulant combination with second-generation antipsychotics on weight gain, metabolic changes, prolactin levels, and sedation in youth with clinically relevant aggression or oppositionality. J Child Adolesc Psychopharmacol. 2009;19(5):563–573.
9. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA J Am Med Assoc. 2009;302(16):1765–1773

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Patients without claims history demonstrating appropriate glucose monitoring:

Patient Info		Claims History	Provider Response
Patient	Jane Doe	Annual Glucose Monitoring	☐ Tested On
DOB	1/1/1995	-No claims found	☐ Scheduled for
Member ID	ABC123		☐ Not my patient
			☐ Testing unnecessary Explain:
			☐ Other
Patient	John Doe	Annual Glucose Monitoring	☐ Tested On
DOB	1/1/2005	-Last test date: 2/1/2012	☐ Scheduled for
Member ID	XYZ098		☐ Not my patient
			☐ Testing unnecessary Explain:
			☐ Other

Please indicate the status of this required laboratory work and fax this report within 30 days to DMAP at 503-947-2596.

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119
DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor
Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Appendix B: Metabolic Monitoring Technical Specification

Indicator	Children Who Are Using Antipsychotic Medications Without Diabetes Screening
Eligible Population	
Inclusion	All enrolled Medicaid members under 18 years old at the time of a paid pharmacy claim for any antipsychotic (Table B1) with a service date during the reporting period AND a day supply greater than or equal to 5 days.
Reporting Period	35 days prior to the report date.
Exclusion	• Members with diabetes. There are two ways to identify members with diabetes: by pharmacy data and by claim/encounter data. The organization must use both methods to identify members with diabetes, but a member need only be identified by one method to be excluded from the measure. Members may be identified as having diabetes during the 24 months prior to the reporting date. a) Pharmacy data. Members who were dispensed insulin or oral hypoglycemics/ antihyperglycemics during the measurement year or year prior to the measurement year on an ambulatory basis. This include all agents in standard therapeutic class 58, excluding Metformin. Metformin can be used to mitigate weight gain associated with antipsychotic use and is not strictly an indicator of diabetes. b) Claim/encounter data. Members who had two face-to-face encounters in an outpatient setting or non-acute inpatient setting, on different dates of service, with a diagnosis of diabetes (Table B2), or one face-to-face encounter in an acute inpatient or ED setting, during the 24 months prior to the reporting date. Refer to Table B3 for codes to identify visit type.
Numerator	Patients without a glucose test (Table B4) or an HbA1c test (Table B5) performed within the 12 months prior to the report date.
Denominator	Eligible Population

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor
Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Antipsychotics
ARIPIPRAZOLE
ASENAPINE MALEATE
CHLORPROMAZINE HCL
CLOZAPINE
FLUPHENAZINE DECANOATE
FLUPHENAZINE HCL
HALOPERIDOL
HALOPERIDOL DECANOATE
HALOPERIDOL LACTATE
ILOPERIDONE
LOXAPINE SUCCINATE
LURASIDONE HCL
MOLINDONE HCL
OLANZAPINE
OLANZAPINE/FLUOXETINE HCL
PALIPERIDONE
PALIPERIDONE PALMITATE
PERPHENAZINE
PERPHENAZINE/AMITRIPTYLINE HCL
PIMOZIDE
PROCHLORPERAZINE EDISYLATE
PROCHLORPERAZINE MALEATE
QUETIAPINE FUMARATE
RISPERIDONE
RISPERIDONE MICROSPHERES
THIORIDAZINE HCL
THIOTHIXENE
TRIFLUOPERAZINE HCL
ZIPRASIDONE HCL

Table B1 Antipsychotics

Description	ICD-9-CM Diagnosis
Diabetes	250, 357.2, 362.0, 366.41, 648.0

Table B2 Codes to Identify Diabetes[16]

Description	CPT	UB Revenue
Outpatient	99201-99205, 99211-99215, 99217-99220, 99241-99245, 99341-99345, 99347-99350, 99384-99387, 99394-99397, 99401-99404, 99411, 99412, 99420, 99429, 99455, 99456	051x, 0520-0523, 0526-0529, 057x-059x, 082x-085x, 088x, 0982, 0983
Nonacute inpatient	99304-99310, 99315, 99316, 99318, 99324-99328, 99334-99337	0118, 0128, 0138, 0148, 0158, 019x, 0524, 0525, 055x, 066x
Acute inpatient	99221-99223, 99231-99233, 99238, 99239, 99251-99255, 99291	010x, 0110-0114, 0119, 0120-0124, 0129, 0130-0134, 0139, 0140-0144, 0149, 0150-0154, 0159, 016x, 020x,021x, 072x, 080x, 0987
ED	99281-99285	045x, 0981

Table B3: Codes to Identify Visit Type[16]

Description	CPT	LOINC
Glucose test	80047, 80048, 80050, 80053, 80069, 82947, 82950, 82951	1518-0, 1554-5, 10450-5, 14995-5, 17865-7

Table B4 Codes to Identify Diabetes Screening[16]

CPT	CPT Category II	LOINC
83036, 83037	3044F, 3045F, 3046F	4548-4, 4549-2, 17856-6, 59261-8, 62388-4

Table B5 Codes to Identify HbA1c Tests[16]

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119
DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor
Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Follow Up Care for Children Prescribed Their First ADHD Medication

Recommendations

- Fax reports biweekly to promote follow up care for children prescribed their first ADHD medication as defined by the Healthcare Effectiveness Data and Information Set (HEDIS®) 2013 specification
- Reports to contain:
    - Dashboard comparing the target provider to other Medicaid providers and providers within their specialty
    - Provide list of patient with their first ADHD prescription within the last 2 weeks
    - Form indicating the status of a scheduled follow up visit for each patient for the provider to complete and return to the Medical Assistance Program
    - Educational materials highlighting recommendations for monitoring and management of ADHD pharmacotherapy in children

Background

According to the Center for Disease Control's report on the results of the National Health Interview Survey from 2004-2006, 8.4% of American children 6-17 had at one point been diagnosed with Attention Deficit Hyperactivity Disorder (ADHD).[1] The report also indicated the diagnosis of ADHD was more prevalent in children covered by a Medicaid program (11.6%). Given the observed annual increase of the percentage of children with the diagnosis of ADHD (3%), this figure is likely even higher now. Additionally the study does not capture the rate of undiagnosed ADHD. A CDC report indicated that 4.3% of children 4-17 years old had both a diagnosis of ADHD and were receiving pharmacologic treatment. Of all children 6-17 enrolled in the Oregon Medicaid program in January 2013, 10.6% had a prior claims history of ADHD (ICD-9 314.XX).

Phenylethylamine central nervous system (CNS) stimulants have been used for over half a century for the treatment of ADHD and hyperkinetic disorders. These drug products are chemical variants of amphetamine or methylphenidate, with various formulations to control the release rate of the active agents. The primary mechanism of action is the increase of synaptic dopamine and norepinephrine.[2,3] Safety monitoring should include assessments of cardiovascular risk and elevations in heart rate (HR) and blood pressure (BP), height and weight reductions and sleep disturbances. [4,5]All of these medications are Drug Enforcement Agency (DEA) schedule II substances, indicating a high risk of physical dependence, misuse and abuse.[6]

The non-traditional CNS stimulant modafinil has been studied for the treatment of ADHD.[5,7] Modafinil's mechanism of action is unclear. Both modafinil and the R-isomer armodafinil are FDA approved to "improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea, narcolepsy and shift work disorder."[7,8] The safety and efficacy of these agents in children is unclear and neither agent is approved for use in children.[7,8] Monitoring parameters are similar to traditional stimulants (amphetamine and methylphenidate derivatives). Both of these medications are DEA Schedule IV controlled substances, indicating a lower risk of dependence and misuse when compared to traditional stimulants.[6–8]

Several alternatives to stimulants have been used for the treatment of ADHD. Immediate and extended release formulations of clonidine and guanfacine (alpha-2 adrenergic agonists) have been used in the treatment of ADHD, either as monotherapy or adjunctive therapy.[4,5,9] Developed initially as antihypertensives, cardiovascular symptoms generally present as reduced, rather than increased blood pressure.[2] Other common side effects include somnolence, fatigue and dizziness. Atomoxetine is a selective norepinephrine reuptake inhibitor indicated for the treatment of ADHD in children over six years old.[10] Atomoxetine has an FDA black box warning for an increased risk of suicidal ideation and must therefore be monitored closely. Cautions should be used in prescribing atomoxetine with comorbid bipolar disorder due to concerns of precipitating manic episodes. Atomoxetine has been shown to cause sleep disturbances manifesting as either somnolence or insomnia. Other side effects include increases in HR and BP, slowing of growth of height and weight, and aggressive behavior.

Behavioral and environmental interventions have been investigated for the treatment of ADHD. The 2011 Agency for Healthcare Research and Quality (AHRQ) systematic review of ADHD treatments found high quality evidence supporting effectiveness of parent behavior training for the management of ADHD symptoms in preschoolers.[9] A recent Oregon Health Evidence Review Commission (HERC) draft guidance recommended the coverage of patient behavior training in preschool age children and behavioral treatment in children over the age of six.[11] The American Academy of Pediatrics (AAP) systematic review and clinical practice guidelines agree with the AHRQ findings for preschool children.[4] The AHRQ report assessed the data for behavioral interventions in other age groups as either low quality or insufficient to support treatment recommendations. The AAP cites the same evidence as the AHRQ, but deemed the evidence sufficient to recommend the use of behavioral interventions in elementary school age children and adolescents with or without the use of pharmacotherapy.

Regular monitoring of ADHD pharmacotherapy is essential for efficacy and safety. In 2009 the Children's Health Insurance Program Reauthorization Act (CHIPRA) identified 25 core health care quality measures including "Follow-up care for children prescribed attention-deficit/hyperactivity disorder (ADHD) medication."[12,13] Measures were taken from 121 public submissions. These were narrowed to 25 based on expert opinion on validity, feasibility, and importance. This ADHD measure was ranked 13th by the expert panel. This metric identifies both initiation and continuation phases. The initiation phase identifies patients 6-12 with at least one follow up visit within 30 days in pharmacotherapy naïve patients upon issuing of the first ADHD medication. The continuation phase monitors these patients for at least two additional follow up appointments over the following 270 days. As part of Oregon's Medicaid Demonstration project, the Oregon Health Authority Metrics and Scoring Committee adopted the ADHD metrics as a performance measure for all Coordinated Care Organizations (CCO).[14,15] The Metrics and Scoring Committee reported that Statewide monitoring rates were 52.3% for initial follow up and 61% for continuation phase follow up.[16] The AAP guidelines recommend a patient-specific follow up schedule, with frequent telephone and face-to-face evaluations during titration and follow up at least every three months for the first year.[17] Neither the AHRQ or DERP reports discuss monitoring or follow up schedules in detail.[5,9] Despite limited evidence supporting the HEDIS® specification, it provides a standard which can be compared to other programs both locally and nationally.[18]

RetroDUR Intervention

As part of the efforts of the Division of Medical Assistance Programs (DMAP) to improve the use of psychotropics in foster children, a dashboard was created for CCOs to monitor newly started ADHD medication which are paid for by the FFS program (i.e. carve-out medications).[18] This FFS RetroDUR proposal adapts the CCO dashboard to target fee for service patients. The new program will send a fax reminder to providers to schedule appointments for the initiation phase and continuation phase consistent with the HEDIS® measure and AAP guideline recommendations (Appendix A).[19] These notifications will contain a list of patients recently started on ADHD medications, educational material describing AAP guidelines and monitoring parameters. Faxes will be sent every two weeks containing all new starts since the previous notification.

Provider feedback will also be solicited on:

1. Action Taken
    - Already scheduled follow within 30 days
    - Already scheduled quarterly follow up
    - Will schedule appointments
    - Will not schedule the appointments
        - Explain_____
    - Not my patient/ no longer my patient
    - Patient Deceased
    - Neither clinician or patient associated with this office
    - Other_____
2. Provider Satisfaction
    - This information was useful
    - I agree with the recommendation in general
    - This information will change my future practice
    - Please do not send further notifications

Biweekly messages will not be sent to providers exceeding 75% of either initiation or continuation phase follow up. For these outstanding providers, a “Thank you” message will be sent quarterly (Appendix B).

Reporting follow up rates by practice site may be an alternative strategy to providing clinician-specific rates. Assigning practice sites is dependent on the accuracy of National Provider Identifier Standard data. This option may be considered based on the Pharmacy & Thera

References

1. Pastor PN, Reuben CA, National Health Interview Survey (U.S.) NC for HS (U. S. *Diagnosed attention deficit hyperactivity disorder and learning disability, United States, 2004-2006: data from the National Health*

Interview Survey. Hyattsville, Md.: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2008.

2. Westfall T, Westfall D. Adrenergic Agonists and Antagonists. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011. Available at: http://www.accessmedicine.com/content.aspx?aID=16661344. Accessed August 1, 2013.

3. Spencer T. Attention-Deficit/Hyperactivity Disorder. In: *CURRENT Diagnosis & Treatment: Psychiatry.* 2nd ed. New York: McGraw-Hill; 2008:Chapter 35. Available at: http://www.accessmedicine.com/content.aspx?aID=3290305. Accessed August 1, 2013.

4. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *PEDIATRICS*. 2011;128(5):1007–1022. doi:10.1542/peds.2011-2654.

5. McDonagh M, Peterson K, Thakurta sujata, Low A. Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder. Final Update 4 Report. *Drug Eff Rev Proj*. 2011. Available at: http://derp.ohsu.edu/final/ADHD_final%20report_update%204_December%202011.pdf. Accessed July 23, 2012.

6. Controlled Substance Schedules. *US Dep Justice Drug Enforc Adm Off Divers Control*. Available at: http://www.deadiversion.usdoj.gov/schedules/. Accessed August 1, 2013.

7. Provigil(R) (modafinil) Full Prescribing Information. 2010. Available at: http://provigil.com/media/PDFs/prescribing_info.pdf. Accessed August 1, 2013.

8. Nuvigil(R) (armodafinil) Tablets (C-IV) Full Prescribing Information. 2010. Available at: http://www.nuvigil.com/PDF/Full_Prescribing_Information.pdf. Accessed August 1, 2013.

9. Charach A, Dashti B, Carson P, et al. Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long- Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment. *AHRQ*. 2011;44. Available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/191/818/CER44-ADHD_20111021.pdf. Accessed July 30, 2013.

10. Highlights of Prescribing Information. Strattera(R) (atomoxetine hydrochloride). 2011. Available at: http://www.ncbi.nlm.nih.gov/books/NBK84427/. Accessed August 1, 2013.

11. Draft Coverage Guidance: Treatment of Attention Deficit Hyperactivity Disorder. 2012. Available at: http://www.oregon.gov/oha/OHPR/pages/herc/coverage-guidance.aspx. Accessed August 1, 2013.

12. Follow-Up Care for Children Prescribed ADHD Medication (ADD). 2013. Available at: https://physicians.prospectmedical.com/physician/PMS/Secure/p4p/HEIDIS%20Section/Educational%20Tools/HEIDIS%20Measures/Follow-

Up%20Care%20for%20Children%20Prescribed%20ADHD%20Medication%20(ADD).pdf. Accessed June 17, 2013.

13. Initial Core Set of Children's Healthcare Quality Measures | Agency for Healthcare Research & Quality (AHRQ). Available at: http://www.ahrq.gov/policymakers/chipra/listtable.html. Accessed July 30, 2013.

14. Oregon Health Policy Board: Oregon's Medicaid Demonstration. Available at: http://www.oregon.gov/oha/OHPB/Pages/health-reform/cms-waiver.aspx.

15. Follow Up Care for Children Prescribed ADHD Medication (NFQ 0108). 2013. Available at: http://www.oregon.gov/oha/CCOData/Follow%20Up%20Care%20for%20Children%20Prescribed%20ADHD%20Medication%20-%20FINAL.pdf.

16. Oregon Health Authority Statewide Revised Baseline Data 2011. Available at: http://www.oregon.gov/oha/CCOData/State%20Level%20Baseline%20Data%20(2011)%20--%20Revised%20June%202013%20(clean).pdf. Accessed August 1, 2013.

17. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. Supplemental Information: Implementing the Key Action Statements: An Algorithm and Explanation for Process of Care for the Evaluation, Diagnosis, Treatment and Monitoring of ADHD in Chldren and Adolescents. *PEDIATRICS*. 2011;128(5):SI1–21. Available at: http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654/suppl/DC1. Accessed May 9, 2013.

18. Oregon selected for a national pilot project to improve the use of psychotropic medications among children in foster care. 2012. Available at: http://www.oregon.gov/oha/news/Documents/2012-0413-joint-foster-care-psych-meds.pdf.

19. HEDIS 2013. *Natl Comm Qual Assur - HEDIS Qual Meas*. Available at: http://www.ncqa.org/HEDISQualityMeasurement/HEDISMeasures/HEDIS2013.aspx. Accessed July 29, 2013.

20. Brown RT, Freeman WS, Perrin JM, et al. Prevalence and Assessment of Attention-Deficit/Hyperactivity Disorder in Primary Care Settings. *PEDIATRICS*. 2001;107(3):e43–e43. doi:10.1542/peds.107.3.e43.

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119
DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor
Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Appendix A: Provider Letter for ADHD Follow-Up Care

Date: mm/dd/yyyy

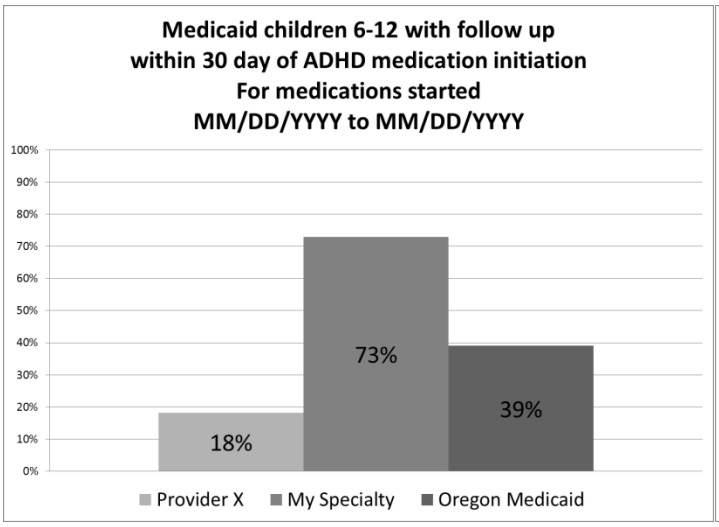
Attention: Provider X
Fax: 541-123-4567

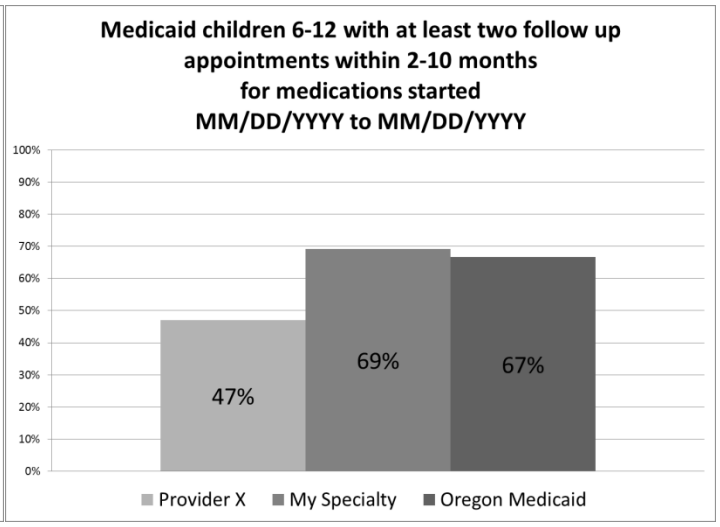
Re: Scheduled follow-up for children on ADHD medications

The Division of Medical Assistance Programs and all Coordinated Care Organizations encourage providers to follow the American Academy of Pediatrics and the Agency for Healthcare Research and Quality recommendations for follow up care in children receiving pharmacotherapy for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The following pages contain a list of Fee-For-Service (FFS) Medicaid patients that you are identified by the pharmacy claim as the prescriber of the first ADHD medication. We encourage you to schedule at least one follow up appointment within thirty days of initiation and at least 2 appointments 2-10 months after initiation.

The figures below reflect the proportion of patients for which you initiated ADHD medications with initial follow up and maintenance phase follow by any provider. Overall Medicaid rates and rates for your specialty are included for reference.





If you have any questions or comments regarding this policy, please call 503-945-6513 or fax 503-947-2596.

We thank you for your cooperation.

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119
DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor
Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Highlights of the American Academy of Pediatrics (AAP) 2011 Recommendations for Treatment and Management of Attention Deficit Hyperactivity Disorder (ADHD)

- Use rating scales for the diagnosis and monitoring of symptoms such as the Vanderbilt ADHD assessment tool available at: http://www.nichq.org/toolkits_publications/complete_adhd/03VanAssesScaleParent%20Infor.pdf
- The Conners' Parent and Teacher rating scales (CPRS & CTRS) may also be useful in screening for ADHD and comorbid conditions in select populations
- Review school records including report cards, suspensions, and progress reports
- Monitor for sleep disturbances at baseline and at each follow up visit
- Monitor height, weight, blood pressure (BP) and heart rate (HR) at baseline and at all follow up visits regardless of pharmacologic agent
    - Stimulants and atoxmoxetine may increase BP and HR and slow growth in height and weight
    - Clonidine and guanfacine may decrease BP and HR
- Stimulants may be titrated every 3-7 days
- Guanfacine and clonidine may take 2-4 weeks to see full therapeutic effects
- Atomoxetine may take 4-6 weeks to see full therapeutic effects and monitored for signs of suicidal ideation
- For non-response to a stimulant, consider switch to a CNS agent of a different chemical group (i.e. methylphenidate to amphetamine or vice versa).
- Poor symptom control should prompt neuropsychological and psychoeducational assessments, possibly by a psychologist or neuropsychologist

AAP Minimum Follow-Up Schedule for Patients Receiving ADHD Drugs

Initiation and Titration	At least once within 30 days of initiation
First Year of Therapy	Every 3 months
After First Year	Twice yearly, with telephone follow up with each refill

AAP ADHD Treatment Recommendations

Age	Strength	Therapy
Preschool 4-5 Years	Strong	Parental/Teacher Behavioral Therapy
	Recommended	Methylphenidate
Elementary School Age 6-11 Years	Strong	FDA Approved, Age Appropriate Medications +/- Behavioral & Environmental Therapy
Adolescents 12-18 years	Strong	FDA Approved, Age Appropriate Medications
	Recommended	Behavioral & Environmental Therapy

*Modafinil (Provigil®) and armodafinil (Nuvigil®) have not been demonstrated to be safe or effective in the treatment of ADHD in children and do not have FDA approval for ADHD

Other Useful References

- American Academy of Pediatrics 2011 ADHD Guideline Implementation Guide: http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654/suppl/DC1
- Parent's Guide to ADHD: http://www.effectivehealthcare.ahrq.gov/ehc/products/191/1148/adhd_con_fin_to_post.pdf
- CCO Incentive Measures and data specifications available at: http://www.oregon.gov/oha/Pages/CCO-Baseline-Data.aspx
- Brown RT, Freeman WS, Perrin JM, et al. Prevalence and Assessment of Attention-Deficit/Hyperactivity Disorder in Primary Care Settings. *PEDIATRICS*. 2001;107(3):e43–e43. doi:10.1542/peds.107.3.e43 http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.107.3.e43

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

The following is a list of FFS Medicaid patients that you are identified by the pharmacy claim as the prescriber of the first ADHD medication. We encourage you to schedule at least one follow up appointment within thirty days of initiation and at least 2 appointments 2-9 months after initiation.

Please complete the form below and fax back to 503-947-2596.

Member ID	Patient Name	Date of Birth	Drug Name	First Rx Fill Date	Action Taken
XYZ1234	Doe, Jane	MM/DD/YYYY	Guanfacine	MM/DD/YYYY	☐ Already scheduled follow within 30 days ☐ Already scheduled quarterly follow up ☐ Will schedule appointments ☐ Will not schedule the appointments Explain_____ ☐ Not my patient/ no longer my patient ☐ Patient Deceased ☐ Neither clinician or patient associated with this office ☐ Other_____
ABC9876	Doe, John	MM/DD/YYYY	Methylphenidate	MM/DD/YYYY	☐ Already scheduled follow within 30 days ☐ Already scheduled quarterly follow up ☐ Will schedule appointments ☐ Will not schedule the appointments Explain_____ ☐ Not my patient/ no longer my patient ☐ Patient Deceased ☐ Neither clinician or patient associated with this office ☐ Other_____

Please check all that apply:

- ☐ This information was useful
- ☐ I agree with the recommendation in general
- ☐ This information will change my future practice
- ☐ Please do not send further notifications

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Appendix B: Exceptional Provider Thank You Letter

Date: mm/dd/yyyy

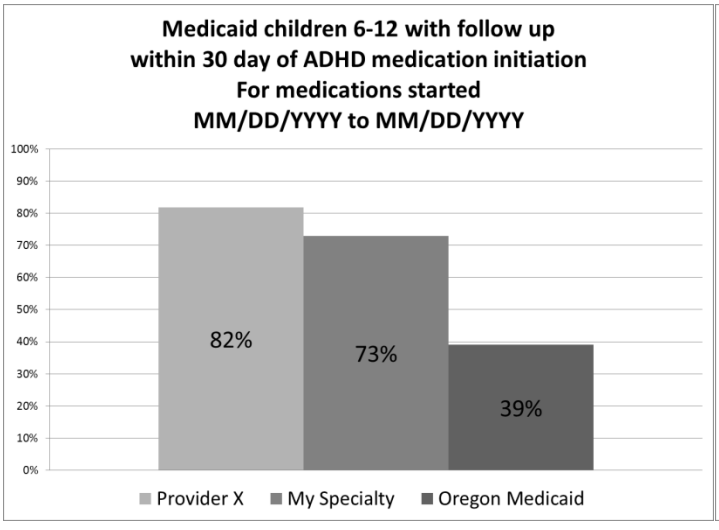
Attention: Provider X
Fax: 541-123-4567

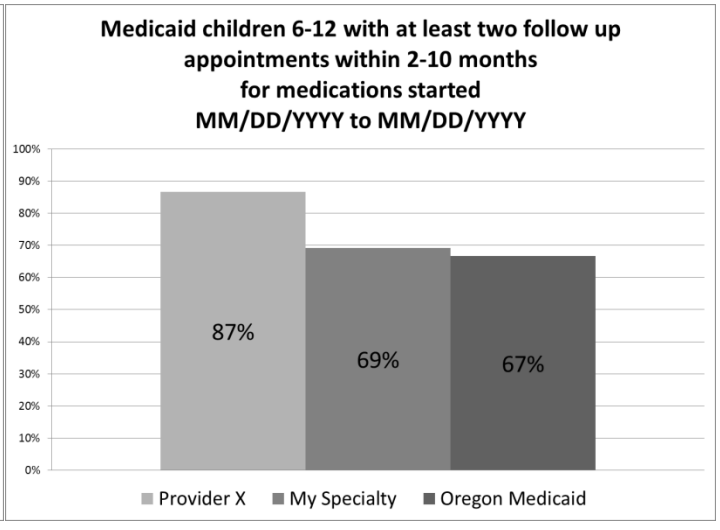
Re: Your excellence in follow up care for children receiving ADHD medications

You were identified as an exceptional provider based on the frequency of follow up care for children started on attention deficit hyperactivity disorder (ADHD) medications. For children 6-12 started on their first ADHD medication, at least one follow up visit was scheduled for XX% of your patients. Over the next 9 months, there were at least two follow up visits for XX% of those new starts.

The Division of Medical Assistance Programs and all Coordinated Care Organizations encourage providers to follow the American Academy of Pediatrics (AAP) and the Agency for Healthcare Research and Quality (AHRQ) recommendations for follow up care in children receiving pharmacotherapy for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). We appreciate your efforts to follow the AAP guidelines and AHRQ recommendations and the delivery of exceptional care to our members.

The figures below reflect the proportion of patients for which you initiated ADHD medications with initial follow up and maintenance phase. Overall Medicaid rates and rates for your specialty are included for reference.





If you have any questions or comments regarding this policy, please call 503-945-6513 or fax 503-947-2596.

Please check all that apply:

- ☐ This information was useful
- ☐ I agree with the recommendation in general
- ☐ This information will change my future practice
- ☐ Please do not send further notifications

Highlights of the American Academy of Pediatrics (AAP) 2011 Recommendations for Treatment and Management of Attention Deficit Hyperactivity Disorder (ADHD)

- Use rating scales for the diagnosis and monitoring of symptoms such as the Vanderbilt ADHD assessment tool available at: http://www.nichq.org/toolkits_publications/complete_adhd/03VanAssesScaleParent%20Infor.pdf
- The Conners' Parent and Teacher rating scales (CPRS & CTRS) may also be useful in screening for ADHD and comorbid conditions in select populations
- Review school records including report cards, suspensions, and progress reports
- Monitor for sleep disturbances at baseline and at each follow up visit
- Monitor height, weight, blood pressure (BP) and heart rate (HR) at baseline and at all follow up visits regardless of pharmacologic agent
    - Stimulants and atomoxetine may increase BP and HR and slow growth in height and weight
    - Clonidine and guanfacine may decrease BP and HR
- Stimulants may be titrated every 3-7 days
- Guanfacine and clonidine may take 2-4 weeks to see full therapeutic effects
- Atomoxetine may take 4-6 weeks to see full therapeutic effects and monitored for signs of suicidal ideation
- For non-response to a stimulant, consider switch to a CNS agent of a different chemical group (i.e. methylphenidate to amphetamine or vice versa).
- Poor symptom control should prompt neuropsychological and psychoeducational assessments, possibly by a psychologist or neuropsychologist

AAP Minimum Follow-Up Schedule for Patients Receiving ADHD Drugs

Initiation and Titration	At least once within 30 days of initiation
First Year of Therapy	Every 3 months
After First Year	Twice yearly, with telephone follow up with each refill

AAP ADHD Treatment Recommendations

Age	Strength	Therapy
Preschool 4-5 Years	Strong	Parental/Teacher Behavioral Therapy
	Recommended	Methylphenidate
Elementary School Age 6-11 Years	Strong	FDA Approved, Age Appropriate Medications +/- Behavioral & Environmental Therapy
Adolescents 12-18 years	Strong	FDA Approved, Age Appropriate Medications
	Recommended	Behavioral & Environmental Therapy

*Modafinil (Provigil®) and armodafinil (Nuvigil®) have not been demonstrated to be safe or effective in the treatment of ADHD in children and do not have FDA approval for ADHD

Other Useful References

- American Academy of Pediatrics 2011 ADHD Guideline Implementation Guide: http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654/suppl/DC1
- Parent's Guide to ADHD: http://www.effectivehealthcare.ahrq.gov/ehc/products/191/1148/adhd_con_fin_to_post.pdf
- CCO Incentive Measures and data specifications available at: http://www.oregon.gov/oha/Pages/CCO-Baseline-Data.aspx
- Brown RT, Freeman WS, Perrin JM, et al. Prevalence and Assessment of Attention-Deficit/Hyperactivity Disorder in Primary Care Settings. *PEDIATRICS*. 2001;107(3):e43–e43. doi:10.1542/peds.107.3.e43 http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.107.3.e43

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Retrospective Drug Use Review for the Use of Psychotropic Medications in Children

Recommendations

- Send providers an annual request for additional clinical data for children receiving any of the following regimens:
    1. Five or more chronic psychotropics in children
    2. Two or more chronic antipsychotics in children
    3. Psychotropics in children under 6 years old
        - Non-stimulants under 6 years old
        - CNS Stimulants under 4 years old
- Profile request to contain:
    1. Indications and target symptoms for all current medications
    2. Request for clinical rationale for regimen
    3. List of psychosocial interventions being used or barriers to using these interventions
    4. Dates of the last assessment of safety and efficacy (e.g. plasma concentrations, liver function, glucose, etc.)
    5. Documentation that risks, benefits, and alternatives have been discussed with the caregiver

Background

The 2003 National Comorbidity Survey Replication – Adolescent Supplement (NCS-A) found 49.5% of the 10,123 adolescents surveyed had a DSM-IV diagnosable mental health disorder.[1] Of adolescents with at least one diagnosable mental health disorder, 42% meet diagnostic criteria for disorders in two or more major diagnostic classes. There is significant clinical trial data investigating single or dual agent therapy for specific disorders. Yet there is a lack of clinical trial data or consensus guidelines to guide the treatment of complex patients with multiple overlapping disorders seen in daily practice. In the second quarter of the 2012-13 fiscal year, 19% of Oregon Medicaid children receiving at least one psychotropic had received at least three concurrently for over 90 days (Table 1). One percent of all of Oregon Medicaid children receiving a psychotropic received five or more psychotropics concurrently for at least 90 days (See Appendix A for complete details on determinations of concurrency and chronicity).

Pediatric Psychotropic Quarterly Report

All OHP

Fiscal Year 2012 - 2013

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar		
	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	1,479	3,097	48%	1,431	3,052	47%
Five or more concurrent psychotropics	152	10,588	1%	153	10,939	1%
Three or more concurrent psychotropics	2,033	10,588	19%	2,075	10,939	19%
Two or More Concurrent Antipsychotics	149	10,588	1%	147	10,939	1%
Under 18 years old on any antipsychotic	3,115	10,588	29%	3,069	10,939	28%
Youth five years and younger on psychotropics	266	10,588	3%	283	10,939	3%

Table 1 Pediatric Psychotropic Measures for Federal Fiscal Year 2012-2013

The AHRQ systematic review of antipsychotics in children found mixed strength evidence for the use of antipsychotics in children.[2] There was moderate strength of evidence for the improvement of clinical global impression (CGI) scores with the use of second generation antipsychotics over placebo in patients with ADHD & Disruptive Behavior Disorder, Bipolar Disorder, and Schizophrenia. Moderate strength evidence was also found supporting improvements in behavioral symptoms in children with ADHD & Disruptive Behavior Disorder. Improvements in tics associated with Tourette Syndrome also had moderate strength evidence to be superior to placebo. Outside of these outcomes, the AHRQ report found only low quality or no evidence for the use of antipsychotics in children. The report also noted that many of these studies excluded patients receiving adjunctive therapy or multiple mental health diagnoses. None of these studies evaluated the combination of multiple antipsychotics. For Oregon Medicaid, 28% of children receiving at least one psychotropic are receiving an antipsychotic (Table 1). Of these children, 147 were receiving two antipsychotics concurrently for over 90 days.

Very few psychotropic medications are approved in the use of children under the age of six years. Mixed amphetamine salts and dextroamphetamine have FDA-approval for the treatment of ADHD in children as young as three.[3,4] Only methylphenidate immediate release is currently recommended by the American Academy of Pediatrics (AAP) for children under six.[5] Two second-generation antipsychotics (aripiprazole and risperidone) are FDA approved for use in children under 10 years old.[6,7] Irritability in patients with autistic spectrum disorder is the approved indication for both of these agents in this population. The AHRQ systematic review of antipsychotics found clinical trial data insufficient or of low quality for the use of antipsychotics for controlling autistic symptoms. Likewise, AHRQ found evidence for the use of first generation antipsychotics in children under six for any indication was lacking. The only other psychotropics with FDA approved uses in children have multiple indications, which include physical health conditions (e.g. antihistamines, antiepileptics). In

the second quarter of the 2012-13 fiscal year 3% (n=283) of Oregon Medicaid children receiving at least one psychotropic were under six years of age. This excludes members receiving a psychotropic for which there is a diagnosis history suggesting a physical health indication (e.g. antiepileptic medication and a history of seizures) or for a stimulant in children over three years old.

Oregon legislation recognizes the importance of the management of psychotropics in foster children and requires additional scrutiny of these therapies.[8] An assessment by a qualified mental health professional is required prior to prescribing a psychotropic for foster children under six years of age, receiving any antipsychotic, or prescribed three or more psychotropics, except in emergency situations. Annual medication reviews are also required for these foster children. Currently the Drug Use Research and Management (DURM) group assists the Child Welfare program to identify and evaluate these cases. The Oregon Health Authority and the Department of Human Services have partnered together with the Center for Health Care Strategies (CHCS) on a technical assistance grant to improve the use of psychotropic medications in foster children.[9] Part of this effort includes the development of national standards for quality measures for psychotropics. The National Committee for Quality Assurance (NCQA) recently solicited public comment on proposed quality metrics for the use of psychotropics in children.[10] These measures are similar to the metrics developed as part of the work with CHCS. The three regimens in table 2 have been targeted by the CHCS workgroup as representing the most complex cases and warrant particularly careful monitoring.[8] A comparison of provider specialties and prescribing rates for these regimens in included in the supplemental information which will be provided during the executive session.

Retrospective Drug Use Review (RetroDUR) Proposal

DMAP will solicit safety and efficacy case profiles to monitor the risks and benefits of these therapies. DMAP will send profile requests for all Medicaid children meeting criteria, rather than restricting requests to Fee-For-Service (FFS) patient. Since most psychotropics are “carve out” medications paid for by the FFS program, management and utilization of these medications falls to the FFS program.[11,12]

The goals of this policy are:

- Promote due diligence by clinicians
- Provide continuity of care for patients across clinicians over time
- Gather information on the therapeutic goals of these regimens
- Evaluate pattern of use to guide future interventions
- Increase provider awareness of how their prescribing practices compare to other provider in the Medicaid population

The therapeutic goals of psychopharmacologic therapy, particularly in foster children, are not always effectively communicated between clinicians due to a variety of factors within and outside of the control of clinicians and caregivers. To fill in these knowledge gaps, each profile request will provide:

- Patient identifiers
- Currently prescribed psychotropics

DMAP will provide a claims-based patient profile upon request containing demographics, mental health diagnosis history, prescription history and status on quality metrics (Appendix C). A provider report card will be included in the profile request comparing providers to overall Medicaid rates as well as providers within their specialty.

Each profile will solicit:

- Indication(s) and target symptoms for all current medications
- Rationale for therapy
- Evaluation of alternative strategies
- Assessment of key risk factor
- Verification that caregivers have been notified of risk-to-benefit profiles and alternative therapy options
- Provider impressions of the initiative

The transfer of some types of mental health treatment data has additional protections under HIPAA regulations. The restriction applies to “psychotherapy notes.” HIPPA regulations state:
OCR HIPAA Privacy page 3 states.

> …
> *A covered entity may disclose protected health information to another covered entity for certain health care operation activities of the entity that receives the information if:*

- *Each entity either has or had a relationship with the individual who is the subject of the information, and the protected health information pertains to the relationship; and*
- *The disclosure is for a quality-related health care operations activity*

…

Uses and Disclosures of Psychotherapy Notes. Except when psychotherapy notes are used by the originator to carry out treatment, or by the covered entity for certain other limited health care operations, uses and disclosures of psychotherapy notes for treatment, payment, and health care operations require the individual's authorization. See 45 CFR 164.508(a)(2).

…

47 "Psychotherapy notes" means notes recorded (in any medium) by a health care provider who is a mental health professional documenting or analyzing the contents of conversation during a private counseling session or a group, joint, or family counseling session and that are separated from the rest of the of the individual's medical record. ***Psychotherapy notes excludes*** *medication prescription and monitoring, counseling session start and stop times, the modalities and frequencies of treatment furnished, results of clinical tests, and any summary of the following items: diagnosis, functional status, the treatment plan, symptoms, prognosis, and progress to date.* [Emphasis Added]

Therefore, the information send and the information requested are HIPAA protected, but not considered psychotherapy notes requiring patient's authorization to disclose. Facsimile transmissions are considered a HIPAA compliant medium. The provider message includes the above HIPAA language to ensure providers can be confortable of the legality of these disclosures.

The answers to these clinical questions will provide a picture of provider treatment pattern for different specialty areas. These patterns may identify opportunities for provider education on appropriate use or resource limitations that the OHA may wish to address. It may also identify best practices for the management of complex patients. If prescribing patterns consistently deviate from appropriate care or there is a general lack of response, more intense interventions may be considered.

RetroDUR quarterly reporting will include:

- Number and rate of provider responses
- Provider impressions and satisfaction
- Response to each of the five questions
- The Pediatric Psychotropic Quarterly report (Table 1)

References

1. Merikangas KR, He J, Burstein M, et al. Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2010;49(10):980–989. Available at: http://www.sciencedirect.com/science/article/pii/S0890856710004764. Accessed August 5, 2013.

2. Seida JC, Schouten JR, Mousavi SS, et al. First- and Second- Generation Antipsychotics for Children and Young Adults. *Agency Healthc Res Qual*. 2012;39. Available at: http://www.ncbi.nlm.nih.gov/books/NBK84643/. Accessed July 30, 2013.

3. Dexedrine(R) Full Prescribing Information. 2007.

4. Adderall(R) Full Prescribing Infomration. 2007.

5. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *PEDIATRICS*. 2011;128(5):1007–1022. doi:10.1542/peds.2011-2654.

6. Aripiprazole Full Prescribing Information. 2008.

7. Risperidone Full Prescribing Infomration. 2009.

8. Oregon Revised Statute 418.517 Use of Psychotropic Medications. *Chapter 418 — Child Welf Serv*. Available at: http://www.leg.state.or.us/ors/418.html. Accessed July 23, 2012.

9. Oregon selected for a national pilot project to improve the use of psychotropic medications among children in foster care. 2012. Available at: http://www.oregon.gov/oha/news/Documents/2012-0413-joint-foster-care-psych-meds.pdf.

10. Public Invited to Help Shape New Antipsychotic Medication Use Measures for Medicaid and CHIP. *NCQA Newsroom*. 2013. Available at: http://www.ncqa.org/Newsroom/2013NewsArchives/NewsReleaseApril292013.aspx. Accessed May 9, 2013.

11. *Oregon Administrative Rules Division 121 Pharmaceutical Services*. Available at: http://arcweb.sos.state.or.us/pages/rules/access/numerically.html. Accessed January 11, 2013.

12. *Oregon Administrative Rules Division 141 Oregon Health Plan*. Available at: http://arcweb.sos.state.or.us/pages/rules/access/numerically.html. Accessed January 11, 2013.

Appendix A: Technical Specification

Indicator	Youth five years and younger on psychotropics
Description	
Eligible Population	
Inclusion	All enrolled Medicaid members under 18 years old at the time of a paid pharmacy claim for any psychotropic (Table A1) with a service date during the reporting period AND a day supply greater than or equal to 5 days.
Reporting Period	35 days prior to the report date.
Exclusion	Claims for a psychotropic medication which has a physical health indication (Table A3) AND at least one medical claim prior to the report date for the associated physical health condition (Table A4).
Numerator	Members less than six years old as of the pharmacy claim date of service receiving any psychotropic other than a stimulant (Table A5). OR Members less than four years old as of the pharmacy claim date of service receiving a stimulant (Table A5).
Denominator	Eligible Population

Indicator	Five or more concurrent psychotropics
Description	
Eligible Population	
Inclusion	All enrolled Medicaid members under 18 years old at the time of a paid pharmacy claim for any psychotropic (Table A1) with a service date during the reporting period AND a day supply greater than or equal to 5 days.
Reporting Period	35 days prior to the report date.
Exclusion	Claims for a psychotropic medication which has a physical health indication (Table A3) AND at least one medical claim prior to the report date for the associated physical health condition (Table A4).
Concurrency	Maximum Gap in Therapy 32 days Minimum Duration of Therapy 90 days Minimum Overlap 90 days
Numerator	Members with greater than or equal to five concurrent psychotropics
Denominator	Eligible Population

Indicator	Two or More Concurrent Antipsychotics
Description	
Eligible Population	
Inclusion	All enrolled Medicaid members under 18 years old at the time of a paid pharmacy claim for any psychotropic (Table A1) with a service date during the reporting period AND a day supply greater than or equal to 5 days.
Reporting Period	35 days prior to the report date.
Exclusion	None
Concurrency	Maximum Gap in Therapy 32 days Minimum Duration of Therapy 90 days Minimum Overlap 90 days
Numerator	At least two concurrent antipsychotic medications (Table A2)
Denominator	Eligible Population

Psychotropic Generic Name
ALPRAZOLAM
AMITRIP HCL/CHLORDIAZEPOXIDE
AMITRIPTYLINE HCL
AMOBARBITAL SODIUM
AMOXAPINE
AMPHET ASP/AMPHET/D-AMPHET
ARIPIPRAZOLE
ARMODAFINIL
ASENAPINE MALEATE
ATOMOXETINE HCL
BUPROPION HBR
BUPROPION HCL
BUSPIRONE HCL
BUTABARBITAL SODIUM
CARBAMAZEPINE
CHLORAL HYDRATE
CHLORDIAZEPOXIDE HCL
CHLORPROMAZINE HCL
CITALOPRAM HYDROBROMIDE
CLOMIPRAMINE HCL
CLONAZEPAM
CLONIDINE
CLONIDINE HCL
CLORAZEPATE DIPOTASSIUM
CLOZAPINE
DESIPRAMINE HCL
DESVENLAFAXINE SUCCINATE
DEXMETHYLPHENIDATE HCL
DEXTROAMPHETAMINE SULFATE
DIAZEPAM
DIVALPROEX SODIUM
DOXEPIN HCL
DULOXETINE HCL
ESCITALOPRAM OXALATE
ESTAZOLAM
ESZOPICLONE
FLUOXETINE HCL
FLUPHENAZINE DECANOATE
FLUPHENAZINE HCL
FLURAZEPAM HCL
FLUVOXAMINE MALEATE
GABAPENTIN
GUANFACINE HCL
HALAZEPAM

Psychotropic Generic Name
HALOPERIDOL
HALOPERIDOL DECANOATE
HALOPERIDOL LACTATE
HYDROXYZINE HCL
HYDROXYZINE PAMOATE
ILOPERIDONE
IMIPRAMINE HCL
IMIPRAMINE PAMOATE
ISOCARBOXAZID
LAMOTRIGINE
LISDEXAMFETAMINE DIMESYLATE
LITHIUM CARBONATE
LITHIUM CITRATE
LORAZEPAM
LOXAPINE SUCCINATE
LURASIDONE HCL
MAPROTILINE HCL
MEPHOBARBITAL
MEPROBAMATE
METHAMPHETAMINE HCL
METHYLPHENIDATE
METHYLPHENIDATE HCL
MIDAZOLAM HCL
MILNACIPRAN HCL
MIRTAZAPINE
MODAFINIL
MOLINDONE HCL
NEFAZODONE HCL
NORTRIPTYLINE HCL
OLANZAPINE
OLANZAPINE PAMOATE
OLANZAPINE/FLUOXETINE HCL
OXAZEPAM
OXCARBAZEPINE
PALIPERIDONE
PALIPERIDONE PALMITATE
PAROXETINE HCL
PAROXETINE MESYLATE
PEMOLINE
PENTOBARBITAL
PENTOBARBITAL SODIUM
PERPHENAZINE
PERPHENAZINE/AMITRIPTYLINE HCL
PHENELZINE SULFATE

Psychotropic Generic Name
PHENOBARBITAL
PHENOBARBITAL SODIUM
PHENTERMINE HCL
PIMOZIDE
PROCHLORPERAZINE EDISYLATE
PROCHLORPERAZINE MALEATE
PROTRIPTYLINE HCL
QUAZEPAM
QUETIAPINE FUMARATE
RAMELTEON
RISPERIDONE
RISPERIDONE MICROSPHERES
SECOBARBITAL SODIUM
SELEGILINE
SERTRALINE HCL
TEMAZEPAM
THIORIDAZINE HCL
THIOTHIXENE
TOPIRAMATE
TRANYLCYPROMINE SULFATE
TRAZODONE HCL
TRIAZOLAM
TRIFLUOPERAZINE HCL
TRIFLUPROMAZINE HCL
TRIMIPRAMINE MALEATE
VALPROATE SODIUM
VALPROIC ACID
VENLAFAXINE HCL
VILAZODONE HYDROCHLORIDE
ZALEPLON
ZIPRASIDONE HCL
ZIPRASIDONE MESYLATE
ZOLPIDEM TARTRATE

Table A1 Psychotropic Medications

Antipsychotics
ARIPIPRAZOLE
ASENAPINE MALEATE
CHLORPROMAZINE HCL
CLOZAPINE
FLUPHENAZINE DECANOATE
FLUPHENAZINE HCL
HALOPERIDOL
HALOPERIDOL DECANOATE
HALOPERIDOL LACTATE
ILOPERIDONE
LOXAPINE SUCCINATE
LURASIDONE HCL
MOLINDONE HCL
OLANZAPINE
OLANZAPINE/FLUOXETINE HCL
PALIPERIDONE
PALIPERIDONE PALMITATE
PERPHENAZINE
PERPHENAZINE/AMITRIPTYLINE HCL
PIMOZIDE
PROCHLORPERAZINE EDISYLATE
PROCHLORPERAZINE MALEATE
QUETIAPINE FUMARATE
RISPERIDONE
RISPERIDONE MICROSPHERES
THIORIDAZINE HCL
THIOTHIXENE
TRIFLUOPERAZINE HCL
ZIPRASIDONE HCL

Table A2 Antipsychotics

Generic Drug Name	Physical Health indication
CARBAMAZEPINE	Convulsive Disorder
CLONAZEPAM	Convulsive Disorder
DIAZEPAM	Convulsive Disorder
DIVALPROEX SODIUM	Convulsive Disorder
GABAPENTIN	Convulsive Disorder
HYDROXYZINE HCL	Allergic Rhinitis
HYDROXYZINE PAMOATE	Allergic Rhinitis
LAMOTRIGINE	Convulsive Disorder
OXCARBAZEPINE	Convulsive Disorder
TOPIRAMATE	Convulsive Disorder
VALPROATE SODIUM	Convulsive Disorder
VALPROIC ACID	Convulsive Disorder

Table A3 Psychotropics with Physical Health Indications

Indication	ICD9	Description
Convulsive Disorder	345	EPILEPSY AND RECURRENT SEIZURES
Convulsive Disorder	3450	GENERALIZED NONCONVULSIVE EPILEPSY
Convulsive Disorder	34500	Generalized nonconvulsive epilepsy, without mention of intractable epilepsy
Convulsive Disorder	34501	Generalized nonconvulsive epilepsy, with intractable epilepsy
Convulsive Disorder	3451	GENERALIZED CONVULSIVE EPILEPSY
Convulsive Disorder	34510	Generalized convulsive epilepsy, without mention of intractable epilepsy
Convulsive Disorder	34511	Generalized convulsive epilepsy, with intractable epilepsy
Convulsive Disorder	3452	Petit mal status
Convulsive Disorder	3453	Grand mal status
Convulsive Disorder	3454	LOCALIZATION-REL EPILEPSY & EPILEPTIC SYN W/CPS
Convulsive Disorder	34540	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, without mention of intractable epilepsy
Convulsive Disorder	34541	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, with intractable epilepsy
Convulsive Disorder	3455	LOCALIZATION-REL EPILEPSY & EPILEPTIC SYN W/SPS
Convulsive Disorder	34550	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures, without mention of intractable epilepsy
Convulsive Disorder	34551	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures, with intractable epilepsy
Convulsive Disorder	3456	INFANTILE SPASMS
Convulsive Disorder	34560	Infantile spasms, without mention of intractable epilepsy
Convulsive Disorder	34561	Infantile spasms, with intractable epilepsy
Convulsive Disorder	3457	EPILEPSIA PARTIALIS CONTINUA
Convulsive Disorder	34570	Epilepsia partialis continua, without mention of intractable epilepsy
Convulsive Disorder	34571	Epilepsia partialis continua, with intractable epilepsy
Convulsive Disorder	3458	OTHER FORMS OF EPILEPSY AND RECURRENT SEIZURES
Convulsive Disorder	34580	Other forms of epilepsy and recurrent seizures, without mention of intractable epilepsy
Convulsive Disorder	34581	Other forms of epilepsy and recurrent seizures, with intractable epilepsy
Convulsive Disorder	3459	UNSPECIFIED EPILEPSY
Convulsive Disorder	34590	Epilepsy, unspecified, without mention of intractable epilepsy
Convulsive Disorder	34591	Epilepsy, unspecified, with intractable epilepsy
Allergic Rhinitis	477	ALLERGIC RHINITIS
Allergic Rhinitis	4770	Allergic rhinitis due to pollen
Allergic Rhinitis	4771	Allergic rhinitis due to food
Allergic Rhinitis	4772	Allergic rhinitis due to animal (cat) (dog) hair and dander
Allergic Rhinitis	4778	Allergic rhinitis due to other allergen
Allergic Rhinitis	4779	Allergic rhinitis, cause unspecified

Table A4 Physical Health Indications for Psychotropics

Generic Drug Name
AMPHET ASP/AMPHET/D-AMPHET
ARMODAFINIL
DEXMETHYLPHENIDATE HCL
DEXTROAMPHETAMINE SULFATE
LISDEXAMFETAMINE DIMESYLATE
METHAMPHETAMINE HCL
METHYLPHENIDATE‡
METHYLPHENIDATE HCL‡
MODAFINIL

Table A5 Stimulants

‡Methylphenidate and Methylphenidate HCL are considered the same agent

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Appendix B: Provider Message

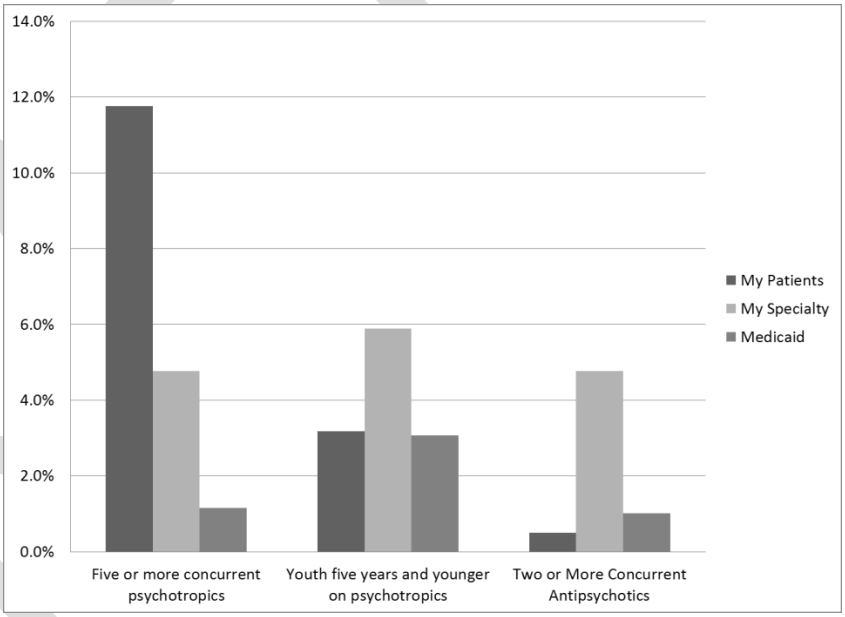
Date: mm/dd/yyyy

Attention: Provider X
Fax: 541-123-4567

Re: Patients Subject to Psychotropic Case Reviews

The Division of Medical Assistance Programs (DMAP) is requesting additional clinical data for patients meeting one or more of the following criteria:

- Five or more chronic psychotropics in children
- Two or more chronic antipsychotics in children
- Psychotropics in children under 6 years old (except stimulants in children 3-5)



The chart on the right shows your prescribing patterns for Medicaid patients. Prescribing patterns for your specialty and rates across all providers are included for your reference

The intention of this program is not to prohibit these regimens. The goal is to promote continuity and quality of care through centralized monitoring and support. The therapeutic goals of psychopharmacologic therapy, especially in foster children, are not always effectively communicated between clinicians due to a variety of factors within and outside of the control of clinicians and caregivers.

Following is a list of patients with a recent prescription written by you subject to this policy. complete these forms and fax to DMAP at 503-947-2596.

If you have any questions or comments regarding this policy or would like a claims-based profile for any of these patients, please call 503-945-6513 or fax 503-947-2596.

OSU Oregon State University College of Pharmacy
Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Patient Name	Doe, John	Date of Birth	MM/DD/YYYY	Member ID	XYZ1234

Please answer the questions below and fax to DMAP at 503-947-2596.

If you have any questions or comments regarding this policy, please call 503-945-6513 or fax 503-947-2596. Additional pages may be used if more space is required. *Please refer to the fax cover sheet for HIPAA requirements & restrictions.*

1. The indication(s) and target symptoms for all psychotropics current prescribed to this patient by any provider

Most Recent Prescriber	Last Fill Date	Drug & Strength	Daily Dose	Indication(s) & Target Symptoms
Nurse X	MM/DD/YY	Drug A - α mg	X units daily	
Nurse X	MM/DD/YY	Drug B - β mg	X units daily	
Nurse X	MM/DD/YY	Drug C - χ mg	X units daily	
Doctor Zhivago	MM/DD/YY	Drug D - δ mg	X units daily	
Nurse X	MM/DD/YY	Drug E - ε mg	X units daily	

2. Please answer each of these questions which apply to this patient
   a. Explain why 5 or more psychotropics are required for this patient

   b. Explain why two concurrent antipsychotics are being used

   c. Explain why psychotropics are being used in a child under five years old

3. Please indicate the psychosocial intervention strategies being used for this patient. If none are being used, please explain why.

4. As applicable to the currently prescribed medications, please indicate the last evaluation for metabolic and cardiovascular risk (laboratory monitoring and physical assessment) and therapeutic/toxic plasma concentrations.

5. Who is the provider primarily tasked with care coordination? What barriers, if any, make care coordination challenging?

6. Does the child, parents and/or caregivers understand the risks, benefits and alternatives to this strategy?

Please check all that apply:

- ☐ This information was useful
- ☐ This information will change my future practice
- ☐ Other_____
- ☐ Not my patient/ no longer my patient
- ☐ Patient Deceased
- ☐ Neither clinician or patient associated with this office

OSU Oregon State University College of Pharmacy

Drug Use Research & Management Program

OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Appendix C: Claims-Based Patient Profile

OSU Oregon State University College of Pharmacy

Drug Use Research & Management Program

OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Patient

Member ID:	FAKE-AA1571DH
Patient:	, FAKE-AA1571DH
DOB:	9/15/1997
Age:	15
City:	Some Place
Zip:	99999

Screening Results as of :7/30/2013

Description
Under 18 years old on any antipsychotic

Mental Health Diagnosis History

Group	First Dx	Last Dx	ICD9	Diagnosis
Other				
	08/24/06	08/24/06	31532	Mixed receptive-expressive language disorder
	08/24/06	08/24/06	3154	Developmental coordination disorder
	03/17/06	03/17/06	3155	Mixed development disorder
	11/15/07	09/04/12	3158	Other specified delays in development
	02/26/05	12/11/06	3181	Severe intellectual disabilities
	09/21/04	09/21/04	3182	Profound intellectual disabilities
	06/30/04	06/30/04	78079	Other malaise and fatigue
	09/15/06	11/01/06	78095	Excessive crying of child, adolescent, or adult
Autism				
	04/07/09	11/27/12	29901	Autistic disorder, residual state
Developmental Disorders				
	10/25/08	09/07/09	319	Unspecified intellectual disabilities

OSU Oregon State University College of Pharmacy

Drug Use Research & Management Program

OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

OSU Oregon State University College of Pharmacy

Drug Use Research & Management Program

OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

DIVISION OF MEDICAL ASSISTANCE PROGRAMS
Policy & Planning Section
John A. Kitzhaber, MD, Governor

Oregon Health Authority
500 Summer Street NE, E35
Salem, Oregon 97301-1077
Voice: (503) 945-6513
Fax: (503) 947-1119

Mental Health Prescription History

Status	First Fill	Last Fill	Medication	Route	Dose	Per Day	Last Prescriber	Specialty	Telephone
Current	11/16/07	07/05/13	AMITRIPTYLINE HCL	PO	10 mg	3	Dr. MT	Physician-pediatrics	555-555-5555
Current	09/07/11	07/05/13	RISPERIDONE	PO	1 mg/mL	1	Dr. MT	Physician-pediatrics	555-555-5555
Past	02/09/07	03/06/09	DIAZEPAM	PO	2 mg	6.6667	Dr. 15	#Type!	555-555-5555
Past	04/17/07	10/15/07	TOPIRAMATE	PO	25 mg	1	Dr. MT	Physician-pediatrics	555-555-5555

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Policy Evaluation: Palivizumab Prior Authorization

In August 2012, The Oregon Health Plan (OHP) adopted drug use criteria for palivizumab (Synagis®). Palivizumab is a respiratory syncytial virus (RSV) protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.[1] Drug use criteria was developed in response to a drug use evaluation (DUE) done in May 2011.[2] The DUE incorporated the 2009 American Academy of Pediatric (AAP) guidelines[3] and an analysis[2] of the Oregon Fee-For-Service (FFS) Medicaid program during the 2009-2010 RSV season. Previously, OHP FFS covered palivizumab without restriction. Results from the 2011 DUE suggested improper timing and exceeding the recommended five doses of palivizumab provided no health benefit and directly increased costs. The current prior authorization (PA) criteria limits use of palivizumab to high risk infants identified by the AAP, to five monthly doses and to use during the months of highest RSV activity. The PA criteria also account for variability in season onset and offset, due to geographic and population differences throughout Oregon. In 2012, the cost per member per month (PMPM) was $1.85 and in 2013 it was $1.06 PMPM. Additionally, claims decreased by 40% PMPM.[4] The purpose of this drug use evaluation is to further assess the impact of the palivizumab prior authorization on use outside of established criteria and survey for unintended harm.

A literature search of Cochrane Reviews and Medline was performed to identify changes in practice since the 2011 DUE.

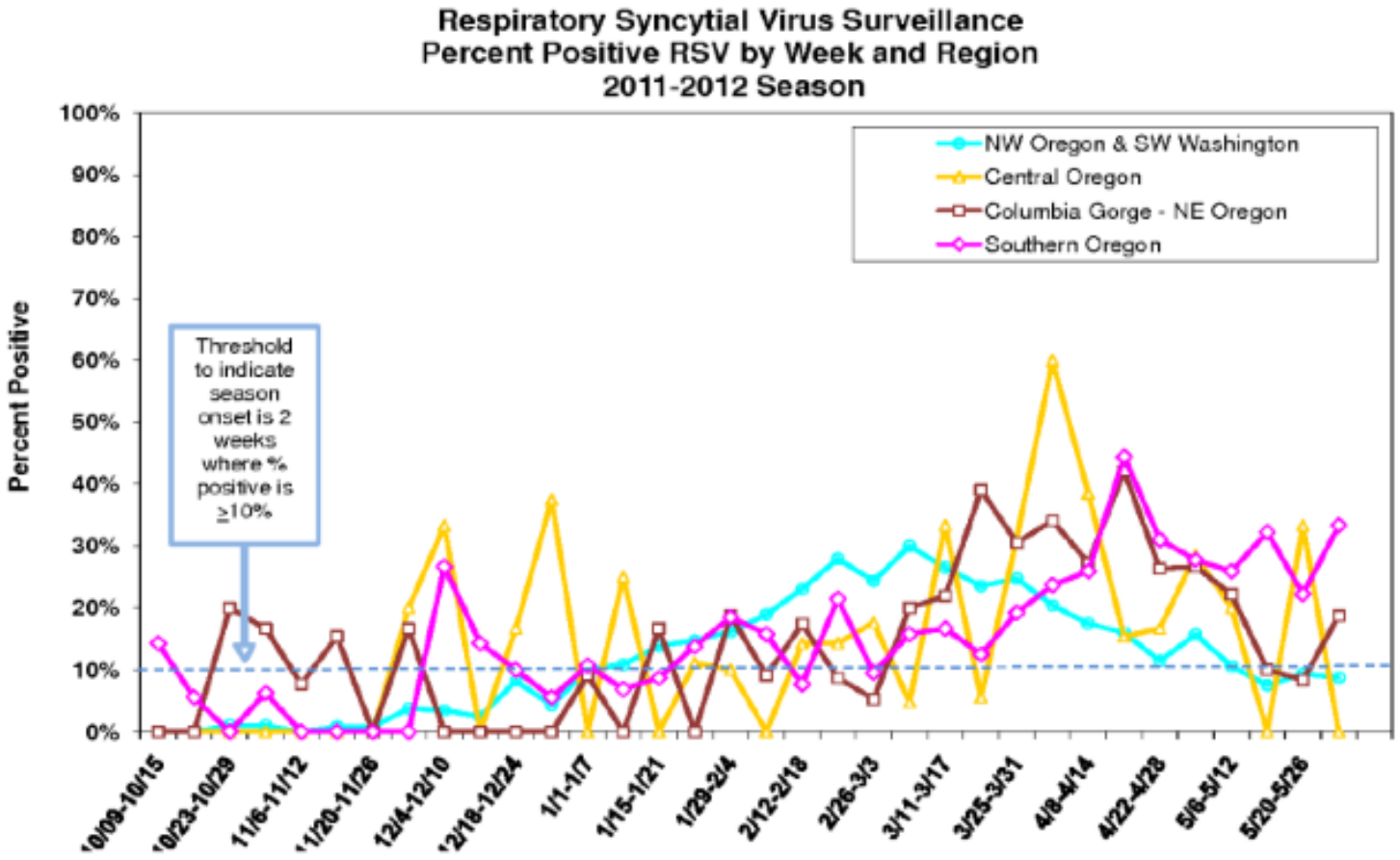
Two updated Cochrane Reviews[5,6] were identified using search term “respiratory syncytial virus.” “Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children” [5] assessed the effectiveness and safety of palivizumab prophylaxis in reducing the risk of complications in high-risk infants and children, as well, as the cost-effectiveness of prophylaxis in infants and children in different risk groups. Seven good-quality studies were included, however, it was noted most of the outcomes relied on data from two studies. High quality evidence from three studies including 2,831 participants showed a reduced risk of hospitalizations with palivizumab prophylaxis compared to placebo (RR 0.49, 95% CI 0.37-0.64), with an ARR of 5.2% (NNT 20), and a statistically non-significant reduction in all-cause mortality (RR 0.69, 95% CI 0.42-1.15). Cost-effectiveness could not be fully clarified due to the variety of methods used to perform analyses. These findings confirm current recommendations. In June 2013, a separate Cochrane Review, “Palivizumab for prophylaxis against respiratory syncytial virus in children with cystic fibrosis” was published.[6] However, their search yielded only one study, which was not enough to draw firm conclusions from.

The New England Journal of Medicine published the multicenter, double-blind, randomized, placebo-controlled MAKI trial in May 2013.[7] This was a good-quality trial of 429 healthy preterm infants born at the gestational age of 33 to 35 weeks in Holland. The primary endpoint was number of parent reported wheezing days in the first year of life. The results were 1.8% (930/53,075 days) in the RSV-prevention group versus 4.5% (2,309/51,726 days) in the placebo group ($p<0.001$), with an ARR of 2.7% (NNT 37). The patient population was healthy preterm infants in Holland and is not representative of population indicated for RSV treatment in Oregon. Furthermore, the correlation between wheezing episodes and pulmonary damage is not well understood.

A search of the Oregon RSV surveillance and the Centers for Disease Control and Prevention surveillance identified 2011-2012 and 2012-2013 RSV season statistics. It is not mandatory to report RSV in Oregon but active surveillance is performed using volunteer laboratories. The Oregon Health Authority reports a weekly surveillance report that is a culmination of 22 laboratories in Oregon and SW Washington.[8] The National Respiratory and Enteric Virus Surveillance System (NREVSS) also report RSV regional and national trends.[9] Eight Oregon laboratories contribute to the NREVSS. Trends in RSV season onset and offset were examined to verify the current policy aligns with highest level of RSV activity.

For 2011–2012, the start of the RSV season in region 10, which includes Oregon, was late December, peaked the week of March 3, 2012, and the season lasted 18 weeks.[10] According to RSV-Oregon surveillance there were 1,428 positive RSV tests during the 2011-2012 season.[11] Figure 1 represents the 2011-2012 RSV season by region. The onset in NW Oregon/SW Washington region was later than the other regions of Oregon.

Figure 1.[11] 2011-2012 RSV Surveillance from RSV-Oregon by region



The start of the 2012-2013 RSV season in Oregon was the week ending December 8, 2012, which was 3 weeks earlier than the previous season.[9] Figure 2 shows no distinct regional differences in season onset. The season lasted 19 weeks, ending the week of May 5, 2013. Figure 3 shows a graphical representation of the 2012-2013 RSV season.[9] There were 2,437 positive RSV tests during this season represented in Figure 3.

Figure 2.[8] 2012-2013 RSV Surveillance from RSV-Oregon by region

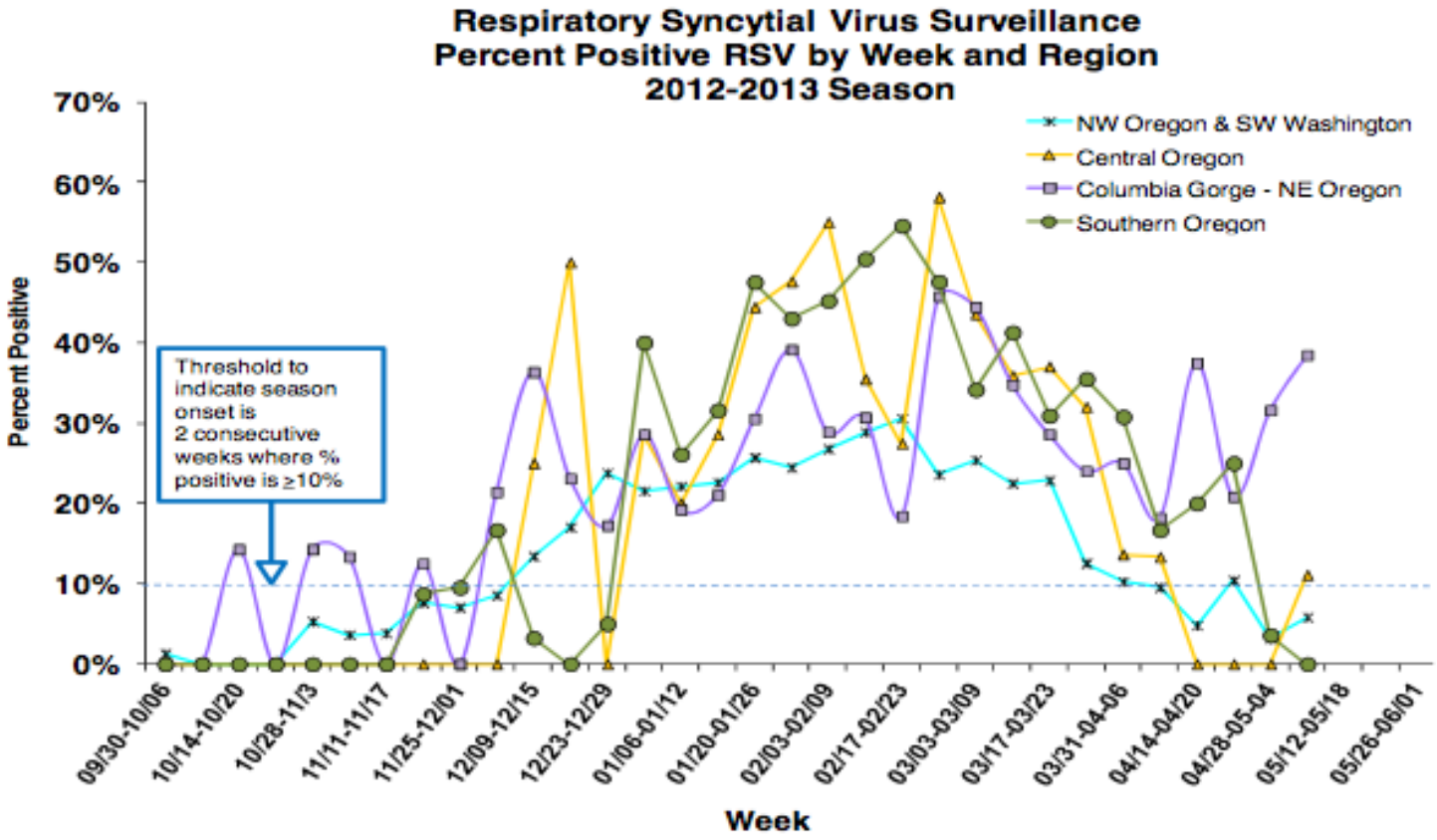
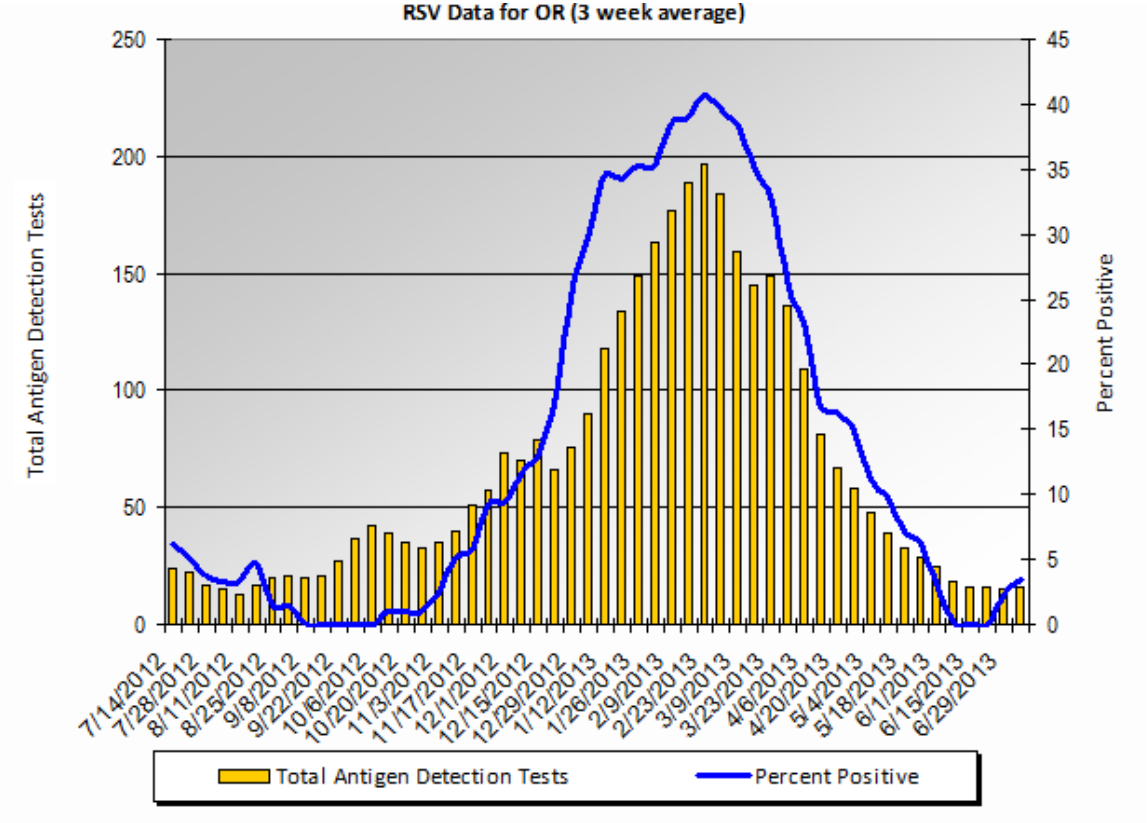


Figure 3.[8] RSV detection data from NREVSS for Oregon



Methods:

Paid FFS drug and professional claims from October 1, 2011 through June 30, 2013 were examined. Patients with dual eligibility for Medicare as identified by a benefit indicator of BMM or BMD were excluded. Patients of interest were identified if they had a claim for palivizumab. Palivizumab drug claims were identified using all National Drug Codes (NDCs) with a First DataBank Generic Sequence Number of 59245 or 59246. Palivizumab professional claims included procedure code of C9003 or 90378. No minimum enrollment restrictions were applied.

The control group included patients with an index claim (none in previous 90 days) for palivizumab in the 2011-12 RSV season (10/1/2011 – 9/30/2012). The study group included patients with an index denied claim for palivizumab in the 2012 – 13 RSV season (10/1/2012 – 9/30/2013) with an Explanation of Benefit (EOB) code equal to "1056-Prior Authorization Required", without a concurrent EOB of "2017 - Patient enrolled in MCO" and without a prior paid or rejected claim for an palivizumab in the 90 days. The study group was further categorized according to prior authorization (PA) disposition at 14 days and palivizumab therapy at 30 days: a) those who requested a PA, were approved and received palivizumab, b) those who requested a PA and were denied, c) those not requesting PA but still receiving palivizumab and those not requesting a PA and with no claim for palivizumab.

Demographics were determined from the Medicaid enrollment record at the time of the index event. Co-morbidity was determined from International Classification Diagnosis (ICD-9) codes on professional claims from birth until six months after the index event.

The primary outcomes were: 1) proportion of patients over 24 months old at initial dose, 2) proportion of patients treated outside the RSV season (before November or after April), and 3) proportion of patients exceeding treatment over 5 months. The length of therapy was estimated for the pharmacy claims assuming each patient to have one treatment, and the length was simply the sum of all the day's supply for their palivizumab claims for that year (pharmacy claims only). Where a patient had two claims on the same day to accommodate dosing, the claims were counted as one and day's supply was also counted once.

Secondary outcomes included the change in palivizumab costs and utilization, which were quantified as a monthly per member per month (PMPM) value. Costs were defined as the paid amount per claim and do not include any subsequent manufacturer rebate. Utilization was defined as the number of claims paid. Finally, the database was queried for the proportion of patients with a hospital or emergency department claim associated with active RSV infection (ICD-9 = 079.6) from the time of the index event and six months following the index event.

Results:

In the control group, 89 patients received palivizumab, with 84 accessing via FFS pharmacy claims and 5 via FFS professional claims. In the study group, 28 patients encountered the PA intervention, 12 (42.9%) had a PA approved, 1 (3.6%) did not submit a PA request, but received palivizumab, and 15 (53.6%) did not submit a PA nor receive palivizumab (see Table 1). There were no PA denials. Demographics were similar for the control and study group (see Table 1).

Table 1. Demographics*

		Control		Study Group							
				Total Study		*PA Approved*		*No PA w/ Drug*		*No PA, No Drug*	
Total	**n=**	**89**	**(%)**	**28**	**(%)**	**12**	**(%)**	**1**	**(%)**	**15**	**(%)**
Age in Months											
	Mean (months)	8.2		8.3		7.3		2		9.5	
	Range	1-44		1-22		1-18		2		4-22	
	>24	2	2.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	>12 and ≤ 24	20	22.5%	8	28.6%	3	25.0%	0	0.0%	5	33.3%
	>6 and ≤ 12	16	18.0%	6	21.4%	4	33.3%	0	0.0%	2	13.3%
	≤ 6	51	57.3%	14	50.0%	5	41.7%	1	100.0%	8	53.3%
Female		44	49.4%	12	42.9%	3	25.0%	0	0.0%	9	60.0%
Non-White		24	27.0%	7	25.0%	3	25.0%	1	100.0%	3	20.0%

*Note: Age shown is age in months as of first palivizumab claim

The control group had a greater proportion of patients meeting the criteria with <28 weeks gestation (11.2%) compared to the study group (3.6%). All other co-morbidities were similar at baseline (see Table 2). There were 15 patients that did not submit a PA and did not receive treatment. Of particular interest were the 7 patients in this group who had qualifying co-morbidities: 5 patients had patent ductus arteriosus (PDA), which puts them in group B, 2 were 31-32 weeks gestation, which puts them in group E and 1 had 25-26 weeks of gestation which puts them in group C.

Table 2. Co-morbidities – ICD9 present from date of birth to 6 months after Index Claim (age is age at index claim)*

Criteria Group	Age in months	Diagnosis (ICD9 code) n=	Control		Study Group							
					Total Study		*PA Approved*		*No PA w/ Drug*		*No PA, No Drug*	
			89	(%)	28	(%)	1	(%)	1	(%)	1	(%)
Group A or B	**<24**	**CHD or CLD** (746xx, 747xx, 748xx)	29	32.6%	10	35.7%	5	41.7%	0	0.0%	5	33.3%
Group C	**<12**	**<28 wks gestation** (76521, 76522, 76523, 76524)	10	11.2%	1	3.6%	0	0.0%	0	0.0%	1	6.7%
Group D	**<12**	**Neuromuscular diagnosis** (358xx)	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Group E	**< 6**	**29 to ≤32 wks gestation** (76525 or 76526)	8	9.0%	2	7.1%	0	0.0%	0	0.0%	2	13.3%
Group F	**<3**	**33 to 34 wks gestation** (76527 or 76528)	4	4.5%	0	0.0%	1	0.0%	0	0.0%	0	0.0%
None of the above			42	47.2%	16	57.1%	7	58.3%	1	100.0%	8	53.3%
Any of the above			47	52.8%	12	42.9%	5	41.7%	0	0.0%	7	46.7%

No patients over the age of 24 months received initial treatment with palivizumab in the study group vs. 2 (2.2%) in the control group (see Table 3). Similarly, patients did not receive drug therapy outside the RSV season in the study group compared to 13 (15.5%) before November and 7 (8.3%) after April in the control group (see Table 3). Furthermore, there were no patients receiving treatment for longer than 5 months in the study group vs. 14 patients (16.7%) in the control group (see Table 3).

Table 3. Primary Outcomes

Outcome	**Control n= 89 (%)**		**Total Study n=28 (%)**	
Patient > 24 months old	2	2.2%	0	0.0%
	n=84* (%)		**n=12* (%)**	
Claims before November	13	15.5%	0	0%
Claims after April	7	8.3%	0	0%
Therapy > 5 months	14	16.7%	0	0%

*pharmacy claims only

Secondary outcomes included utilization, costs, and hospitalizations. There was decreased utilization PMPM and cost PMPM (see Figure 4 and 5) in the study group. The average seasonal PMPM decreased from $2.03 in control group to $1.31 in study group (see Figure 5). This is an estimated $105,000 per year cost avoidance. No patients in the control or the study group were hospitalized or had emergency department visits within 6 months of the index claim.

Figure 4. Palivizumab Utilization July 2011 – June 2013

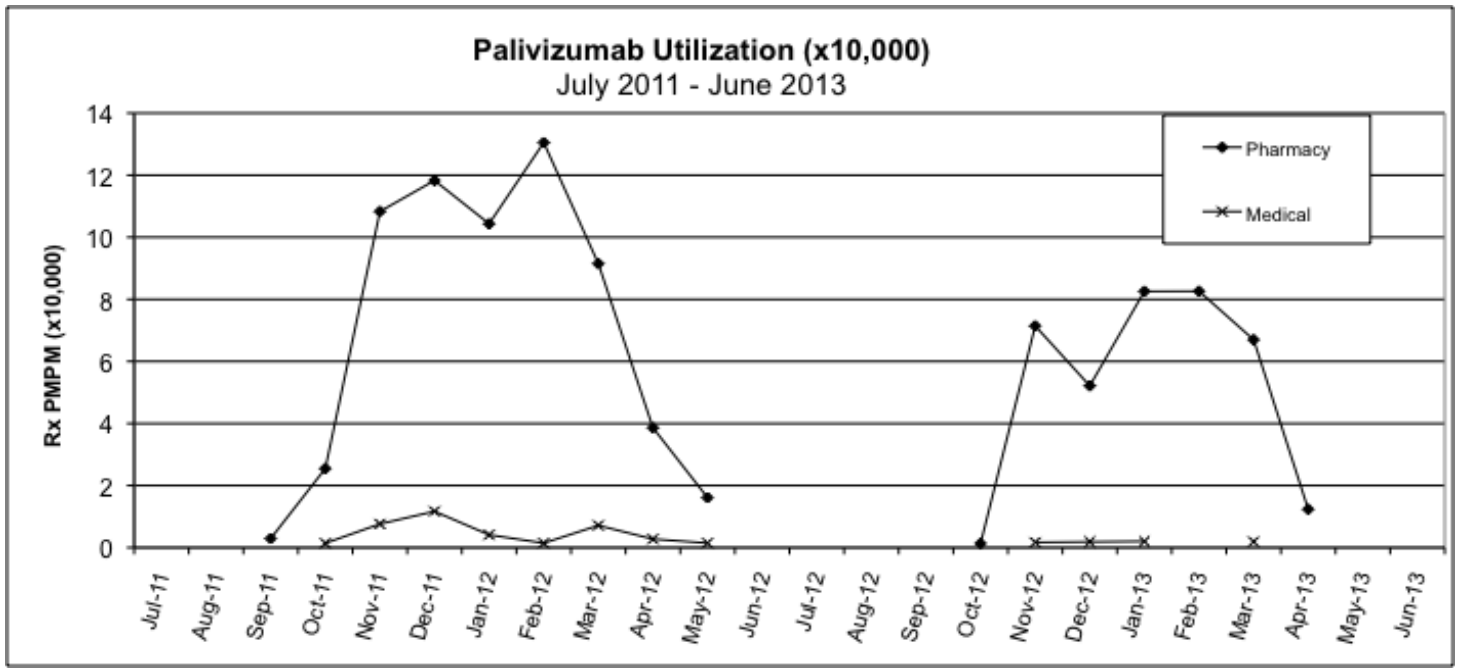
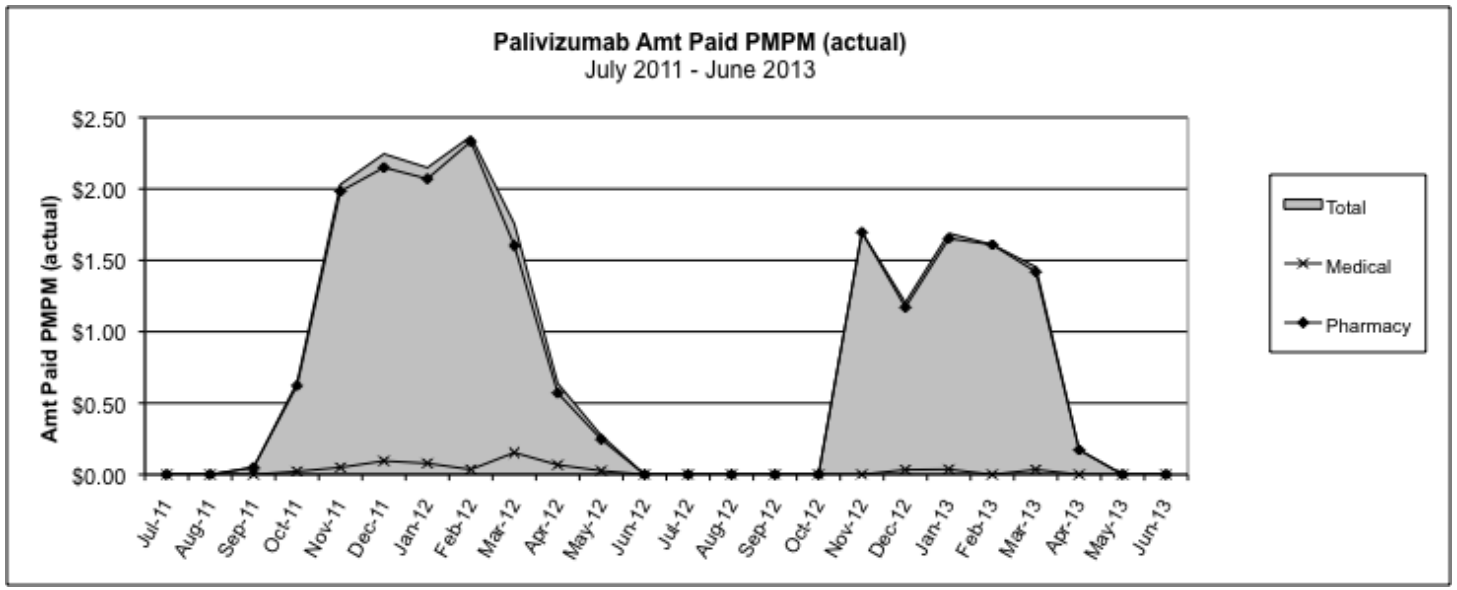


Figure 5. Palivizumab Costs July 2011 – June 2013



Discussion:

In this observational study, all of the primary outcomes were reduced to zero in the study group. The PA eliminated use of palivizumab outside of the established criteria, which correlated with decreased utilization and cost.

The results are similar to a retrospective study conducted by SelectHealth plans, which incorporated data from three RSV seasons from 2005-2008 to evaluate implementation of PA criteria for palivizumab.[12] This 500,000-member health plan used the 2006 AAP guideline to develop prior authorization criteria. Results suggested significant drug cost avoidance without an increase in the cost or incidence of ER visits or inpatient hospitalizations associated with RSV infections.

There were no hospitalizations or emergency room visits within 6 months of index claim. Prior authorizations can create a barrier to treatment due to administrative burden, which may be reflected by patients with qualifying co-morbidities not receiving treatment. Eight patients with qualifying co-morbidities did not request a PA or receive drug. Five individuals had a diagnostic code of PDA, which is group B. Group B also must have one of

the following qualifiers: receiving treatment for congestive heart failure, moderate to severe pulmonary hypertension, or cyanotic heart disease. It is possible the patients did not have one of these qualifiers but this information could not be captured by ICD-9 codes. According to the AAP, palivizumab is indicated for children who are <24 months of age with hemodynamically significant cyanotic or acyanotic CHD.[3] This definition is further classified into groups that are not at increased risk of RSV. PDA is categorized as hemodynamically insignificant heart disease, and therefore does not warrant immunoprophylaxis.[3] One patient was found with a medical diagnosis of "acute bronchiolitis due to RSV." This patient was a premature twin, in which both twins did not receive palivizumab despite having qualifying co-morbidities and were 5 months at the start of RSV season. Despite likely qualifying for immunoprophylaxis, these 3 patients had no subsequent hospital or emergency encounters.

This study is limited because it is observational and a small, disproportional sample. Selection bias is minimized by including patients in the study group who encountered the PA request rather than only patients with paid claims. Administrative claim studies are prone to follow-up bias which is a primary concern in this study. More than 90% of professional claims are submitted within 6 months of the service date. Thus patients with index events after January 2013 may have incomplete follow-up that could affect the number of hospitalizations and emergency encounters in the study group. Additional limitations to retrospective claim data are the chance for miscoding and the inability to define all criteria from the claims. For example, group F, which included patients <90 days at the start of the RSV season, gestational age of $\leq$32-34 weeks and 6 days, and at least one of the following risk factors: daycare attendance or siblings <5 years old, was not included as a primary outcome because no specific ICD-9 correlated to this group. This may account for patients who did not fit any of the pre-specified diagnostic descriptions, but had an approved PA. Finally, prior authorizations often influence patients to pay cash for treatment. However, this is a Medicaid population and palivizumab is a high cost drug so this is unlikely.

In conclusion, the palivizumab PA policy was associated with prescribing patterns that conformed to the desired criteria. The policy reduced to zero the primary outcomes of: proportion of patients over 24 months old at initial dose, proportion of patients treated outside the RSV season (before November or after April), and proportion of patients treated over 5 months. This was reflected in decreased utilization PMPM and decreased cost PMPM with an estimated gross cost avoidance of $105,000 in the last season. It did not result in increased hospitalizations and emergency room visits during 2012-2013 but there is a potential for follow-up bias in the study group.

Recommendations:

- **Continue the palivizumab PA for the 2013-2014 RSV season with no adjustments.**
- **Follow-up study needed in December or January to ensure safety indicators remain acceptable.**

References:

1. Synagis (palivizumab). Prescribing Information. MedImmune. Available at: http://www.medimmune.com/docs/default-source/pdfs/prescribing-information-for-synagis.pdf. Accessed August 10, 2013.
2. Oregon State University Drug Use Research & Management. Drug Use Evaluation: Synagis (palivizumab). 2011. Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/evaluations/articles/2011_05_synagis_due.pdf. Accessed July 2, 2013.
3. Committee on Infectious Diseases. From the American Academy of Pediatrics: Policy statements--modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics*. 2009;124(6):1694–1701.
4. Oregon State University Drug Use Research & Management. OHP FFS Average Cost PMPM Top 40 Drugs. 2013. Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/reports/topdrugs/2013/TopDrugs_2013_Q1.pdf. Accessed July 11, 2013.
5. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. *Cochrane Database of Syst Rev*. 2013;4:CD006602.
6. Robinson KA, Odelola OA, Saldanha IJ, Mckoy NA. Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis. *Cochrane Database of Syst Rev.* 2013;6:CD007743.
7. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med*. 2013;368(19):1791–1799.
8. Oregon Health Authority. Oregon's Weekly Respiratory Syncytial Virus Surveillance Report. 2013. Available at: http://public.health.oregon.gov/DiseasesConditions/CommunicableDisease/DiseaseSurveillanceData/Documents/RSV/RSV_Oregon.pdf.
9. Center for Disease Control. CDC - NREVSS: RSV State Trends. Available at: http://www.cdc.gov/surveillance/nrevss/rsv/state.html#OR. Accessed July 11, 2013.
10. Center for Disease Control. Respiratory Syncytial Virus Activity — United States, July 2011–January 2013. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6208a1.htm?s_cid=mm6208a1_w. Accessed July 11, 2013.
11. Oregon Health Authority. Oregon's Weekly Respiratory Synctial Virus Surveillance Report. 2012. Available at: http://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/rsv/Documents/RSV_Oregon.pdf. Accessed July 11, 2013.
12. Buckley BC, Roylance D, Mitchell MP, Patel SM, Cannon HE, Dunn JD. Description of the outcomes of prior authorization of palivizumab for prevention of respiratory syncytial virus infection in a managed care organization. *J Manag Care Pharm*. 2010;16(1):15–22.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Abbreviated Class Update: Newer Diabetes Medications

Month/Year of Review: September 3013
Last Review: June 2009 (pramlintide, exenatide, sitagliptin)
March 2011 (pramlintide, sitagliptin, saxagliptin, exenatide, liraglutide)

End date of literature search: July 2013
Source: Health Resources Commission
OSU DURM

Current PDL Status:

Preferred

Drug Class	Drug
Incretin Enhancers	sitagliptin
Biguanide	metformin
Sulfonylurea (second generation)	glimepiride, glipizide, glyburide
Thiazolidinedione (TZD)	Pioglitazone
Insulin	various preparations

Non-preferred

Drug Class	Drug
Alpha-glucosidase inhibitors	acarbose, miglitol
Amylin analog	pramlintide
Dipeptidyl peptidase-4 (DPP-4) inhibitor or incretin enhancer	linagliptin, saxagliptin
Glucagon-like, peptide-1 (GLP-1) agonist or incretin mimetic	exenatide, exenatide ER, liraglutide
Insulin	various preparations
Meglitinide	nateglinide, repaglinide
Sulfonylureas (first generation)	chlorpropamide,

	tolazamide, tolbutamide
Thiazolidinedione (TZD)	**rosiglitazone**
Others - bile acid sequestrant	**colesevelam**
Others – dopamine agonist	**bromocriptine**

Research Questions:

- Are canagliflozin and/or alogliptin more effective than preferred PDL treatments for patients with type 2 diabetes mellitus (DM)?
- Are canagliflozin and/or alogliptin a safer alternative to preferred PDL treatments for patients with type 2 DM?
- Are there indications or subpopulations where canagliflozin and/or alogliptin may be more effective or safer than other available agents?
- Are there new guidelines and/or evidence that suggest that sulfonylureas should not be a preferred second-line option after metformin?

Conclusions:

- There is moderate evidence that canagliflozin is more effective than placebo in lowering glycated hemoglobin (A1C) (-0.77% to -1.06%) in type 2 DM patients. Canagliflozin treatment is associated with genital mycotic infections and hypotension. There is a concern of potential increased risk of cardiac events and fractures that needs further study.
- There is moderate evidence that alogliptin lowered A1C in type 2 DM patients by 0.4%-0.9% compared to placebo. Alogliptin is generally well tolerated but there are outstanding concerns over risk of acute pancreatitis, hepatotoxicity, hypersensitivity reactions and cardiovascular risk that need to be further delineated.
- Guidelines and systematic reviews suggest that sulfonylureas are an appropriate second-line therapy for most patients with type 2 DM. Long-term outcome data suggests that sulfonylureas may reduce the incidence of microvascular risk.

Recommendations:

- Prior authorize canagliflozin as a third –line treatment option for patients unable to tolerate or have contraindications to metformin and/or sulfonylurea therapy.
- Prior authorize alogliptin as a third –line treatment option for patients unable to tolerate or have contraindications to metformin and/or sulfonylurea therapy.
- Sulfonylurea therapies should be considered a preferred second-line treatment option for patients without contraindications or tolerance issues.

Reason for Review:

Newer drugs for the treatment of diabetes mellitus was reviewed by the Oregon Health Resources Commission (HRC) in June 2009[1]. Since this review additional new agents for the treatment of diabetes have been approved. In addition, National guidelines have been revised and there is a shift toward a more patient centered approach to treatment management. This review will analyze the comparative effectiveness of the newer medications for diabetes and incorporate important updates and revisions as they are related to this class since the last review. New evidence-based guidelines have been released and new systematic reviews were also updated and will be included.

Author: Kathy Sentena, Pharm.D.

Previous HRC Conclusions/June 2009:

- Evidence was insufficient to determine long term effectiveness of pramlintide when added to prandial insulin compared to conventional insulin therapy, with or without concurrent oral agents, in patients with type 2 DM.
- Evidence was insufficient to determine long term effectiveness of sitagliptin.
- No studies met inclusion criteria for exenatide.

Background:

Type 2 diabetes is a prevalent disease which affects an estimated 25.6 million people in the United States.[2] Despite a variety of treatments a significant number of patients fail to meet A1C goals and within three years of being diagnosed 50% of patients require combination therapy to control rising glucose levels. According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have diabetes by 2050.[4] Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with type 2 diabetes and add pharmacotherapy for persistent elevated glucose levels. Guidelines recommend a goal A1C of ≤6.5% to ≤ 7% but in all cases should be tailored according to patient specific factors, such as concomitant comorbidities.[5,6] A number of therapeutic options are available for management of glycemic variances associated with diabetes yet no agent has demonstrated clear superiority.[7] Classes of anti-hyperglycemic agents (AHA) currently available are: alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, GLP-1 analogues, insulins, meglitinides, sulfonylureas, TZDs, bile acid sequestrants, dopamine-2 agonists and amylin mimetics.

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, A1C, severe adverse events (SAE) and hypoglycemia rates. A1C is often used as a surrogate outcome to assess comparative efficacy of different AHA therapies, as hyperglycemia has been shown to correlate with microvascular complications and potentially macrovascular outcomes.[6] Available data is limited to short-term studies, which prevents the assessment of the durability of available AHAs to control glucose levels long-term and to compare the effectiveness of AHAs on outcomes such as microvascular and macrovascular complications. Differing definitions of hypoglycemia also complicate the comparisons of safety between the differing AHA agents. Available evidence suggests that metformin is likely to reduce the incidence of cardiovascular disease based on data from the United Kingdom Prospective Diabetes Study (UKPDS) trial.[6] UKPDS data has also indicated a reduced incidence of microvascular risk with sulfonylurea and insulin therapy. TZDS, alpha-glucosidase inhibitors and dopamine-2 agonists have studies that suggest reduced cardiovascular disease events but additional data is needed.[6] The long-term effect of many of the AHAs on complications of diabetes is unknown.

Methods:

A Medline literature search ending in July 2013 for new systematic reviews and randomized controlled trials (RCTs) for diabetic treatments was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, the following were reviewed: five clinical treatment guidelines[5,6,], four systematic reviews[8-11] and ten RCTs [19-22,25-30].

Author: Kathy Sentena, Pharm.D.

Systematic Reviews:

CADTH- Second-Line Pharmacotherapy for Type 2 Diabetes – Update[8]

A CADTH Optimal Use Report, including a systematic review and network meta-analysis (NMA), was done in July of 2013 to update their previous recommendation for AHA therapies in patients not at A1C goals despite optimal metformin use. Previous analysis and recommendations from a similar 2010 report suggest that there were no apparent differences in efficacy of AHA agents and sulfonylureas were recommended for those requiring a second-line treatment beyond metformin monotherapy. The recent update analyzed 56 trials using the GRADE evaluation method. Eight AHA classes were included: sulfonylureas, DPP-4 inhibitors, TZDs, GLP-1 analogues, basal insulin, alpha-glucosidase inhibitors, meglitinides, and biphasic insulin. Outcomes that were tracked were mortality, diabetes-related complications, A1C, body weight, hypoglycemia and severe adverse events (SAE). Changes from baseline A1C for all included AHA classes were found to be -0.64 (95% Crl: -0.91 to -0.38) to -1.06 (95% Crl: -1.32 to -0.80), with all classes significantly lowering A1C compared to metformin monotherapy. Significantly greater changes in baseline body weight (1.7 to 3.1 kg), compared to metformin monotherapy, were found for sulfonylureas, insulin (basal and biphasic), TZDs, and meglitinides. Weight neutral classes were DPP-4 inhibitors and alpha-glucosidase inhibitors. AHA agents found to cause significant weight loss compared to metformin were GLP-1 analogues. Hypoglycemia rates were significantly higher for sulfonylureas (OR 7.5), insulins (OR 4.1 to 7.0) and meglitinides (OR 8.3). Incidence of severe hypoglycemia was low for all classes (0.1% to 1.6% of total population). Severe adverse events occurred in patients at a rate of 0.7% to 9.1%, with the exception of two long-term extension trials in which SAE rates were as high as 21%. There was insufficient evidence to determine clinically important differences between the classes of AHA agents in regards to long-term complications.

CADTH- Third-Line Pharmacotherapy for Type 2 Diabetes – Update[9]

A second CADTH Optimal Use Report was done in July of 2013 to update previous recommendations for third-line treatment options for patients with diabetes. This report updates the August 2010 version, specifically including an analysis of GLP-1 analogues that were not approved at the time of previous report. The systematic review evaluated the comparative efficacy and safety of third-line AHA treatment in patients that were not reaching A1C goals on metformin and sulfonylurea therapy. This review included 41 trials of the following classes of AHA agents: alpha-glucosidase inhibitors, meglitinides, TZDs, DPP-4 inhibitors, GLP-1 analogues, basal insulin, bolus insulin, and biphasic insulin. Changes from baseline A1C were statistically significantly lower, -0.72% to -1.15%, for all classes studied except alpha-glucosidase inhibitors and meglitinides. Basal and biphasic insulin produced the greatest A1C lowering. Similar to the review of second-line agents, basal insulin, biphasic insulin, rapid acting insulin, and TZDs all produced significant increases in weight, 1.9-5.0 kg, when compared to metformin and a sulfonylurea alone. For this same comparison, DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral and GLP-1 analogues were shown to produce significant decreases in weight (-1.6 kg, 95% Crl, -2.8 to -0.4). Data revealed uncertain results regarding meglitinides effect on weight, with a trend toward increased body weight. The risk of hypoglycemia was found to be increased for TZDs, DPP-4 inhibitors, basal insulin and GLP-1 analogues when compared to placebo when given in combination with metformin and a sulfonylurea. Active treatment comparisons showed hypoglycemia risk was highest with the insulin preparations, with basal insulin having significantly less risk of hypoglycemia compared to biphasic and bolus regimens. Severe hypoglycemia was rare, making comparisons difficult. There was insufficient data to compare the effect of the AHA classes on the occurrence of the long-term complications of diabetes.

Cochrane- Sulphonylurea Monotherapy for Patients with Type 2 Diabetes Mellitus (Review)[10]

A systematic review of 72 trials was analyzed to compare sulfonylureas, first and second generation, with other AHAs in the treatment of type 2 diabetes. The primary outcome was all-cause mortality and cardiovascular mortality. Study durations ranged from 24 weeks to over 10 years. All studies were associated with

bias and individual comparisons were comprised of a small number of participants. First-generations sulfonylureas were associated with an increased risk of cardiovascular mortality compared to placebo (RR 2.63, 95% CI 1.32 to 5.22, p=0.006). Comparison of first-generation sulfonylureas to insulin showed no significant differences in all-cause mortality rates. When compared to insulin, first-generation sulfonylureas were not shown to increase cardiovascular mortality and were favored over alpha-glucosidase inhibitors for adverse events. Second-generation sulfonylureas were shown to not be significantly different from metformin, TZDs, insulin, meglitinides, or incretin-based therapies for the outcome of all-cause mortality. Cardiovascular mortality was not found to be different between second-generation sulfonylureas and metformin, insulin, TZDs and meglitinides. Based on data from three trials, second-generation sulfonylureas were favored over metformin for the composite outcome of non-fatal macrovascular events (RR 0.67, 95% CI 0.48 to 0.93, p=0.02). Second-generation sulfonylureas weren't found to be significantly different in adverse events compared to placebo, metformin, TZDs, alpha-glucosidase inhibitors, or meglitinides. Second generation sulfonylureas were less likely than alpha-glucosidase inhibitors to be associated with drop-outs due to adverse events. Metformin and TZDs were favored over second-generation sulfonylureas for severe hypoglycemia (RR 6.11, 95% CI 1.57 to 23.79, p=0.009). No difference was found between meglitinides and second-generation sulfonylureas in for severe hypoglycemia. Data on third-generation sulfonylureas was lacking for all-cause mortality, cardiovascular mortality and other macrovascular and microvascular outcomes. None of the outcomes met the criteria for firm RRR in a trial sequential analysis and therefore the authors concluded that additional studies are needed in order to support recommending sulfonylurea monotherapy.

Cardiovascular Safety of Sulfonylureas: A Meta-analysis of Randomized Controlled Trials[11]

The cardiovascular safety of sulfonylureas was examined in a meta-analysis by Monami, et al. This analysis included randomized trials that compared sulfonylureas to active treatment or placebo in patients with type 2 diabetes. One hundred fifteen trials were included, lasting at least 6 months in duration, with a mean duration of 70 weeks. Patients had a mean age of 56.6 years, mean duration of diabetes of 6.3 years and mean A1C of 8.4%. Types of sulfonylureas included were three second generation agents available in the United States (US) (glimepiride, glyburide, and glipizide), four first generation agents available in the US (chlorpropamide, tolazamide, tolbutamide and acetohexamide), two second generation agents not available in the US (glibenclamide, gliquidone) and one mixed generation agent not available in the US (gliclazide). The quality of the trials were accessed using Jadad parameters but no minimum score was required. The principle outcome was the incidence of major cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI) and stroke, and acute coronary syndrome and/or heart failure reported as serious adverse events of sulfonylureas compared to placebo or active treatment. Secondary outcomes were fatal and non-fatal MI and stroke, all-cause and cardiovascular mortality and severe hypoglycemia.

Sulfonylureas were not found to have a significant difference in the occurrence of MACE compared to active treatment and placebo (MH-OR: 1.08 [0.86 to 1.36], p=0.52). However, sulfonylureas were found to have a significantly higher incidence of MACE compared to DPP-4 inhibitors in a subgroup analysis. The incidence of MI was not found to be different between sulfonylureas and active treatment and placebo. The analysis of 16 trials found the risk of stroke to be significantly higher with sulfonylureas (MH-OR: 1.28 [1.03 to 1.60], p=0.026). The risk of stroke was found to be significant when compared to DPP-4 inhibitors and with glimepiride (MH-OR: 4.22 [1.65 to 10.79], p=0.003). In the analysis of 88 trials, sulfonylureas were found to increase all-cause mortality significantly compared to other treatments and placebo (MH-OR: 1.22 [1.01 to 1.49], p=0.047). Cardiovascular mortality rates were not found to be significantly different between sulfonylureas and other treatments. Sulfonylureas were found to have a higher incidence of hypoglycemia when compared to metformin and placebo. The authors concluded that in general sulfonylurea treatment is not associated with a significant increase in cardiovascular risk. Limitations to this meta-analysis are the following; the inclusion of sulfonylureas not applicable to the most commonly used treatments in the US, the lack of reporting of cardiovascular events and sample size limitations.

Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitor: Meta-Analysis and Systematic Review[12]

Author: Kathy Sentena, Pharm.D.

In a recent meta-analysis and systematic review Aroda, et al, summarized the overall evidence related to incretin therapies in patients with type 2 diabetes. Exenatide, exenatide weekly, liraglutide, alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin (not available in the US) were included in the analysis. Eighty studies were included for evaluation, lasting from 12-52 weeks with the change from baseline A1C being the primary outcome. Seventy-six percent of the included studies were comparisons of combined treatments. GLP-1 were found to result in mean A1C changes of -1.1% to -1.6%. DPP-4 inhibitors were associated with decreases of -0.6% to -1.1% in A1C. Specifically, reductions from baseline in A1C were the following; alogliptin -0.70% (95% CI -0.90 to -0.50); linagliptin -0.60% (95% CI -0.80 to -0.40); saxagliptin -0.71% (95% CI -0.89 to -0.54); sitagliptin -0.70% (95% CI -0.78 to -0.63) and vildagliptin -0.98% (95% CI -1.46 to -0.52). GLP-1 analogues were associated with significant weight loss and DPP-4 inhibitors trended toward weight loss.

Oral Diabetes Medications for Adults with Type 2 Diabetes. An Update[13]

An AHRQ review was updated in March 2011 to include the benefit and harms of AHAs in patients with type 2 diabetes. The following treatments were included: metformin, second generation sulfonylureas, thiazolidinediones, meglitinides, DPP-4 inhibitors and GLP-1 agonists. Randomized controlled trials lasting 3 months or longer and enrolling at least 40 subjects were included. Studies were evaluated according to the Jadad criteria for quality and given an overall grade for the strength of evidence. The analysis found that there was a high strength of evidence that most AHA agents reduced A1C to a similar extent, approximately one percent compared to baseline values. The DPP-4 inhibitors were the only exception, which did not lower A1C as much as metformin (moderate strength of evidence). Most combination therapies were shown to decrease A1C by and additional one percent. There was high strength of evidence that metformin had beneficial effects on body weight and lipids compared to other AHAs. There was high strength of evidence that sulfonylureas were associated with a higher risk of mild-to-moderate hypoglycemia as monotherapy and when used in combination with other AHAs. There was limited data on long-term clinical outcomes for many of the AHAs.

New Guidelines:

ADA/EASD Guideline – Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[6]

The ADA/EASD recently updated their 2008 guideline recommendations in 2012. Recommendations were based on evidence and expert opinion. Due to the complex nature of treating patients with type 2 diabetes the guideline replaced their previous algorithm of recommendations with a more patient-centered approach, which takes into consideration patient preferences and tolerances. The guideline also recommends that a variety of factors should be taken into account when considering if the patient is a candidate for more stringent or less stringent glucose control. Metformin is suggested as the most commonly recommended first-line choice. If metformin is not an option then sulfonylureas/glinides, pioglitazone or DPP-4 inhibitors are considered good options. GLP-1 analogues may be an appropriate first-line choice for those with specific weight loss concerns. AHAs not already mentioned may be appropriate for specific patients but are less commonly recommended initially to due adverse effects and modest lowering of A1C. For patients requiring a dual glucose lowering treatment, the guidelines recommend a second oral AHA, a GLP-1 analogue or basal insulin. If triple therapy is required, insulin was found to provide the most A1C lowering.

NICE Guideline – Type 2 Diabetes: Newer Agents[14]

A short clinical guideline was produced in May of 2009 to update current NICE guidelines on recommendations for therapy for elevated glucoses in patients with type 2 diabetes. An evidence based, clinical pathway outlines preferences for 1st, 2nd and 3rd line therapies with exceptions for each based on specific patient characteristics. In general metformin is considered the first-line therapy, sulfonylureas as the preferred second-line treatment option and insulin is

recommended third line. DPP-4 inhibitors (only sitagliptin approved at the time of the guideline) are to be considered second-line in patients with a high risk of hypoglycemia (or the consequences), or for those whom a sulfonylurea or metformin is not tolerated or contraindicated. For those unable to use insulin, DPP-4 inhibitors are also recommended as a third-line treatment. TZDS are recommended as second-line agents in patients who are at elevated risk of hypoglycemia (or the consequences) or if they are not candidates for metformin or sulfonylurea therapy. TZDs are to be considered third-line in patients unable to use insulin. GLP-1 analogues (only exenatide approved at the time of guideline) are recommended as third-line agents if patient weight is of particular concern. Long-acting insulins (insulin detemir and insulin glargine) were recommended, in lieu of preferred first line NPH, if patient requires a caregiver for injections and use of a long-acting insulin would decrease injections to once-daily, decrease hypoglycemia, or patient would require multiple doses of NPH in addition to oral AHAs.

* This guideline was also updated in 2010 to include the suspension of marketing of rosiglitazone by the European Medicines Agency due to the risks of treatment exceeding benefit and again in 2011 to due to new recommendations on the risk of bladder cancer with pioglitazone.

AACE Guidelines – American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm 2013 Consensus Statement[5]

AACE recently updated guidelines for comprehensive diabetes management and hyperglycemia treatment algorithm in 2013. Recommendations for pharmacotherapy are similar to the previous 2009 algorithm and use A1C to guide treatment selection.[5,14] Monotherapy is recommended for those patients with A1C <7.5%, with metformin being the agent of choice for initial therapy. Alternatives to metformin are GLP-1 analogues, DPP-4 inhibitors and alpha-glucosidase inhibitors. Other agents that are options but should be used with caution are TZDs, sulfonyulureas/glinides and SGLT2s. Dual therapy is recommended for patients with an A1C $\geq$7.5% or for those unable to obtain their goal A1C on monotherapy. Metformin in combination with a second agent is preferred or any combination with complimentary mechanisms of action. GLP-1 analogues and DPP-4 inhibitors are recommended as the preferred dual pharmacotherapy options (with metformin), followed by TZDs, SGLT2s and basal insulin, all which should be used with caution. Additional potential combination therapy includes (in order of preference): colesevelam, bromocriptine, alpha-glucosidase inhibitors and sulfonylureas/glinides. For patients with an A1C >8%, a third AHA may be considered. GLP-1 analogues are preferred, followed by TZDs, SGLT2s, basal insulin, DPP-4 inhibitors, colsevelam, bromocriptine, alpha-glucosidase inhibitors and sulfonylureas/glinides. For patients with an A1C >9.0% insulin is recommended.

IDF Guidelines- Global Guideline for Type 2 Diabetes[16]

In 2012 the International Diabetes Federation (IDF) updated its 2005 guidelines for the treatment and management of diabetes. Recommendations were made based on available evidence and expert opinion. Metformin was recommended as initial therapy. For second-line therapy sulfonylureas are recommended with other options including alpha-glucosidase inhibitor, DPP-4 inhibitors, TZD or meglitinides. Insulin (basal or pre-mix) or a third oral agent is recommended third-line. Other third-line options are alpha-glucosidase inhibitors, DPP-4 inhibitors, TZD or a GLP-1 analogue. Insulin is recommended as the only fourth-line agent.

ACP Guideline – Oral Pharmacological Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians[17]

This 2012 Guideline provides recommendations for AHAs based on comparative efficacy and safety for the outcomes of A1C, lipids, weight, all-cause mortality, cardiovascular and cerebrovascular morbidity, retinopathy, nephropathy, neuropathy, hypoglycemia, liver injury, congestive heart failure, severe lactic acidosis, cancer, server allergic reactions, hip and nonhip fractures, pancreatitis, cholecystitis, macular edema or decreased vision and gastrointestinal side effects. Additional data on safety and effectiveness of subgroups was also studied. Trial quality was rated via Jadad and the overall evidence was graded using the GRADE system. Metformin is recommended first-line for most patients based on high quality evidence but no specific second-line therapy is suggested.

Author: Kathy Sentena, Pharm.D.

One hundred and four trials were used for the A1C comparison of medications used for the treatment of type 2 diabetes. Comparison of monotherapy treatments showed similar A1C lowering across the groups, average of 1%, with the exception of metformin compared to DPP-4 inhibitors. Metformin was shown to decrease A1C to a greater extent than DPP-4 inhibitors by a mean difference of -0.37% (moderate quality of evidence). Combination therapy was shown to be more effective than monotherapy with the metformin and sulfonylurea combination producing the largest mean decrease (-1.0%), metformin and DPP-4 inhibitors with a -0.69 men decrease and metformin with a TZD with a -0.66 mean decrease. There was insufficient evidence provided on GLP-1 analogue combination therapy (moderate to high quality evidence). Moderate to high quality evidence demonstrated that metformin therapy resulted in more weight loss compared to TZDs, sulfonylureas and DPP-4 inhibitors. Metformin was also had the most favorable effect on low density lipoprotein (LDL) compared to TZDs, sulfonylureas and DPP-4 inhibitors (moderate-high quality of evidence). TZDs had them most effect on increasing high density lipoprotein (HDL) compared to metformin and sulfonylureas. Metformin was favored with moderate quality of evidence over sulfonylureas and for decreasing triglyceride (TG) levels. For many of the long-term outcomes only low-quality or insufficient evidence was available for analysis. Nephropathy rates (based on albumin levels) were the only long-term outcomes with moderate quality of evidence, in which pioglitazone was shown to decrease urinary albumin ratio to a greater extent than metformin.

Severe hypoglycemia rates were similar across treatment groups. Sulfonylureas were shown to increase mild and moderate hypoglycemia rates compared to metformin, TZDS, DPP-4 inhibitors, GLP-1 analogues and meglitinides based on low to high quality evidence. Combination therapy with metformin and a sulfonylureas also was shown to increase hypoglycemia compared to combinations containing TZDs. Moderate quality of evidence from observational studies favored metformin over sulfonylureas and sulfonylureas over TZDs for risk of congestive heart failure (CHF). Combination therapy of TZD and sulfonylureas doubled the risk of CHF compared to metformin and sulfonylurea combination therapy. There was high quality of evidence that sulfonylureas were associated with less fracture risk than TZDs.

New Safety Alerts:

Pioglitazone and Bladder Cancer- FDA Safety Review[18]

In August of 2011 the FDA issued label changes to be made to pioglitazone prescribing information detailing the findings of a potential increased risk of bladder cancer when the drug is used beyond one year. The FDA made these recommendations based on a five year interim analysis of a 10 year epidemiological study which found no increased risk in bladder cancer overall but there was an increased risk in those whom had been taking pioglitazone for the longest time and at the highest doses. The FDA recommends against using pioglitazone in those with active bladder cancer and cautions against its use in those with a history of bladder cancer.

Incretin Mimetic Drugs and Pancreatitis/Pre-cancerous Findings in the Pancreas[19]

In March of 2013 the FDA announced that it is investigating the findings of a potential risk of pancreatitis and pre-cancerous cellular changes (pancreatic duct metaplasia) in patients with type 2 diabetes taking incretin mimetic type drugs (exenatide, liraglutide, sitagliptin, saxagliptin, alogliptin, and linagliptin). Current labeling includes warnings of acute pancreatitis with these agents. There is no conclusive link of pancreatic cancer and incretin mimetics. The FDA is involved in ongoing evaluations to gain additional information.

New Primary Literature:

Author: Kathy Sentena, Pharm.D.

New Drug Evaluation- Canagliflozin (Invokana ®)[20]

FDA Indications:
Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor, which is a new class of AHAs. SGLT2 inhibitors work by preventing reabsorption of glucose by the kidney and increaseing urinary glucose excretion. This results in mild osmotic diuresis and net calorie loss. Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Canagliflozin is not to be used for the treatment of type 1 diabetes or diabetic ketoacidosis.[18]

Clinical Efficacy Data (see evidence table below):
Canagliflozin was studied in over 10,000 patients in multiple trials as monotherapy and in combination with other agents (metformin, sulfonylurea, metformin and sulfonylurea, metformin and TZD and insulin). Active treatment comparisons were between canagliflozin and sitagliptin and canagliflozin and glimepiride. At this time only four trials have been published and available to be critically evaluated. In all studies the primary endpoint was the change in baseline A1c at specified durations. Important secondary endpoints were percent of subjects obtaining an A1c <7.0%, fasting plasma glucose levels, and percent change in body weight.

CANATA-M was a poor to fair quality, phase III trial comparing canagliflozin 100mg and 300mg daily to placebo in 584 patients for 26 weeks.[21] Patients in the main study had a mean HbA1c of 8.0% and a mean duration of diabetes of 4.3 years. A substudy of patients with elevated glucose concentrations was also conducted and included patients with a mean HbA1c of 10.6% and duration of diabetes of 4.9 years. The primary endpoint was the change in baseline HbA1c at week 26. An important secondary endpoint was the percent of patients achieving HbA1c <7%. Canagliflozin 100mg and canagliflozin 300mg both reduced HbA1c to a greater extent than placebo, -0.77, -1.03 and 0.14%, respectively ($p<0.001$ for both comparisons). There were also a greater percentage of patients that obtained a HbA1c <7% compared to placebo, with a NNT of 2-4. Patients in the high glycemic substudy also experienced greater HbA1c lowering compared to placebo. The lack of blinding details as it relates to patients, caregivers and outcomes assessors limits the ability to determine the likelihood of bias represented in the results. Description of randomization methodology was also lacking.

A 52 week, head to head comparison of canagliflozin 300 mg and sitagliptin 100 mg, on background metformin and sulfonylurea therapy, was studied in the CANTATA-D2 trial.[22] This was a fair quality, phase III, DB, RCT of 755 patients with type 2 diabetes whom were previously inadequately controlled on metformin and sulfonylurea therapy. Included patients had a mean duration of diabetes of 9.2 years with a mean A1C of 8.1%. The primary endpoint was change in baseline A1C at week 52. Canagliflozin was shown to be noninferior and superior to sitagliptin with A1C changes of -1.03% and -0.66%, respectively. Improvements in FPG, body weight and systolic blood pressure were significantly greater with canagliflozin compared to sitagliptin. When A1C changes were analyzed according to baseline A1C subgroups, the greatest difference was shown in those with the highest baseline A1cs ($\geq$9.0%). The overall discontinuation rate was high (38.5%) and occurring in 44% of the sitagliptin group and 33% in the canagliflozin group. Last observation carried forward imputation was used to provide results for missing data. This method may introduce assessment bias especially in circumstances such as in this study where there was a higher percentage of drop out in the active comparator group (sitagliptin) which assumes no change, potentially overestimating the true treatment effect of canagliflozin.

In a small fair quality, phase III, PC, RCT canagliflozin 100mg and 300mg was studied for 26 weeks in patients with type 2 diabetes and chronic kidney disease (eGFR $\geq$30 and <50 ml/min /1.73 m^2).[23] Patients were a mean age of 69 years old with a baseline A1C of 8.0% and eGFR of 39 ml/min/1.73m^2. Canagliflozin 100mg and

300mg decreased A1C to a greater extent than placebo, -0.33%, -0.44% and -0.03%, respectively ($p<0.05$). Reduction in FPG were also greater for canagliflozin but not significantly so.

Recently, a trial was published on the use of canagliflozin, 100mg and 300mg daily, compared to glimepiride, 6-8 mg daily, in patients (n=1452) uncontrolled on metformin (CANTATA-SU).[24] This was a fair quality, phase III, DB, randomized, non-inferiority trial lasting 52 weeks. The mean patient age was 57 years with a mean baseline A1C of 7.8%. As with the other studies, the primary endpoint was the change from baseline in A1C. Canagliflozin 100 mg and 300mg were shown to be non-inferior to glimepiride and canagliflozin 300 mg was shown to be superior to glimepiride. A1C changes were -0.82%, - 0.93%, -0.81% for canagliflozin 100 mg, canagliflozin 300 mg and glimepiride, respectively. The percent of patients obtaining an A1C <7% was similar between groups. Both canagliflozin groups were associated with significant decreases in body weight compared to the glimepiride group.

FDA approval summary documents for canagliflozin noted that the efficacy of canagliflozin is attenuated as renal function declines.[24] FDA statements include the need for future research related to the risk of cardiovascular events and fracture risk, which were shown to be increased in canagliflozin groups but correlation to canagliflozin treatment is not definitive and studies are ongoing.[25]

Clinical Safety[20]:
The most common adverse effects associated with canagliflozin were fatigue, female genital mycotic infections, urinary tract infections, increased urination and male genital mycotic infections. Hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration as a result of osmotic diuresis with potential decreases in intravascular volume have also been associated with canagliflozin treatment. Patients at increased risk of osmotic diuresis were those over 75 years of age, use of loop diuretics and moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2). Dose-related increases in serum creatinine were also noted. Slightly higher rates of hypoglycemia were experienced in canagliflozin groups compared to placebo and were more common when canagliflozin was combined with insulin or sulfonylureas.

Lab abnormalities were seen in patients randomized to canagliflozin, including hemoglobin elevations and dose-related increases in potassium, magnesium and phosphate. Changes in LDL levels of 4.4 mg/dL (4.5%) in the canagliflozin 100mg group and 8.2 mg/dL (8.0%) in the 300mg group were demonstrated.

Conclusion: Canagliflozin is has been shown to be modestly effective in lowering A1C as monotherapy and in combination with other AHA agents, with A1C lowering from -0.63% to -1.06%. Canagliflozin is unlikely to cause hypoglycemia as monotherapy and has demonstrated positive effects on FPG, BP, HDL and body weight while negatively impacting LDL levels. The use of canagliflozin in patients with chronic renal failure has been shown to be effective, but efficacy is attenuated with declining renal function. There is insufficient evidence to determine the impact of canagliflozin therapy on cardiovascular risk and fractures.

New Drug Evaluation- Alogliptin (Nesina ®), Alogliptin + Pioglitazone (Oseni ®) and Alogliptin + Metformin (Kazano®)

FDA Indications:
Alogliptin is a DPP-4 inhibitor available as a single agent and in combination with pioglitazone (Oseni) and metformin (Kazano).[26,27,28] Alogliptin and its combination products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM. Alogliptin should not be used for

the treatment of type 1 diabetes or diabetic ketoacidosis. Alogliptin differs from currently offered agents by being more selective and potent at inhibiting the DPP-4 enzyme but the clinical relevance of this is unknown.

Clinical Efficacy Data (see evidence table below):
Alogliptin 12.5 mg and 25 mg have been extensively studied in many trials. Due to lack of details on randomization, treatment allocation, blinding and high attrition rates not all studies were able to be adequately evaluated for internal and external validity and are therefore not included in the evidence table. Alogliptin studies were of similar design, enrolling patients 18-80 years with A1C of 7-10% (except for alogliptin and insulin trial, which patients had an A1C $\geq$8%) for 26 weeks with a 4-week run-in period.[29-34] The primary endpoint was the change in A1C from baseline at week 26 or 52. Key secondary endpoints were: changes in fasting plasma glucose, number of patients obtaining an A1C <7.0% and changes in baseline body weight.

Nauke, et al studied aloglitptin 12.5 mg and 25mg with metformin compared to placebo in patients with a baseline A1C of 8% and mean age of 55 years.[29] Change in A1C was -0.6% for both alogliptin groups compared to a placebo decrease of -0.1%, p<0.001 for both groups. Results were similar when alogliptin was studied with pioglitazone in a study by Prately, et al.[30] Patients were allowed to continue background metformin and/or sulfonylurea. Decreases in baseline A1C for alogliptin 12.5 mg and alogliptin 25 mg were -0.66% and 0.8%, respectively, compared to a placebo A1C increase of 0.19%. Smaller but still significant A1C changes were shown in a trial by Pratley, et al that compared alogliptin 12.5 mg and 25 mg to placebo with background glyburide therapy.[31] Decrease from baseline A1C were -0.38% for alogliptin 12.5 mg and -0.52% for alogliptin 25 mg compared to placebo 0.01% (p<0.001 for both groups). A poor-fair study by Rosenstock, et al found A1C decreases for alogliptin significantly more than placebo when patients were on background insulin therapy with or without metformin.[32] Changes from baseline A1C were -0.13%,-0.63%, -0.71% for placebo, alogliptin 12.5 mg and alogliptin 25 mg, respectively. Defronzo, et al compared alogliptin 12.5 mg and 25 mg to placebo and pioglitazone 15, 30 and 45 mg, as well as the combination of alogliptin 12.5 mg and all pioglitazone doses and alogliptin 25 mg and all pioglitazone doses.[33] Decreases in A1C were greater for alogliptin and pioglitazone combination therapy compared to pioglitazone alone ($p\leq0.001$ for all groups). Changes from baseline A1C were similar for alogliptin 12.5 mg and pioglitazone 15 mg (-0.7%) and for alogliptin 25 mg and pioglitazone 30mg (-0.9%). The combination of alogliptin and pioglitazone was superior to pioglitazone alone with decreases in A1C ranging from -1.25% to -1.6%. Changes in fasting plasma glucose and percent of subjects obtaining an A1C <7% were significantly more for alogliptin 25mg compared to placebo in all studies. A study of alogliptin 25mg, metformin (≥1500 mg) and pioglitazone 30mg (A/M/P) was compared to pioglitazone 45mg and metformin (≥1500mg) (P/M).[34] At week 52 least squares mean change from baseline in A1C were significantly greater for the A/M/P compared to P/M, -0.70% and -0.29% (p<0.001), respectively. Significantly more patients were able to achieve an A1C of ≤7%, with a NNT of 8.

Evaluation of efficacy data for alogliptin was limited by high drop out rates that were highest in the study using alogliptin and insulin together (47%) and ranged from 11-40% in other studies. In the alogliptin and insulin trial, high attrition rates can be attributed to a large number of patients requiring hyperglycemic rescue, which was determined by A1C at 12 weeks compared to FPG. An additional concern with data analysis in light of data imputation due to drop outs is the sustained efficacy of alogliptin out to 52 weeks. True efficacy is difficult to determine due to high drop out rates and differing rates of attrition between alogliptin and placebo groups which introduce selection and attrition bias.

Clinical Safety:
The adverse effects that alogliptin therapy is most commonly associated with are; nasopharyngitis, headache, upper respiratory infection and urinary tract infections. Studies showed that alogliptin was weight neutral and hypoglycemia rates were similar to placebo. Discontinuations due to adverse effects were low (2% to 5%). Studies of alogliptin were found to be associated with a higher incidence of serious cardiovascular events compared to placebo. This increase may

be due to study design and implementation, however, the association can not be ruled out and is being further evaluated. Additional FDA post marketing study requirements are a cardiovascular outcomes trial (EXAMINE study), an enhanced pharmacovigilance program to monitor for liver abnormalities, serious cases of pancreatitis and severe hypersensitivity reactions as well as three pediatric studies.[35] Combination products, Oseni and Kazano, carry black box warnings due to congestive heart failure risk with pioglitazone and lactic acidosis risk with metformin.[27,28]

Conclusion

Alogliptin is a moderately effective agent to treat glucose abnormalities in patients with type 2 DM as monotherapy and as a combination product. Placebo adjusted mean FPG changes from baseline ranged from -4 to -28 and mean A1C reductions were 0.4%-0.6% for alogliptin monotherapy compared to placebo, with the 25mg alogliptin dose being only slightly more effective than the 12.5 mg dose.[34] Alogliptin does not appear to have any advantages over currently available DPP-4 inhibitors and is associated with similar adverse reactions (infections, skin reactions, hepatoxicity, hypersensitivity reactions, pancreatitis and renal safety issues).[26,35] Alogliptin has been shown to be weight neutral with a low risk of hypoglycemia. Additional studies are needed to determine safety and efficacy of chronic use as randomized trial durations were limited to 52 weeks.

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:

1.) Microvascular Outcomes
2.) Macrovascular Outcomes
3.) Hypoglycemic Episodes
4.) Adverse Effects leading to discontinuation

Primary Study Endpoints:

1.) Changes in HbA1c
2.) Changes in weight

Evidence Table

CANTATA-M[21]

Stenlöf, et al Phase III, RCT, DB, PC 17 Countries	1. Canagliflozin 100mg QD (C100) 2. Canagliflozin 300mg QD (C300) 3. Placebo QD (P)	Mean Age (main study): 55 Mean Age (substudy): 49 Female: 55% Main study baseline A1C: 8.0% Substudy baseline A1C: 10.6% **Inclusion**: Patients 18-80 years with type 2 DM with the either of the following: not on a AHA with A1C of ≥7.(and ≤10.0% or on AHA monotherapy (except PPARγ) or metformin plus sulfonylurea combination therapy with A1C of ≥6.5 and ≤9.5% at screening and A1C ≥7 and ≤10.0% and FPG of <150 mmol/L at week -2. Substudy: A1C of >10.0 and ≤12.0% at screening or week -1 and FPG ≤19.4 mmol/l at week -1. **Exclusion**: FPG >15 mmol/l during pre-treatment phase (or >19.4 mmol/l for the substudy), type 1 DM, hereditary glucose-galactose malabsorption, primary renal glucosuria or CV disease, tx with other SGLT2	Main Study: 1. 195 2. 197 3. 192 Sub-study: 1. 47 2. 44	26 weeks	<u>Change from Baseline in A1C at 26 weeks :</u> C100: -0.77% C300: -1.03% P: 0.14% LS Mean Change C100: -0.91% (95% CI -1.1 to -0.7, p<0.001) LS Mean Change C300: -1.16% (95% CI -1.3 to -1.0, p<0.001) <u>Fasting Plasma Glucose:</u> C100: -1.5 mmol/l (27 mg/dl) C300: -1.9 mmol/l (34 mg/dl) P: 0.5 mmol/l (9 mg/dl) LS Mean Change C100: -2.0 mmol/l (95% CI -2.3 to -1.6, P<0.001) LS Mean Change C300: -2.4 mmol/l (95% CI -2.8 to -2.0, p <0.001) <u>Subjects reaching A1C <7.0%:</u> C100: 44.5% C300: 62.4% P: 20.6% P<0.001 for both doses <u>Changes in Baseline body weight:</u> C100: -2.5 kg (2.8%) C300: -3.4kg (3.9% P: -0.5 kg (-0.6%) LS Mean Change C100: -2.2% (95% CI -2.9 to -1.6, p<0.001)	NA NA C100 ARR: 24 NNT: 4 C300 ARR: 42 NNT: 2 NA	<u>Urinary tract infection:</u> C100: 14 (7.2%) C300: 10 (5.1%) P: 8 (4.2%) <u>Males genital mycotic infection:</u> C100: 2 (2.5%) C300: (5.6%) P: 0 <u>Female genital mycotic infection:</u> C100: 10 (8.8%) C300: 8 (7.4%) P: 4 (3.8%) <u>Hypoglycemia:</u> C300: 3.6% C100: 3.0% P: 2.6% <u>Withdrawal due to Adverse Events:</u> C100: 6 (3.1%) C300: 4 (2.0%) P: 2 (1.0%)	NA NA NA NA	**Quality Rating: Poor-Fair** **Internal Validity: RofB** Selection: not described Performance: double-blind treatment design was stated but no details on blinding were provided Detection: details were not provided Attrition: mITT analysis was used with LOCF fo missing data. Overall 13.1% discontinued treatment prior to 26 weeks **External Validity** Recruitment: recruited from 17 countries Patient Characteristics: almost half of patients had prior exposure to glucose lower therapy, but HbA1c lowering was similar regardless of prior treatment. Patients with mild to moderate renal impairment were included. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.

CANTATA-D2[22]									
Schern-thaner, et al Phase III, RCT, DB, active control, non-inferiority trial 17 countries	1. Canagliflozin 300 mg (C300) 2. Sitagliptin 100 mg (S100) * Both groups on background metformin and sulfonylurea	Age: 56 years Female: 43.5% Main study baseline A1C: 8 % Male: 56% <u>Inclusion:</u> Subjects 18 years and older, type 2 diabetes diagnosis, on stable doses or adjustment period of metformin (1500-2000mg dose) and sulfonylurea (at least half of maximum labeled dose) therapy and A1C ≥7.0% and ≤ 10.5%. <u>Exclusion</u>: Prior AHA therapy other than metformin and sulfonylurea up to 12 weeks prior to study enrollment, type 1 diabetes, uncontrolled hypertension, cardiovascular disease and eGFR <55 mL/min/1.73m^2.	1. 378 2. 378	52 weeks with 2 week prior single-blind placebo run-in	<u>Change from Baseline in A1C at 52 weeks :</u> C300: -1.03% S100: -0.66% LS means: -0.37 (95% CI -0.50 to -0.25) noninferiority and superiority was achieved <u>Fasting Plasma Glucose:</u> C300: -1.7 mmol/l (29 mg/dl) S100: -0.3 mmol/l (2.2 mg/dl) LS Mean Change: -1.3 mmol/l P<0.001 LS Mean Change C300: -2.4 mmol/l (95% CI -2.8 to -2.0, p <0.001) <u>Subjects reaching A1C <7.0%:</u> C300: 47.6% S100: 35.3% <u>Changes in Baseline body weight:</u> C300: -2.3 kg (-2.5%) S100: 0.1 kg (0.3%) LS Mean Change: -2.8%, p<0.001	NA NA NA	<u>Urinary tract infection:</u> C100: 15 (4.0%) S100: 10 (5.6%) <u>Males genital mycotic infection:</u> C300: 19 (9.2%) S100: 1 (0.5%) <u>Female genital mycotic infection:</u> C300: 26 (15.3%) S100: 7 (4.3%) <u>Severe Hypoglycemia:</u> C300: 4.0% S100: 3.4% <u>Withdrawal due to Adverse Events:</u> C300: 20 (5.3%) S100: 11 (2.9%)	NA NA NA NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. High and different levels of attrition may have affected the ability to maintain randomization. Performance: Study was double-blind with study personnel remaining blinded to treatment allocation. Detection: Investigators and local sponsor personnel were blinded to treatment assignment. Attrition: mITT analysis was used with LOCF for missing data. Potential for bias due to only 39% of patients completed 52 week study, most withdrawals due to rescue therapy. **External Validity:** Recruitment: 140 centers in 17 countries. Patient Characteristics: Patients with almost 10 years of diabetes and moderate A1cs were included. Not studied in newly diagnosed and those with cardiovascular disease. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
Canagliflozin and Chronic Kidney Disease[23]									
Yale, et al Phase III, DB,	1. Canagliflozin 100mg (C100)	Age: 69 yrs Female: 36-46% Baseline A1C: 8.0% Baseline eGFR: 39	1. 90	26 weeks with 2 week single-blind placebo run-in	<u>Change from Baseline in A1C at 26 weeks :</u> C100: -0.33% C300: - 0.44%	NA	<u>Urinary tract infection:</u> C100: 5 (5.6%) C300: 7 (7.9%)	NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via

PC	2. Canagliflozin 300mg (C300) 3. Placebo (P)	ml/min/1.73 m^2 Mean duration of DM: 16.3 years Inclusion: Type 2 diabetes, stage 2 chronic kidney disease (eGFR ≥30 and <50 ml/min/1.73 m^2, ≥25 years old, A1C ≥7.0 and ≤10.5%, not on AHA therapy or on stable regimen for ≥8 weeks Exclusion: FPG >15.0 mmol/l, type 1 diabetes, renal disease requiring treatment, and cardiovascular diseases or disorders.	2. 89 3. 90		P: -0.03% LS Mean Change C100: -0.30% (95% CI -0.5 to -0.1, p<0.05) LS Mean Change C300: -0.40% (95% CI -0.6 to -0.2, p<0.001) Fasting Plasma Glucose: C100: -0.83 mmol/l (15 mg/dl) C300: -0.65 mmol/l (12 mg/dl) P: -0.03 mmol/l (0.5 mg/dl) LS Mean Change C100: -0.85 mmol/l (95%CI -1.6 to -0.1) p-value not calculated since C300 not SS LS Mean Change C300: -0.67 mmol/l (95% CI -1.4 to -0.1, not SS) Subjects reaching A1C <7.0%: C100: 27.3% C300: 32.6% P: 17.2% Changes in Baseline body weight: C100: -1.2 kg (1.2%) C300: -1.4kg (1.5%) P: -0.3 kg (-0.3%) LS Mean Change C100: -	NA NA	P: 5 (5.6%) Males genital mycotic infection: C100: 1 (1.7%) C300: 1 (2.1%) P: 0 Female genital mycotic infection: C100: 1 (1.3%) C300: 1 (2.4%) P: 0 Severe Hypoglycemia: C300: 4 (4.7%) C100: 1 (1.2%) P: 1 (1.1%) Withdrawal due to Adverse Events: C100: 4 (4.4%) C300: 2 (2.2%) P: 5 (5.6%)	NA NA NA NA	interactive voice-response system. Performance: double-blind treatment design was stated but no details on blinding were provided. Detection: details were not provided Attrition: mITT analysis was used with LOCF for missing data. Overall 12.9% discontinued treatment prior to 26 weeks **External Validity:** Recruitment: from 89 centers in 19 countries. Patient Characteristics: Most patients (98%) were on background AHA therapy, 74% of these were on insulin. Outcomes: The accepted surrogate outcome o A1C was used for efficacy measure.

					1.6% (95% CI -2.3 to -0.8) LS Mean Change C300: -1.8% (95% CI -2.6 to -1.0)				
CANTATA-SU[24]									
Cefalu, et al Phase III, DB, non-inferiority, RCT 157 centers and 19 countries	1. Canagliflozin 100mg (C100) 2. Canagliflozin 300mg (C300) 3. Glimepiride 6-8mg (G) * All patients on background metformin	Age: 57 yrs Male: 52% Baseline A1C: 7.8% Mean duration of DM: 6.6 years <u>Inclusion:</u> Type 2 diabetes, 18-80 years old, A1C ≥7.0 and ≤9.5%, and stable metformin dose for at least 10 weeks. <u>Exclusion:</u> History of severe hypoglycemia requiring treatment, FPG ≥15 mmol/L, (eGFR <55 ml/min/1.73 m^2, SrCr ≥124 µmol/L for men or SrCr ≥115 µmol/L for women or TZD in prior 16 weeks.	1. 483 2. 485 3. 482	52 weeks with 2-week placebo run-in period	<u>Change from Baseline in A1C at 26 weeks :</u> C100: -0.82% C300: - 0.93% G: -0.81% LS Mean Change C100: -0.01% (95% CI -0.11 to -0.09) C100 non-inferior to glimepiride LS Mean Change C300: -0.12% (95% CI -0.22 to -0.02) C300 superior to glimepiride (no p-value given) <u>LS Mean Change in Fasting Plasma Glucose:</u> C100: -1.35 mmol/l (24 mg/dl) C300: -1.52 mmol/l (27 mg/dl) G: -1.02 mmol/l (18 mg/dl) <u>Subjects reaching A1C <7.0%:</u> C100: 54% C300: 60% G: 56% p-value not given <u>Changes in Baseline body weight:</u>	NA NA NA NA	<u>Urinary tract infection:</u> C100: 31 (6%) C300: 31 (6%) G: 25 (5%) <u>Males genital mycotic infection:</u> C100: 17 (7%) C300: 20 (8%) G: 3 (1%) <u>Female genital mycotic infection:</u> C100: 26 (11%) C300: 34 (14%) G: 5 (2%) <u>Severe Hypoglycemia:</u> C300: 3 (<1%) C100: 2 (<1%) G: 15 (3%) <u>Withdrawal due to Adverse Events:</u> C100: 25 (5%) C300: 32 (7%) G: 28 (6%)	NA NA NA NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. Performance: Study was double-blind. Detection: Investigators and local sponsor personnel were blinded to treatment assignment. Attrition: mITT analysis was used with LOCF for missing data. Overall attrition was 18-22% with similar rates between the groups. **External Validity:** Recruitment: 157 centers in 17 countries. Patient Characteristics: Patients had an approximate 7 year history of diabetes who were predominately white. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.

					C100: -3.7 kg (4.2%) C300: -4.0kg (4.7%) G: 0.7 kg (1%) P<0.0001 for both doses				
ALOGLIPTIN PLUS METFORMIN[29]									
Nauk, et al Phase III, PC, DB, RCT	1. Alogliptin 12.5mg (A12.5 2. Alogliptin 25mg (A25) 3. Placebo * All on background metformin (>1500mg) therapy	Mean Age: 54-56 years Male: 47-54% Baseline A1C: 7.9-8.0% Inclusion: 18-80 years, type 2 diabetes, A1C 7-10%, BMI 23-45 kg/m^2, stable metformin dose. Exclusion: Current AHA treatment other than metformin, abnormal labs, heart disease, glucocorticoid or weight loss drug use.	1. 213 2. 210 3. 104	26 weeks with 4 week single-blind run-in period	<u>Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.6% A25: -0.6% P: -0.1 P<0.001 for both <u>Fasting Plasma Glucose LS mean change:</u> A12.5: -19 mg/dl A25: -17 mg/dl P: 0.0 mg/dl P<0.001 for both <u>Subjects reaching A1C <7.0%:</u> A12.5: 110 (52%) A25: 92 (44%) P: 19 (18%) P<0.001 <u>LS Mean differences in Baseline body weight compared to placebo:</u> A12.5: -0.0 kg (95% CI -0.7 to 0.7) A25: -0.3 kg (95% CI -0.9 to 0.4)	NA NA A12.5 ARR: 34 NNT: 3 A25 ARR: 26 NNT: 4 NS	<u>Upper Respiratory Infection:</u> A12.5: 68 (32%) A25: 5 (2%) P: 7 (7%) <u>Withdrawal due to Adverse Events:</u> A12.5: 7 (3%) A25: 4 (2%) P: 1 (1%)		**Quality Rating: Poor-fair** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice-response system. Performance: Double-blind design but no details provided. Detection: Details on outcome assessment not described. Attrition: FAS analysis with LOCF. Attrition rates ranged from 17-31%. **External Validity:** Recruitment: Patients were from 115 sites in 15 countries. Patient Characteristics: Patients were predominately white, a mean duration of diabetes of 6 years and mean metformin dose of ~1850mg. Outcomes: The accepted surrogate outcome o A1C was used for efficacy measure.
ALOGLIPTIN PLUS PIOGLITAZONE[30]									
Prately, et al	1. Alogliptin 12.5 mg (A12.5)	Mean Age: 55 yrs. Mean baseline A1C 8.0%	1. 2. 9081	26 weeks with 4 week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.66%		<u>Hypoglycemia:</u> A12.5: 5.1% A25: 7.0% P: 5.2%		**Quality Rating: Fair** **Internal Validity: RofB** Selection: Randomization was done via

Phase III, RCT, DB, PC 125 sites	2. Alogliptin 25 mg (A25) 3. Placebo (P) * All on background pioglitazone ± metformin and/or sulfonylurea	Inclusion: type 2 DM, BMI 23-45 kg/m2, A1C 7-10%, ≥ 3 mo. of stable dose TZD with or without metformin or sulfonylurea Exclusion Criteria: Heart disease, abnormal lab values, uncontrolled HTN, and use of other AHAs.			A25: -0.80% P: 0.19% P<0.001 for both <u>Subjects reaching A1C <7.0%:</u> A12.5: 87 (44.2%) A25: 98 (49.2%) P: 18 (18.2%) p=≤ 0.016 for both <u>LS Mean Changes in Baseline body weight from placebo:</u> A12.5: 0.42 kg A25: 0.05 kg P: not given		<u>Upper Respiratory Infection:</u> A12.5: 11 (5.6) A25: 10 (5.0) P: 5 (5.2) <u>Withdrawal due to Adverse Events:</u> A12.5: 6 (3.0%) A25: 6 (3.0%) P: 3 (3.1%)		automated, interactive voice response system. Baseline characteristics were well matched. Performance: Double-blind design but no details were provided. Detection: Blinding of outcomes assessors was not described. Attrition: Patient results were included for those with baseline and at least one post-baseline measurement with LOCF for missing data. Overall attrition was 12%. **External Validity:** Recruitment: Patients from 125 sites. Patient Characteristics: Study participants had few comorbidities, predominantly white and middle-aged. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
ALOGLIPTIN PLUS GLYBURIDE[31]									
Pratley, et al Phase III, RCT DB, PC 124 centers and 16 countries	1. Alogliptin 12.5 mg (A12.5) 2. Alogliptin 25 mg (A25) 3. Placebo (P) * All on background glyburide (5-10mg or greater)	Age: 57 years Female: 45-50% Mean Baseline A1C 8.1% Inclusion Criteria: 18-80 years old, type 2 DM, A1C 7-10% and sulfonylurea therapy ≥3 months Exclusion Criteria: Use of AHA therapy within 3 months of study, BMI <23 or >45 kg/m^2, abnormal lab values, heart disease, use of weight loss drugs, oral glucocorticoids and bosentan within 3 months.	1. 203 2. 198 3. 99	26 weeks with 4 week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.38% A25: -0.52% P: 0.01% P<0.001 for both <u>Subjects reaching A1C <7.0%:</u> A12.5: 60 (29.6%) P: 18 (18.2%) p= 0.057 A25: 69 (34.8%) P: 18 (18.2%) p=0.008 <u>Changes in Baseline body weight:</u> A12.5: 0.60 kg A25: 0.68 kg P: -0.20 kg	NA NS ARR: NNT: NA	<u>Hypoglycemia:</u> A12.5: 32 (15.8%) A25: 19 (19.6%) P: 11 (11.1%) <u>Upper Respiratory Infection:</u> A12.5: 4 (2.0%) A25: 5 (2.5%) P: 6 (6.1%) <u>Withdrawal due to Adverse Events:</u> A12.5: 5 (2.5%) A25: 4 (2.0%) P: 2 (2.0%)		**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Patients randomized according to a permuted block schedule other methodology was not described. Baseline characteristics were well matched. Performance: limited to double-blind designation, details not provided. Detection: no details were provided. Attrition: Levels of attrition ranged from 25-37%, patients with baseline and post-baseline measurement(s) were included with LOCF applied to missing data. **External Validity:** Recruitment: Included patients from 16 countries and 124 centers. Patient Characteristics: Patients were predominately white without significant co-morbidities including heart disease and reduced renal function. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.

ALOGLIPTIN AND INSULIN[32]									
Rosenstock, et al Phase III, RCT DB, PC 110 sites and 13 countries	1. Alogliptin 12.5 mg (A12.5) 2. Alogliptin 25 mg (A25) 3. Placebo (P) * On background insulin therapy ± metformin	Mean Age:55 years Female: 65-85% Mean A1c: 9.3% Inclusion: Patients 18-80 years, A1C ≥8%, BMI 23-45 kg/m^2 and on insulin with or without metformin. Exclusion: heart disease, retinopathy, diabetic gastroparesis, cancer, use of other AHAs, weight loss drugs or glucocorticoids.	1. 131 2. 129 3. 130	26 weeks with 4 week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.63% A25: -0.71% P: -0.13% P<0.001 for both <u>Mean FPG decrease from baseline:</u> A12.5: 0.1 mmol/l (2 mg/dl) A25: -0.6 mmol/l (11 mg/dl) P: 0.3 mmol/l (5.4 mg/dl) <u>Changes in Baseline body weight:</u> A12.5: 0.60 kg A25: 0.7 kg P: 0.6 kg	NA NA NA	<u>Hypoglycemia:</u> A12.5: 26.7% A25: 27.1% P: 24% <u>Any Infection/Infestation</u> A12.5: 43 (33%) A25: 38 (30%) P: 40 (30.1%) <u>Withdrawal due to Adverse Events:</u> A12.5: 1 (0.8%) A25: 6 (4.7%) P: 4 (3.1%)	NA NA	**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Patients randomized with an automated interactive voice response system using a randomization schedule generated before study initiation. Performance: Limited to double-blind designation, details not provided. Detection: no details were provided. Attrition: Analysis was based on FAS. Attrition rates were high; 58% for placebo, 37% for A12.5 and 40% for A25. **External Validity:** Recruitment: Included patients from 13 countries and 110 centers. Patient Characteristics: Patients attended weekly visits to discuss diet and exercise. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
ALOGLIPTIN AND PIOGLITAZONE[33]									
DeFronzo, et al Phase III, DB, PC, DD, RCT 20 countries 327 study sites	1. Alogliptin 12.5 mg (A12.) 2. Alogliptin 2 mg (A25) 2. Pioglitazone 15 mg (P15) 3. Alogliptin 12.5 mg + pioglitazone 15mg (A12.5/P) 4. Alogliptin 2 mg + pioglitazone	Mean Age: 54 years Female: 51.1% Baseline mean A1C 8.5% Inclusion: Patients 18-80 years, type 2 DM, AIC 7.5 -11%, failed metformin monotherapy, normal labs, BMI 23-45 kg/m^2 Exclusion: use of glucocorticoids, weight loss drugs, abnormal labs and heart disease	1. 164 2. 163 3. 164 5. 164	26 weeks with 4-week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks for alogliptin monotherapy :</u> A12.5: -0.7% A25: -0.9% P: -0.1% <u>LS Mean Change from Baseline in A1C at 26 weeks for alogliptin/pioglitazone combination therapy :</u> P15/P: -0.7% P15/A12.5: -1.3% P15/A25: -1.25 P30/P: -0.9%	NA	<u>Any hypoglycemia for pooled groups:</u> Pioglitazone groups: 8 (2.1%) A12.5/all pioglitazone doses: 4 (1.0%) A25/all pioglitazone doses: 6 (1.5%) <u>Any Infection/Infestation for pooled groups:</u> Pioglitazone groups: 26.6% A12.5/all pioglitazone doses: 25.1% A25/all pioglitazone	NA NA	**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Patient randomization details not described. Performance: Limited to double-blind designation, details not provided. Detection: No details provided. Attrition: Attrition rates ranged from 11-46%, with the highest rate in the placebo group. Treatment attrition ranged from 11-28%. FAS with LOCF were used for missing data. **External Validity:** Recruitment: Patients were recruited from 20 countries and 327 sites. Patient Characteristics: Patients were predominately white with the mean duration

	15mg (A12.5/P) 5. Pioglitazone 30 mg (P30) 6. Pioglitazone 30 mg + alogliptin 12.5 mg (P30/A12.5) 7. Pioglitazone 30 mg + alogliptin 25 mg (P30/A25) 8. Pioglitazone 45 mg (P45) 9. Pioglitazone 45 mg + alogliptin 12.5 mg (P45/A12.5) 10. . Pioglitazone 45 mg + alogliptin 25 mg (P45/A25) 11. Placebo (P Alogliptin 25mg + pioglitazone 30mg (A25/P)				P30/A12.5: -1.4% P45/P: -1.0 P45/A12.5: -1.5% P45/A25: -1.6% p≤0.001 for pioglitazone vs. combination therapies (all groups) <u>Subjects reaching A1C <7.0%:</u> All pioglitazone doses: 118 (30.5%) A12.5/all pioglitazone doses: 213 (54.6%) A25/all pioglitazone doses: 218 (55.9%) P<0.001 for all groups compared to pioglitazone alone <u>Changes in Baseline body weight for pooled groups:</u> Pioglitazone groups: 1.5 kg A12.5/P groups: 1.8 kg A25/P groups: 1.9 kg P-value: NS	A12.5/P ARR: 24.1% NNT: 4 A25/P ARR: 25.4 NNT: 4	doses: 30.8% <u>Withdrawal due to Adverse Events:</u> Pioglitazone groups: 11 (2.8%) A12.5/all pioglitazone doses: 6 (2.1%) A25/pioglitazone doses: 6 (1.5%)	NA	of diabetes of 6 years. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
ALOGLIPTIN VS INCREASED PIOGLITAZONE DOSE[34]									

Bosi, et al Phase III, PG, DB, RCT	1. Alogliptin 25 mg (A/P/M)* 2. Pioglitazone 15 mg (P/M)* * All patients were on metformin (≥1500mg or maximum tolerated dose and pioglitazone 30mg	Mean Age: 55 yrs. Female: 49% Inclusion: Patients 18-80 year type 2 DM, systolic BP <160 mm Hg diastolic BP <100 mm Hg, A1C ≥ 7.0 and ≤ 10.0% on metformin and pioglitazone 2 months prior or A1C 7.5% on metformin and other AHA and later A1C ≥ 7.0 and ≤ 10.0% after switching to metformin and pioglitazone for 16 weeks and BMI 23-45 kg/m^2 Exclusion: Elevated BP, heart disease or any other severe disease.	1. 404 2. 399	52 weeks with 4-week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A/P/M: -0.70% P/M: -0.29% P<0.001 <u>Mean FPG decrease from baseline:</u> A/P/M: -0.8 mmol/l (14.4 mg/dl) P/M: -0.2 mmol/l (3.6 mg/dl) P<0.001 <u>Subjects reaching A1C <7.0%:</u> A/P/M: 33.2% P/M: 21.3% P< 0.001 <u>Changes in Baseline body weight:</u> A/P/M: 1.10 kg P/M: 1.60 kg P=0.071	NA NA ARR: 11.9% NNT: 8 NA	<u>Hypoglycemia:</u> A/P/M: 16 (4.0%) P/M: 6 (1.5%) <u>Upper Respiratory Tract Infection:</u> A/P/M: 29 (7.2%) P/M: 16 (4.0%) <u>Withdrawal due to Adverse Events:</u> A/P/M: 12 (3%) P/M: 16 (4.0%)	NA NA NA	**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Randomization methods were unclear, no details were provided. Performance: Double-blind design but no details were provided. Detection: Final analysis investigators blinded to interim analysis results but unknown if allocation was concealed. Attrition: Attrition rates in the alogliptin group were 30% and 40% in the pioglitazone group, this includes patients removed from study to due hyperglycemia rescue. A per protocol analysis was used with LOCF for missing data. **External Validity:** Recruitment: Patients were recruited from multiple sites and countries. Patient Characteristics: Patients were predominately white with a 7 year history of diabetes. Outcomes: The accepted surrogate outcome o A1C was used for efficacy measure.

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis, FAS- full analysis set
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: AHA = antihyperglycemic agent, PPARγ = peroxisome proliferator-activated receptor-γ, FPG = fasting plasma glucose, A1c- hemoglobin A1c

References:

1. Health Resources Commission. Newer Drugs for the Treatment of Diabetes Mellitus. June 2009.
2. National Diabetes Information Clearinghouse (NDIC). National Diabetes Statistics. NIH Publication. Accessed July 2, 2013. Accessed at: http://www.diabtetes.niddk.nih.gov/dm/pubs/statistics/#Diagnosed20.
3. Turner R, Cull C, Frighi V, et al. Glycemic Control with Diet, Sulfonylurea, Metformin, or Insulin in Patients with Type 2 Diabetes Mellitus: Progressive Requirement for Multiple Therapies (UKPDS 49). JAMA 1999;281:2005-2012.
4. Centers for Disease Control and Prevention Press Release. Number of Americans with Diabetes Projected to Double or Triple by 2050. 2010. Accessed July 23, 13. Available at: http://www.cdc.gov/media/pressrel/2010/r101022.html.
5. ACCE Guidelines. American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm 2013 Consensus Statement. Endocr Pract. 2013;19(Suppl 2).
6. Inzucchi S, Bergenstal R, Buse J, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. Diabetes Care 2012; 35:1364-1379.
7. Nathan D, Buse J, Davidson M, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2008;31:1-11.
8. Canadian Agency for Drugs and Technologies in Health. Second-line pharmacotherapy for type 2 diabetes – Update. Ottawa: The Agency;2013. (CADTH optimal use report; vol.3, no. 1a).
9. Canadian Agency for Drugs and Technologies in Health. Third-line pharmacotherapy for type 2 diabetes – Update. Ottawa: The Agency; 2013. (CADTH optimal use report; vol.3, no. 1b).
10. Hemmingsen B, Schroll JB, Lund SS, et al. Sulfonylurea Monotherapy for Patients with Type 2 Diabetes Mellitus (Review). Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD009008. DOI: 10.1002/14651858.
11. Monami M, Genovese S and Mannucci E. Cardiovascular Safety of Sulfonylureas: a Meta-analysis of Randomized Clinical Trials. Diabetes Obes Metab 2013 [published online ahead of print May 2013]. http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1111/dom.12116/pdf. Accessed on August 23, 2013.
12. Aroda V, Henry R, Hans J, et al. Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitors: Meta-Analysis and Systematic Review. Clin Ther. 2012;34:1247-1258.
13. Bennett W, Wilson LM, Bolen S, et al. Oral Diabetes Medications for Adults With Type 2 Diabetes. An Update. Comparative Effectiveness Review No. 27. (Prepared by Johns Hopkins Evidence-based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 11-EHC038. Rockville, MD: Agency for Healthcare Research and Quality. March 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed March 10, 2013.
14. National Institute for Health and Clinical Excellence. Type 2 Diabetes: Newer Agents. 2009. Accessed on Jun 20, 2013. Available at: http://www.nice.org.uk/nicemedia/live/12165/44320/44320.pdf.
15. ACCE/ACE Consensus Statement. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control. Endocr Pract. 2009;15:540-559.
16. International Diabetes Federation Clinical Guidelines Task Force. Global Guidelines for Type 2 Diabetes Mellitus. 2012. Accessed on June 14, 2013. Available at: http://www.idf.org/sites/default/files/IDF-Guidelines-for-Type-2-Diabetes.pdf.
17. Qaseem A, Humphrey L, Sweet D, et al. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med 2012; 156:218-231.
18. Drug Safety Communication. Actos (pioglitazone): Ongoing Safety Review – Potential Increased Risk of Bladder Cancer. 08/04/2011. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm226257.htm. Accessed May 12, 2013.
19. Drug Safety Communication. Incretin Mimetic Drugs for Type 2 Diabetes: Early Communication Reports of Possible Increased Risk of Pancreatitis and Pre-cancerous Findings of the Pancreas. Available at: http://www.fda.gov/Safety /MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm34805.htm. Accessed on May 12, 2013.
20. Janssen Pharmaceuticals, Inc. Invokana Label. US Food and Drug Administration. 2013. Accessed March 12, 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf.

Author: Kathy Sentena, Pharm.D.

21. Stenlöf K, Cefalu W, Kim K, et al. Efficacy and Safety of Canagliflozin Monotherapy in Subjects with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise. Diabetes Obes Metab 2013;15:372-382.
22. Schernthaner G, Gross J, Rosenstock J, et al. Canagliflozin Compared with Sitagliptin for Patients with Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea. Diabetes Care 2013. Published online ahead of print April 5, 2013, doi:10.2337/dc12-2491 Accessed on April 5, 2013.
23. Yale J, Bakris G, Cariou B, et al. Efficacy and Safety of Canagliflozin in Subjects with Type 2 Diabetes and Chronic Kidney Disease. Diabetes Obes Metab 2013;15:463-473.
24. Cefalu W, Leiter L, Yoon K, et al. Efficacy and Safety of Canagliflozin versus Glimepiride in patients with Type 2 Diabetes Inadequately Controlled with Meformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 2 non-inferiority trial. Lancet 2013 [published online ahead of print July 11, 2013]. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60683-2/fulltext. Accessed July 26, 2013.
25. FDA. Canagliflozin Summary Review. Reference ID: 204042. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042Orig1s000SumR.pdf. Accessed April 4, 2013.
26. Takeda Pharmaceuticals America, Inc. Nesina Label. US Food and Drug Administration 2013. Accessed March 10, 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022271s000lbl.pdf.
27. Takeda Pharmaceuticals America, Inc. Oseni Label. US Food and Drug Administration 2013. Accessed March 10, 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022426s000lbl.pdf.
28. Takeda Pharmaceuticals America, Inc. Kazano Label. US Food and Drug Administration 2013. Accessed March 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203414s000lbl.pdf.
29. Nauk M, Ellis G, Fleck P, et al. Efficacy and Safety of Adding the Dipeptidyl Peptidase-4 Inhibitor Alogliptin to Metformin Therapy in Patients with Type 2 Diabetes Inadequately Controlled with Metformin Monotherapy: a Multicentre, Randomised, Double-blind, Placebo-controlled Study. Int J Clin Pract 2009;63:46-55.
30. Prately R, Reusch J, Fleck P, et al. Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Alogliptin added to Pioglitazone in Patients with Type 2 Diabetes: a Randomized, Double-blind, Placebo-controlled Study. Current Med Research and Opin 2009; 25(10):2361-2371.
31. Prately R, Kipnes M, Fledck P, et al. Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Alogliptin in Patients with Type 2 Diabetes Inadequately Controlled by Glyburide Monotherapy. Diabetes Obes Metab 2009;11:167-176.
32. Rosenstock J, Rendell M, Gross J, et al. Alogliptin Added to Insulin Therapy in Patients with Type 2 Diabetes Reduces HbA1c Without Causing Weight Gain or Increased Hypoglycemia. Diabetes Obes Metab 2009;11:1145-1152.
33. DeFronzo R, Burant C, Fleck P, et al. Efficacy and Tolerability of the DPP-4 Inhibitor Alogliptin Combined with Pioglitazone, in Metformin-Treated Patients with Type 2 Diabetes. J Clin Endocrinol Metab 2012;97(5):1615-1622.
34. Bosi E, Ellis G, Wilson C, et al. Alogliptin as a Third Oral Antidiabetic Drug in Patients with Type 2 Diabetes and Inadequate Glycaemic Control on Metformin and Pioglitazone: a 52-week, Randomized, Double-blind, Active-Controlled, Parallel-Group Study. Diabetes Obes Metab 2011;13:1088-1096.
35. FDA. Alogliptin Summary Review. Reference ID: 022271. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022271Orig1s000SumR.pdf. Accessed: April 4, 2013.

Author: Kathy Sentena, Pharm.D.

Appendix 1: Drug Information

NDE: Canagliflozin[18]

Pharmacology: Canagliflozin works by inhibiting the SGLT2, which is responsible for reabsorbing glucose that is filtered by the kidney. Inhibition of SGLT2 causes less glucose reabsorption and lowers the renal threshold for glucose which causes urinary glucose excretion.

Table 1. Pharmacokinetics[18]

Parameter	Canagliflozin
Half-life	10.6-13.1 hours
Metabolism	*O*-glucuronidation
Elimination	33% renal and 52% hepatic
Renal Dose Adjustment	In patients with an eGFR of 45 to <60 mL/min/1.73 m^2 dose should be limited to 100mg daily In patients with a eGRF of 45 mL/min/1.73 m^2 or less canagliflozin is not recommended
Hepatic Dose Adjustment	No adjustment is recommended for patients with Child-Pugh class A-B hepatic impairment Canagliflozin is not recommend for patients with Child-Pugh class C hepatic impairment

Contraindications/Warnings[18]:

- **Contraindications:** Canagliflozin should not be used in patients with a history of severe hypersensitivity to canagliflozin, severe renal impairment or end-stage renal disease (ESRD).
- **Warning:** Hypotension has been associated with canagliflozin treatment. Caution is advised and correction of volume status and hypovolemia in patients with renal impairment, the elderly, and low systolic blood pressure or on diuretics, ARBs, or ACE inhibitors is recommended. It is recommended that renal function be monitored throughout treatment.

Dose[18]

It is recommended that canagliflozin be started at 100mg with the first meal of the day, with the option of increasing the dose to 300mg once daily if tolerated. See table for renal and hepatic dosing.

NDE: Alogliptin[22]

Author: Kathy Sentena, Pharm.D.

Pharmacology: Alogliptin is a DDP-4 inhibitor which slows the inactivation of incretin hormones by the DPP-4 enzyme. Incretin hormones cause insulin release and subsequent glucose lowering.

Table 1. Pharmacokinetics[22]

Parameter	Alogliptin
Half-life	21 hours
Metabolism	60-70% excreted unchanged in the urine
Elimination	76% renal and 13% hepatic
Renal Dose Adjustment	In moderate renal impairment (CrCl ≥30 to <60 mL/min) 12.5 mg once daily is recommended In severe renal impairment (CrCl ≥15 to <30 mL/min)/ESRD (CrCl <15 mL/min or dialysis) 6.25 mg once daily is recommended
Hepatic Dose Adjustment	No adjustment is recommended for patients with Child-Pugh class A-B hepatic impairment Alogliptin has not been studied in patients with Child-Pugh class C hepatic impairment

Contraindications/Warnings[22]:

- **Contraindications:** Alogliptin should not be used in patients with a history of severe hypersensitivity to alogliptin.
- **Warning:** Cases of acute pancreatitis have been reported and patients with signs of pancreatitis should discontinue therapy. There have been postmarketing reports of serious hypersensitivity reactions and hepatic failure with alogliptin. To minimize hypoglycemia, consider lowering the dose of insulin secretagogues or insulins when combining with alogliptin.

Dose[18]

It is recommended that alogliptin be taken as a 25mg tablet daily. See table for renal and hepatic dosing recommendations.

APPENDIX 2:
Suggested PA Criteria

Author: Kathy Sentena, Pharm.D.

Incretin Enhancers

Initiative:

- Optimize appropriate prescribing of incretin enhancers.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs
- Sitagliptin (Januvia®)
- Sitagliptin/metformin (Janumet®)
- Saxagliptin (Onglyza®)
- Saxagliptin/metformin (Kombiglyze XR®
- Linagliptin (Tradjenta®)
- Linagliptin/metformin (Jentadueto®)
- Alogliptin (Nesina®)
- Alogliptin/metformin (Kazano®)
- Alogliptin/pioglitazone (Oseni®)

Covered Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	No: Deny based on appropriateness of therapy.

Author: Kathy Sentena, Pharm.D.

Approval Criteria		
2. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? Contraindications include: • Renal disease or renal dysfunction • Known hypersensitivity to therapies • Acute or chronic metabolic acidosis • Patients at increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) • Increased risk of hypoglycemia	Yes: Go to #3.	No: Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
3. Is the request for sitagliptin (Januvia®) or sitagliptin/metformin (Janumet®)?	Yes: Approve for up to 12 months.	No: Recommend trial of preferred incretin enhancers (sitagliptin or sitagliptin/metformin).

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical Management of Hyperglycemia in Type 2 Diabetes; A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care 31;1-11, 2008.

P&T / DUR Action: *9/26/13 (KS), 4/26/12 (KS), 3/17/11 (KS)*
Revision(s):
Initiated: *7/16/12, 1/1/12*

Author: Kathy Sentena, Pharm.D.

Sodium-Glucose Co-Transporter 2 (SGLT2)

Initiative:

- Optimize appropriate prescribing of SGLT2s.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs
- Canagliflozin (Invokana®)

Covered Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	No: Deny based on appropriateness of therapy.
2. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? Contraindications include: • Renal disease or renal dysfunction • Known hypersensitivity to therapies • Acute or chronic metabolic acidosis • Patients at increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) • Increased risk of hypoglycemia	Yes: Approve for up to 12 months.	No: Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Author: Kathy Sentena, Pharm.D.

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical Management of Hyperglycemia in Type 2 Diabetes; A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care 31;1-11, 2008.

P&T / DUR Action: *9/26/13 (KS)*
Revision(s):
Initiated: *9/26/13*

Author: Kathy Sentena, Pharm.D.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Other lipid Lowering Agents

Month/Year of Review: September 2013
PDL Classes: Other Lipid Lowering Agents
New Drug Evaluation: Icosapent Ethyl (ICP)
Manufacturer: Amarin Pharma Inc

Date of Last Review: May 2012
Source Document: OSU College of Pharmacy
Brand Name: Vascepa®
Dossier Received: Yes

Current Status of PDL Class:

- **Preferred Agents:** CHOLESTYRAMINE POWDER, FENOFIBRATE TABLETS, GEMFIBROZIL TABLET, NIACIN TABLET, NIACIN ER (NIASPAN®)
- **Non-Preferred Agents:** OMEGA-3 ACID ETHYL ESTERS (LOVAZA®), EZETIMIBE (ZETIA®), COLESEVELAM HCL (WELCHOL®), FENOFIBRIC ACID (TRILIPIX, FIBRICOR), COLESTIPOL HCL, MICRONIZED FENOFIBRATE (ANTARA, LOFRIBA)

Previous Conclusions and Recommendation:

- Add other non-statin lipotropics as a class to the PDL
- Make cholestyramine a preferred bile acid sequestrant, which has shown improved cardiovascular (CV) related or stroke outcomes.
- Include gemfibrozil as a preferred lipotropic which as demonstrated improved CV related or stroke outcomes.
- There is no clinical evidence of superiority of one fenofibrate agent over another.
- Make Niaspan and Niacor preferred due to a demonstrated reduction in cardiovascular outcomes.
- Make ezetimibe a non-preferred agent due to insufficient outcome data, and implement the non-PDL prior authorization criteria for use.
- Make Lovaza a non-preferred agent and use the non-PDL prior authorization criteria due to its use as an alternative to a fibric acid derivative and niacin for hypertriglyceridemia.

Research Questions:

- Is there any new comparative evidence for other lipid lowering agents, in reducing cardiovascular mortality or stroke in adult patients?
- Is there any new evidence about comparative harms of other lipid lowering agents in adult patients being treated for hyperlipidemia?
- Are there subpopulations of patients for which one lipid lowering agent is more effective or associated with less harm?
- Is icosapent ethyl (ICP) more effective or safer than other lipid lowering agents in reducing cardiovascular mortality or stroke in adult patients with hypertriglyceridemia?

Conclusions:

- There is insufficient evidence to compare the long-term clinical benefits of combined lipid-modifying therapy with any other lipid lowering class with statin therapy to intensification of statin monotherapy. There is recent evidence that niacin or fibrates in addition to statins has neutral effects on CV outcomes.
- There remains insufficient comparative evidence for drugs within each class.
- There is moderate quality evidence that gemfibrozil may reduce the risk for stroke and CV mortality.
- There is insufficient evidence that the use of omega-3 fatty acids reduces cardiovascular outcomes. They remain a treatment alternative to fibric acid derivatives and niacin for the treatment of high triglycerides.
- There is insufficient evidence to suggest that ICP at a dose of 2g BID when compared to placebo is effective in decreasing risk for pancreatitis and cardiovascular (CV) outcomes in patients with TG levels exceeding 500 mg/dL. The trials have been of insufficient duration to attain sufficient long-term safety and efficacy outcomes.
- There is insufficient evidence comparing ICP to any of the current therapies. When compared to the efficacy of current treatments such as fibrates or niacin, ICP has similar TG lowering ability but there is insufficient data to compare CV risk lowering or pancreatitis risk lowering in any of these therapies. ICP is at least as safe as fibrates or niacin and has significantly fewer treatment-associated adverse effects.

Recommendations:

- Make isocapent ethyl a non-preferred lipotropic agent and use the non-PDL prior authorization criteria due to its use as an alternative to a fibric acid derivative and niacin for hypertriglyceridemia.
- No significant changes in comparative efficacy or safety were found for the other lipid lowering agents. Continue to prefer gemfibrozil and Niaspan due to a demonstrated reduction in cardiovascular outcomes.
- Evaluate comparative costs of other agents in executive session.

Background:

Cardiovascular disease (CVD) includes coronary heart disease, stroke, heart failure, arrhythmias, heart valve disease, congenital heart disease, and hypertension. Abnormal lipid levels can lead to the development of atherosclerosis. There is a known association of elevated low-density lipoprotein (LDL) levels with CVD.[1] Therefore, there has been a strong strategy to focus on LDL reduction to decrease the risk of CVD. Statin therapy has the most robust therapy in preventing CVD events.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III includes guidelines on when to start lipid-lowering therapy and LDL targets for coronary heart disease (CHD) risk reduction.[2] High risk individuals include those with established CHD, other clinical atherosclerotic CVD, or multiple risk factors. These individuals have a 10-yuear CHD risk greater than 20% and their LDL target is less than 100 mg/dl, with an optional goal of less than 70 mg/dl. An update of these guidelines (ATP IV) is anticipated to be released shortly. Statins are the most widely prescribed lipid-lowering agents and are often used as monotherapy. Statins can be combined with other medications, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acids, nicotinic acid, and omega-3 fatty acids. Evidence has demonstrated that combination therapy can lead to better lipid outcomes, but does not reduce cardiovascular death, MI, revascularization, or stroke.[1] There has also been a demonstrated correlation between raised triglycerides and CV disease.[3] However, the reduction of triglycerides has not been shown consistently to be beneficial for stroke or other CV mortality. There has been some controversy as to whether hypertriglyceridemia is an independent risk factor of CHD since patients with these elevated levels often have other CHD risk factors such as central obesity,

diabetes and tobacco or alcohol use.[2,4–6] The Endocrine Society suggests that mild or moderate TG levels put a patient at greater risk for CVD and by treating severe or very severe hypertriglyceridemia in order to decrease risk for pancreatitis, we may be increasing the risk of CHD in these patients though there is no source cited.[7] A meta-analysis and review showed that CV events were significantly increased in patients with hypertriglyceridemia as was incidence of CV death and MI; however all-cause mortality was not significant.[8]

Fibric acid derivatives such as fenofibrate and gemfibrozil have been examined in several studies looking at CHD risk reduction including the FIELD trial, the Helsinki Heart Study and the ACCORD trial.[9] The FIELD study showed a non-significant decrease in coronary events collectively when fenofibrate was compared to placebo, however when non-fatal MI was examined separately from CHD death, there was a significant decrease in non-fatal MI, a non-significant increase in CHD death, and a significant decrease in total CVD events and coronary revascularization.[10] The Helsinki Heart Study looked at gemfibrozil and prevention of CHD risk in patients with borderline high TGs.[11,12] Patients who were originally placed on gemfibrozil had significantly less risk of CHD mortality, but all cause mortality was not statistically significant. [11,12] Gemfibrozil had a significant effect on total cholesterol, HDL-c, LDL-c and TGs therefore correlation between TG levels and cardiac endpoints are difficult to assess as independent risk factors and patients.[11] The ACCORD trial examined CV risk in patients on combination statin and fenofibrate therapy vs statin alone.[9] TG levels were significantly lower in the fenofibrate group though there was no significant difference between the two groups at the follow up in the primary outcome of major fatal or nonfatal CV event or any of the secondary outcomes such as stroke, non-fatal MI or death from any cause.

Niacin has inconsistent LDL-c lowering, requiring high doses which may increase incidence of adverse reactions such as hepatotoxicity, hyperuricemia and hyperglycemia therefore it has historically been most often used in lower doses (<2g) to target TGs with or without a statin.[2,7] Recent evidence from the AIM-HIGH trial, compared coronary heart disease (CHD) risk reduction with niacin/simvastatin combination therapy, indicated that the addition of niacin may actually increase incidence of ischemic strokes and investigators saw no reduction in the primary endpoint of composite death from CHD, non-fatal myocardial infarction(MI), ischemic stroke, hospitalization for acute coronary syndrome and symptom driven coronary or cerebral revascularization.[13]

Prescription omega-3 fatty acids (POM3) with a combination of DHA and EPA (such as Lovaza) have shown to effectively lower serum TG levels, however elevated LDL-c levels have also been observed, the clinical significance of this is unknown.[14,15] In the Japan EPA Lipid Intervention Study (JELIS), increases in LDL-c associated with fish oil was determined to be primarily associated with the DHA component and not EPA.[15,16] Primary endpoints in JELIS included major coronary events, sudden cardiac death, fatal and non-fatal myocardial infarction and other non-fatal events including unstable angina, angioplasty, stenting or coronary artery bypass grafting.[16] Incidence of major coronary events in all patients statistically favored the use of EPA compared to placebo, however when primary and secondary prevention patients were separated the results were insignificant. LDL-c goals were reached in approximately equal proportions of both the EPA and non-EPA group whereas more patients in the EPA group reached non-HDL-c goals.[17] There was lower incidence of CAD in patients who were on EPA and/or who were at their LDL-c and non-HDL-c goal indicating that there may be some protective effect of EPA in patients who have not met non-HDL-c and LDL-c goals but this requires further study. Incidence of CAD did not appear to be directly affected by lowering TGs. ICP contains only EPA instead of both EPA and DHA like most supplements and therefore theoretically doesn't increase LDL as much as EPA/DHA combinations, but also seems less effective for lowering TGs. Omega 3 fatty acid therapy research has produced some evidence of benefit of these agents, and the increase in LDL-c may not be clinically relevant, however further data is required before these agents could be strongly recommended as an alternative to, or adjunct to, standard statin or fibrate therapy.

Methods:

A MEDLINE Ovid search was conducted using all lipid lower agents including: hyperlipidemia, hypercholesterolemia, cardiovascular disease, hydroxyl-3-methyglutaryl coenzyme A (HMG COA) reductase inhibitors, statin, ezetimibe, fibrates, nicotinic acid, niacin, bile acid sequestrant (BAS) and omega-3 fatty acids.

The search was limited to randomized controlled trials and meta-analysis, English language, and to studies conducted in humans from May 2012 to present. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic reviews:

Agency for Healthcare Research and Quality:
At the time of this review, a draft AHRQ review comparing the benefits and harms of combination of statin and other lipid-modifying medication to intensification of statin monotherapy was available, including studies through January 2013.[1] Studies in adults with moderate or high cardiovascular disease risk were included. Fifty-eight RCTs were included in the analysis. The strength of evidence was overall variable across comparisons. Only one comparison had high strength of evidence for serious adverse events and nine comparisons had moderate strength of evidence for LDL and HDL outcomes. All other comparisons and outcomes had low or insufficient evidence, including clinical outcomes of mortality, acute coronary events, and revascularization procedures. Other conclusions related to LDL and HDL outcomes are defined below:

Bile acid sequestrants plus statin therapy
- There is moderate quality evidence that combination therapy with bile acid sequestrants and low potency statin therapy lowers LDL cholesterol up to 14% more compared to intensification of statin monotherapy.
- There was insufficient evidence to compare combined bile acid sequestrant and statin therapy with statin monotherapy on the rates of serious adverse events.

Ezetimibe plus statin therapy
- There is moderate quality evidence that combination therapy with ezetimibe in combination with mid potency statin improves LDL-c compared to high potency statin monotherapy and low quality evidence that it improves HDL-c compared with statin monotherapy.
- There is high quality evidence that high potency statin m monotherapy produces fewer serious adverse events than combination of mid potency statin with ezetimibe.
- In patients with preexisting coronary heart disease and in patients with diabetes, there is moderate quality evidence that ezetimibe in combination with mid potency statin more effectively lowers LDL and low quality evidence for raising HDL as compared to high potency statin monotherapy.

Fibrate plus statin therapy
- There is moderate quality evidence that high potency statin monotherapy lowers LDL up to 15% more than mid potency statin in combination with fibrate.
- Moderate quality evidence demonstrates that mid potency statin in combination with fibrate raises HDL up to 10% more than high potency statin monotherapy.

- There is insufficient evidence to compare fibrate plus statin combination therapy to statin monotherapy on the rates of serious adverse events.

Niacin plus statin therapy
- There is low quality evidence that high potency statin monotherapy lowers LDL up to 12% more than mid potency statin in combination with niacin.
- There is low quality evidence that mid potency statin in combination with niacin raises HDL more than high potency statin monotherapy.
- There is insufficient evidence to compare the combination of niacin and statin to statin monotherapy on the rates of serious adverse events.

Omega-3 Fatty Acid plus statin therapy
- There is insufficient evidence to compare the benefits or serious adverse events of combined lipid-modifying therapy with an omega-3 fatty acid and statin to statin monotherapy on LDL-c and HDL-c, regardless of statin potency.

The authors concluded that the evidence suggests that some combination therapy regimens may confer benefits with respect to lowering LDL levels, including bile acid sequestrants and ezetimibe. However, intensification of statin monotherapy provided benefits or showed little difference with respect to LDL lowering in comparison to combination therapy with fibrates or niacin. There is insufficient evidence to address whether LDL lowering benefits achieved with these medications leads to decreased rates of CV disease. The evidence suggests that providers should tailor therapy based on individual patient needs and concerns for adverse events.

Zhou et al:
A recent systematic review and meta-analysis of RCT's evaluated the effects of fibrate therapy on stroke.[3] Studies were reviewed by 2 authors and quality was assessed using the Jadad score. The analysis included 10 RCTs consisting of 37,791 patients. Pooling the trials showed that fibrate therapy had no effect on the risk of stroke (RR 1.02; 95% CI 0.90 to 1.16). Six trials demonstrated no evidence that fibrate therapy protected against fatal stroke (RR 0.790; 95% CI 0.51 to 1.23) with little heterogeneity. An inverse relationship between total cholesterol lowering and incidence of stroke was observed. Subgroup analysis showed that gemfibrozil therapy was associated with a statistically significant difference on the risk of stroke (RR 0.72; 95% CI 0.53 to 0.98, p=0.04), however this was based on a small subset of patients. Study participants included those with a history of stroke, diabetes, myocardial infarction, coronary disease, or high levels of cholesterol.

Lavigne, et al.:
A systematic review assessed the efficacy of niacin for reducing CVD events.[18] A literature search identified 11 RCTs reporting clinical CVD event data with a minimum of 6 months of follow-up. The quality of each study was assessed using the Jadad scale. The primary analysis looked at the effect of niacin, as monotherapy or as adjunctive treatment, on the composite endpoint of any CVD event (cardiac death, nonfatal MI, hospitalization for acute coronary syndrome, stroke, or revascularization procedure). Overall, the primary composite endpoint of any CV event was significantly less frequent in niacin-treated patients compared with controls (OR 0.66; 95% CI 0.49-0.89; p=0.007, I2=59%). There was no significant difference in stroke risk (OR 0.88; 95% CI 0.5 to 1.54; p=0.65). There was no significant difference in CVD events when analysis was limited to studies in which treatment and control arms differed only with respect to the addition of niacin therapy. Results need to be interpreted with caution as there were significant differences between studies, including comparators, dosing, and population characteristics.

Kotwal, et al.:
Another systematic review evaluated the effect of omega3 fatty acids on CV outcomes.[19] Two investigators reviewed all abstracts and the quality of the studies was assessed using the Jadad criteria. The primary outcome was a composite of CV events (MI, stroke, and CV death). A total of 20 studies were included in a meta-analysis, with a total of 62,851 patients. Twelve studies showed no benefit of omega 3 fatty acids on the primary outcome (RR 0.96, 95% CI 0.90-1.03; p=0.24; I2=47.2%). The definition of composite CV outcome differed slightly between studies. Treatment with omega 3 fatty acids did show to protect against vascular death (RR 0.86, 95% CI 0.75-0.99; p=0.03) but not against sudden death. There was no evidence that treatment with omega 3 fatty acids reduced total mortality or nonvascular mortality. The use of omega-3 fatty acids was associated with an increased risk of side effects (RR .18; 95% CI 1.02-1.37; p=0.03) which were mainly gastrointestinal in nature.

Horizon Scan:
A recent AHRQ Horizon Scan report identified 2 cholesterol ester transfer protein inhibitors currently in Phase III trials for lipid management in coronary artery disease.[20] One human monoclonal antibody for the treatment of hypercholesterolemia is also being studied to decrease CV events in those with hypercholesterolemia.

New Guidelines:
American Diabetes Association (ADA):
The ADA recommendations state combination therapy for lipid-lowering has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended (level A recommendation).[21] The guidelines state that nicotinic acid has been shown to reduce CVD outcomes, but the study was done in a nondiabetic cohort and gemfibrozil has been shown to decrease rates of CVD in patients without diabetes. In one large trial specific to diabetic patients, fenofibrate did not reduce overall cardiovascular outcomes.

Canadian Cardiovascular Society:
The 2009 Canadian Cardiovascular Society Dyslipidemia guidelines have been updated using the GRADE system for recommendations and process.[22] This update recommends using apolipoprotein B or non-HDL cholesterol as alternate lipid markers and introduces the concept of cardiovascular age. No new recommendations on nonstatin pharmacotherapy were made in the 2012 update. Authors state that no studies have demonstrated a decrease in CVD event rate with the addition of lipid modulating drugs to statin therapy. For subjects who do not tolerate statin therapy, favorable LDL effects can be achieved with ezetimibe, bile acid sequestrants, or niacin.

The Endocrine Society Clinical Practice Guidelines:
Clinical practice guidelines were developed for hypertriglyceridemia by an endocrine society task force.[7] The task force used the GRADE approach to develop recommendations. The guidelines recommend that a fibrate be used as a first-line agent for reduction of triglycerides in patients at risk of triglyceride-induced pancreatitis (low quality evidence). They suggest that three drug classes (fibrates, niacin, omega 3 fatty acids) alone or in combination with statins be considered as treatment options in patients with moderate to severe triglyceride levels (low quality evidence).

New Drug Evaluation: Icosapent Ethyl (Vascepa®)

FDA approved indications: ICP is an ethyl ester of eicosapentaenoic acid (EPA) indicated as an adjunct to dietary therapy in the treatment of adult patients with severe hypertriglyceridemia (>500 mg/dL).

Clinical Efficacy Data:
Two pivotal Phase 3, placebo controlled, randomized, double blind trials (MARINE and ANCHOR) led to the approval of Vascepa™ (icosapent ethyl), an omega-3 fatty acid product that is ≥96% EPA, by the FDA on July 26th of 2012. ICP is approved for the treatment of hypertriglyceridemia at a dose of 2g twice daily to be used as an adjunct to diet and exercise in patients with very high TGs (≥500 gm/dL).[23,24] The MARINE and ANCHOR trials looked at two distinctly different populations of patients with differing degrees of hypertriglyceridemia.[23–25]

MARINE Trial
The MARINE trial was evaluated as being of poor-fair quality due to lack of transparency in the randomization and blinding process, short duration and lack of relevant clinical endpoints. This a phase 3, multi center, placebo-controlled, randomized, double-blind study examined patients with TG levels ranging from 500-2000 mg/dL, with or without background statin therapy, who were placed on 4 g QD ICP, 2g QD ICP or placebo for a duration of 12 weeks with a 40 week open label extension period.[23] Patients were predominantly Caucasian and male, 88% and 76% respectively, with a mean age of 52.9+/-9.34 years, and a mean BMI of 30.8+/-4.25 kg/m^2. 28% of patients were diabetic, 25% of patients were on a statin. The primary endpoint for the MARINE trial was placebo-corrected median percentage of change in TG from baseline to week 12 (study end). There was a statistically significant decrease in TGs in the Intent-to-treat (ITT) population; however there was no mention of how missing data was treated (i.e. last observation carried forward, mean of available values etc.). Results showed a significant percent placebo corrected decrease in TGs from baseline in both the 2 g daily and the 4 g daily groups (-19.7 and -33.1 $p<0.01$ for both). The change in LDL-c and HDL-c was non-significant in both cases. The results of the MARINE study showed that ICP is effective at decreasing TGs without the statistically significant LDL-c increase seen with other fish oil products but there is no efficacy data regarding whether this drug prevents pancreatitis or CV events. The ICP 4 g daily dose is what the FDA has approved (2 g BID) and this dose resulted in a greater mean % change from baseline with all study endpoints than the 2 g daily doses though not all of the differences were statistically significant.

ANCHOR Study
The ANCHOR study was a fair quality study due to lack of relevant clinical endpoints, a change in inclusion criteria part-way through the trial, low external validity due to primarily white cohort, and low internal validity due to lack of transparency with blinding, treatment allocation, non-adherence and contamination.[24] This phase 3, multi center, placebo-controlled, randomized, double-blind study looked at patients with TG levels ranging from 200-500 mg/dL despite being at their LDL-c goal with background statin therapy. Patients were placed on 4g QD ICP, 2g QD ICP or placebo for 12 weeks. The population in this trial was primarily Caucasian (96%), with a mean age of 61.4 years and mean BMI of 32.9kg/m^2, 73% of patients had diagnoses of diabetes mellitus, A1c range of 6.5-6.7% and the mean TG level was 259.0 mg/dL. Of the 702 patients who met the eligibility criteria and were randomized, 94.4% of patients completed the trial per protocol, 97.8% were included in the primary analysis, and 100% were included in the safety analysis. [24] This trial developed a protocol amendment after randomization had begun to facilitate enrollment: A1c was increased to >9.5% from 9.0%, the mean of 2 TG qualifying values was ≥185 ,g/dL with ≥1 or the 2 values ≥200 mg/dL, and the upper limit LDL-c was increased to ≤115 mg/dL.[25] Several subgroup analyses were conducted looking at various statin therapies, diabetes and degree of TG elevation. [24] Significant decreases in TG levels were seen with the 4g per day group taking simvastatin, atorvastatin and rosuvastatin as well as the patients in the 2 g per day group taking simvastatin. Higher baseline TG levels (≥289.5 mg/dL) appeared to result in greater TG decreases but

there was no significant difference in TG decrease in patients with diabetes or with low to moderate TG levels (<289.5).[12] Results showed a significant percent placebo corrected decrease in TGs from baseline in both the 2 g daily and the 4 g daily groups but the percent placebo corrected change in LDL-c and HDL-c from baseline was non-significant.[12] Results were assessed based upon an ITT basis and missing data was inputted using the last-observed-carried-forward method. The results of the ANCHOR study reinforce the results of the MARINE study in ICP's ability to decrease TG levels significantly without risk of increased LDL-c levels but as with the MARINE study, there is no data assessing the CV implications of this drug.

REDUCE-IT Study
The REDUCE-IT study is an ongoing trial looking at ICP in patients with TG levels between 150-500 mg/dL who are at high risk for CVD. The primary endpoint for this trial will be composite endpoint of CV death, MI, stroke, coronary revascularization, and hospitalization for unstable angina.[26] Whereas these endpoints are clinically relevant, there is no endpoint of pancreatitis and the patient population is not relevant for the indication of hypertriglyceridemia treatment in patients with serum TG levels ≥500 mg/dL. This trial is more likely an attempt to expand the indications of this drug rather than to illuminate its efficacy in prevention relevant clinical endpoints.

Data from the ICP clinical trials have demonstrated a significant decrease in TG levels without any LDL-c increase, however there are no published studies looking at this drug that have examined outcomes more directly related to patient long term survival, pancreatitis risk or CV events. The JELIS trial showed that EPA (EPA purity of >98%, similar to ICP purity of ≥96%) may have some promise in prevention of some CV events; however the significant limitations of this study beg further examination. Until more studies looking at ICP and its efficacy in relevant clinical outcomes such as pancreatitis and CV risk are completed, or until head-to-head superiority trials can be performed, it is difficult to determine the clinical efficacy of this drug.

<u>Clinical Safety:</u>
The pivotal trials, ANCHOR and MARINE, provide minimal safety outcomes data and are limited to the duration of the trials since there are no follow up safety analyses for these trials. In the short term safety analysis, patients experienced minimal side effects mostly involving GI symptoms and no serious side effects were associated with the study drug.[23,24] In the MARINE trial, 35% of the 4g group and 34% of the 2g group developed a treatment emergent adverse event and 37% of the placebo indicating no difference in incidence of adverse events in patients on the study drug.[11] The only adverse events that occurred in >3% of patients were diarrhea, nausea and eructation, all of which were more common in the placebo group with the exception of nausea which was more common in the 2g group, however it is unclear if these differences were significant. Four patients discontinued the study medication due to treatment emergent adverse events: 1 patient in the 2g group and 3 in the placebo group. Only 2 serious adverse events occurred; coronary artery disease and noncardiac chest pain, however the study investigators concluded that these events were unrelated to the study drug though no details are provided regarding this conclusion. There were no significant changes in vital signs, ECG parameters, ALT/AST, or creatinine kinase in either of the study groups. The ANCHOR trial showed only one adverse event, arthralgia, that occurred in more than 3% of patients with increased incidence in the study groups when compared to placebo, all other adverse events (diarrhea, nausea and nasopharyngitis) were more common in placebo. An important note here is that arthralgia was not a dose dependent adverse event and it was not observed in the MARINE trial, and the ANCHOR trial patient baseline characteristics were outside of the current FDA indications of TG levels >500 mg/dL therefore this adverse event requires further study.

The integrated summary of safety data from Amarin Pharma (May 2012) was derived from 15 clinical studies: 2 phase 1 studies in healthy subjects; 2 phase 3 clinical studies in hypertriglyceridemic patients (MARINE and ANCHOR); 3 drug interaction studies and 8 clinical studies in patients with CNS disorders which are no longer under development due to lack of efficacy.[25] Patients included in the dataset received doses of 0.5-4 g daily (particularly wide dose ranges) and took at least 1 dose of ICP during blinded and open label periods. 55.5% of patients reported all causality treatment emergent adverse events the most common

(occurred in ≥3% of patients) were: diarrhea (6.4%), depression (3.7%), falls (3.7%) and nausea (3.3%). Most treatment emergent adverse events were mild to moderate and considered unrelated to treatment and 4.5% of patients reported a serious adverse event. Most commonly reported adverse events were as follows: non-cardiac chest pain (0.3%), aggression (0.2%), depression (0.2%), psychotic disorder (0.2%), overdose of dothiepin (0.2%), irritability (0.2%), and CAD (0.2%). There were 3 serious adverse events that occurred in the CNS population (there was no information regarding the reason for looking at this population; however omega 3 fatty acids are occasionally used by the psychiatric community to treat depression) that were considered to be treatment related: completed suicide, subdural hematoma and iron deficiency though there were no percentages reported.[14] Two deaths occurred in patients taking ICP, one was a completed suicide in a Huntington's disease patient taking 2 g/day that was considered possibly related and an accidental dothiepin overdose in the 1 g per day group that was determined to be unrelated to treatment. 2.9% of patients reported treatment emergent adverse events that led to discontinuation of the study drug; however there were no individual events that occurred in >1% of patients. When the hypertriglyceridemia placebo controlled integrated data set was examined, a total of 622 patients were treated with ICP and 309 patients received placebo and the incidence of all cause treatment emergent adverse events was reported in 45.8% of ICP patients and 48.9% of placebo patients.[14] Most common side effects (occurring in ≥3% of patients) were: diarrhea (3.7% ICP, 3.9% placebo), nausea (2.6% ICP, 3.9% placebo), and arthralgia (2.6% ICP, 1.3% placebo). There were no significant differences in the subgroups of gender, race, smoking status, age, statin use or alcohol use in the overall integrated summary of safety and there were no dose related trends observed in the incidence of patients with treatment emergent adverse events (TEAEs), treatment related TEAEs, serious adverse events or TEAEs leading to discontinuation.[14] In the hypertriglyceridemia placebo controlled integrated dataset, there were no significant differences in TEAEs in patients due to vital signs, laboratory values, gender, age, race, smoking status or alcohol use.[14] In addition there was no significant increase in fasting plasma glucose, or A1c in diabetic patients when compared with placebo.[14] There was no indication of any increased risk of bleeding with ICP compared to placebo. Liver transaminase levels and cutaneous adverse reactions were similar in both the treatment group and placebo and the incidence was small in both groups.

Overall, ICP was well tolerated and no serious adverse events were significantly associated with the study drug in either of the pivotal trials, MARINE or ANCHOR, other than arthralgia which was seen in some of the phase II trials described in the integrated data set but the current evidence is not sufficient to conclusively attribute this to ICP and will require further investigation.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1. Acute Pancreatitis
2. CV events
3. Hospitalizations
4. Mortality

Primary Study Endpoints:

1. TG levels (% change from baseline to week 12)

Secondary Endpoints:

2. LDL, VLDL, HDL, non-HDL, ApoB, Lp-PLA_2, and C reactive protein % change from baseline to week 12
3. Incidence of adverse events
4. Change in laboratory, vitals and physical assessments.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N=229 patients	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns

MARINE Trial Phase III RCT, DB, MC, PC 12 weeks with an open extention	1. ICP 4 g daily 2. ICP 2 g daily 3. Placebo Permitted concomitant medications: Antihypertensive, antidiabetes drug therapies, tamoxifen, estrogens, and progestins as long as doses were stable ≥4 weeks before screening and were unchanged throughout the study. Statins with or without ezetimibe but only if patient was deemed high risk of CHD Duration: 4-6 week lead-in period followed by a 2-3 week qualifying period. 12 week safety and efficacy period with a 40 week open label extension with all patients getting 4 g daily.	**Demographics (4g/2g/placebo):** Age (yrs) mean: 51.9/53.4/53.4 Age <65 yrs (%): 91/92/93 Men (%): 77/76/76 White (%): 87/88/90 BMI mean (kg/m^2): 30.4/30.8/31.0 Statin use (%): 26/25/24 Baseline TG >750 mg/dL (%): 38/38/42 Diabetes mellitus (%): 29/26/28 **Inclusion Criteria:** ->18 years old -willing to maintain a stable diet -willing to maintain normal current physical activity level -TG ≥500 mg/dL and ≤2000 mg/dL **Exclusion Criteria:** -women who were pregnant or planning to become pregnant or breastfeeding -women of childbearing potential not willing to use accepted birth control methods throughout study -history of pancreatitis BMI >45 kg/m^2 -weight change >3 kg during lead in period -Hgb A1c >9.5% (Patients with diabetes were required to be on stable therapy) -History of stroke /MI/life threatening arrhythmia -TSH >1.5 X ULN or Hx of hypothyroidism or hyroid hormonal therapy not stable for ≥6 weeks before screening -AST/ALT >3xULN or elevated CK -Hx of gall stone within 1 year without cholecystectomy Known nephritic syndrome or >3g daily proteinuria	**Randomized: (4g/2g/placebo)** 77/76/76 **ITT:** 76/73/75 **PP:** 74/70/71 **Attrition (%):** 3.9/7.9/6.6	**No Relevant endpoints linked to patient outcomes** Primary study Endpoint: Placebo corrected median percentage of change in TG from baseline to week 12 I 4g: -33.1%* I 2g:-19.7%^ P<0.0001* P<0.01^	 NA NA	Safety Endpoints Any treatment emergent adverse event I 4g:35% I2g:34% P: 37% No p values provided Patients discontinued drug due to treatment related adverse event I 4g: 0% I 2g: 1.3% P: 3.9% No p values provided	 NA NA	**Quality Rating: Poor-fair** **Internal Validity: RoB** Selection: Patients participated in a 4-6 week lead-in and a 2-3 week qualifying period in which disease state was assessed. There was a 12 week safety and efficacy period which was followed by an open label 40 week extension. Randomization was not described in the text and there were no supplemental materials provided. Baseline characteristics were similar. Performance: No details regarding dosage forms, cross-over or contamination. Detection: Patients and investigators were blinded per statement that study was double blinded but treatment allocation methodology was not specified. Unclear if data analysis group was blinded as well. Attrition: Attrition rates appear to be similar between the groups. The 4 g subgroup was 3.9% but the 2g and placebo groups were 7.9% and 6.6% respectively. Overall attrition was 6.11% which was acceptable as other omega 3 studies looking at hypertriglyceridemia have attrition rates ranging between 1% and 17%. **External Validity:** Recruitment: Not reported. Multicenter study took place in 10 countries. Patient Characteristics: 76% male 86% white 92% <65 yrs old Mean age 52.9 +/- 9.34 Setting: 4-6 week lead in and 2-3 week qualifying periods prior to randomization. Outcomes Significance was set at p=0.01 for the primary endpoint Primary endpoint: placebo corrected median TG % change from baseline Not linked to patient centered outcomes such as fewer hospitalizations, CV data, and incidence of acute pancreatitis or morbidity/mortality. **Statistical Analysis:** STD of 45% in TG measurements and p<0.01 significance level required a sample size of 69 completed patients per treatment group to provide ≥90% power to detect a difference of 30% between treatment and placebo. Primary efficacy analysis was performed using a Wilcoxon rank sum test with the Hodges-Lehmann median and interquartile range.

ANCHOR Trial Phase III RCT, DB, MC, PC	1. ICP 2 g BID 2. ICP 1 g BID 3. Placebo Permitted Concomittant Medications: Atorvastatin, rosuvastatin, simvastatin and ezetimibe. No statement regarding medications allowed for other comorbidities. Duration: A 4-6 week lead in period followed by a 2-3 week qualifying period followed by a 12 week double blind period	**Demographics: (4g/2g/placebo):** Age (yrs mean) 61.1/61.8/61.2 Men (%) 39/40/37 White (%) 97/96/96 BMI (kg/m^2 mean) 32.7/32.9/33.0 Diabetes(%) 73/73/73 A1c (value % n=226/234/227) ** 6.6/6.7/6.5 Statin use Atorvastatin (%) 19/18/19 Simvastatin (%) 58/58/57 Rosuvastatin (%) 24/24/24 Statin efficacy regimens Lower (%) 7/7/6 Medium (%) 64/63/62 Higher (%) 30/30/32 **Inclusion Criteria:** >18 years old, at high risk for CVD per NCEP ATPIII guidelines, willing to maintain stable diet and exercise routine, by first TG qualifying visit > 4 weeks stable statin therapy with optimal LDL potential (>40 mg/dL and <100 mg/dL), TG value ≥200 mg/dL and <500 mg /dL**. **Exclusion Criteria:**** A1c>9.5%, LDL≥115 mg/dL, BMI>45 kg/m^2, weight change of >3 kg from the first visit to the end of the qualifying period, non-HDL <100 mg/dL, proteinuria >3g/day, malignancy, bariatric surgery, long term treatment with antihypertensive and antidiabetic medications, treatment with weight loss drugs, TSH >1.5 x ULN, ALT/AST >3xULN, unexplained creatinine kinase concentrations >3xULN or elevated CK due to known muscle disease. **Demographics were different at the beginning of the trial as there was a follow up change in exclusion criteria to "facilitate enrollment" after the beginning of randomization. A1c, LDL, TG criteria changed. This number is the final criteria.	**Randomized: (4g/2g/placebo)** 233/236/233 **ITT:** 226/234/227 **PP:** 221/225/217 **Attrition (%):** 5.15/4.66/6.86	**No Relevant endpoints linked to patient outcomes**** **Primary study endpoint:** Median placebo adjusted % change in TG levels from baseline to week 12. I 4g: -21.5%* I 2g:-10.1%^ P<0.0001* P=0.0005^	NA NA	**Safety Endpoint:** Any treatment emergent adverse event during double blind treatment period I 4g:45.5% I2g:44.9% P: 48.1% No p values provided Patients discontinued drug due to treatment related adverse event I 4g: 2.14% I 2g:1.69% P: 3.43% No p values provided Arthralgia: I 4g:1.7% I 2g:3.4% P:0.4%	NA NA	**Quality Rating: Poor-Fair** **Internal Validity: RoB** Selection: Patients participated in a 4-6 week lead-in and a 2-3 week qualifying period and there was a 12 week double blind period. Randomization was not described in the text and there were no supplemental materials provided. Baseline characteristics were similar. Performance: No details regarding dosage forms, cross-over or contamination Detection: Patients and investigators were blinded per statement that study was double blinded but treatment allocation methodology was not specified. Unclear if data analysis group was blinded as well. Attrition: The 4 g subgroup was 5.15% but the 2g and placebo groups were 4.66% and 6.86% respectively. Attrition rates appear to be similar. Overall attrition was 5.56% which was acceptable as other omega 3 studies looking at hypertriglyceridemia have attrition rates ranging between 1% and 17%. **External Validity:** Recruitment: Not reported. This was a multi center study taking place in 97 sites across the US. Patient Characteristics: White 96% Male 61% mean age of 61.4 years Setting: 4-6 week lead in and 2-3 week qualifying periods prior to randomization. Outcomes Primary endpoint: TG median placebo adjusted % change from baseline. Not linked to patient centered outcomes such as fewer hospitalizations, CV data, incidence of acute pancreatitis or morbidity/mortality. The study population was not the population of interest for this medication and therefore renders the data from this study somewhat irrelevant. **Statistical Analysis:** STD of 45% in TG measurements and p<0.05 significance level required a sample size of 194 completed patients per treatment group to provide ≥90.6% power to detect a difference of 15% between treatment and placebo and an 80% power to demonstrate non-inferiority with a significance level of p<0.025 of the LDL response between treatment and placebo. Using a Shapiro-Wilk test, p<0.01, the median and interquartile range would be calculated for each treatment group and median differences and Hodges-Lehmann 2 tailed 95% CI would be calculated for each comparison between treatment and placebo. Nonparametric analysis p values were planned using Wilcoxon rank-sum test for each comparison.

References:

1. Agency for Healthcare Research and Quality. Update of Comparative Effectiveness of Lipid-Modifying Agents. Draft Comparative Effectiveness Review. Rockville, MD. 2013.

2. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106(25):3143-421. PMID: 12485966.

3. Zhou Y-H, Ye X-F, Yu F-F, et al. Lipid management in the prevention of stroke: a meta-analysis of fibrates for stroke prevention. *BMC Neurol*. 2013;13:1. doi:10.1186/1471-2377-13-1.

4. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2008;51(15):1512–1524. doi:10.1016/j.jacc.2008.02.034.

5. Hulley SB, Rosenman RH, Bawol RD, Brand RJ. Epidemiology as a guide to clinical decisions. The association between triglyceride and coronary heart disease. *N Engl J Med*. 1980;302(25):1383–1389. doi:10.1056/NEJM198006193022503.

6. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*. 2007;115(4):450–458. doi:10.1161/CIRCULATIONAHA.106.637793.

7. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(9):2969–2989. doi:10.1210/jc.2011-3213.

8. Murad MH, Hazem A, Coto-Yglesias F, et al. The association of hypertriglyceridemia with cardiovascular events and pancreatitis: a systematic review and meta-analysis. *BMC Endocr Disord*. 2012;12:2. doi:10.1186/1472-6823-12-2.

9. ACCORD Study Group, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1563–1574. doi:10.1056/NEJMoa1001282.

10. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366(9500):1849–1861. doi:10.1016/S0140-6736(05)67667-2.

11. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317(20):1237–1245. doi:10.1056/NEJM198711123172001.

12. Tenkanen L, Mänttäri M, Kovanen PT, Virkkunen H, Manninen V. Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. *Arch Intern Med*. 2006;166(7):743–748. doi:10.1001/archinte.166.7.743.

13. AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial. *Am Heart J*. 2011;161(3):538–543. doi:10.1016/j.ahj.2010.12.007.

14. Maki KC, Lawless AL, Kelley KM, et al. Effects of prescription omega-3-acid ethyl esters on fasting lipid profile in subjects with primary hypercholesterolemia. *J Cardiovasc Pharmacol*. 2011;57(4):489–494. doi:10.1097/FJC.0b013e318210fca5.

15. Itakura H, Yokoyama M, Matsuzaki M, et al. The change in low-density lipoprotein cholesterol concentration is positively related to plasma docosahexaenoic acid but not eicosapentaenoic acid. *J Atheroscler Thromb*. 2012;19(7):673–679.

16. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369(9567):1090–1098. doi:10.1016/S0140-6736(07)60527-3.

17. Sasaki J, Yokoyama M, Matsuzaki M, et al. Relationship between Coronary Artery Disease and Non-HDL-C, and Effect of Highly Purified EPA on the Risk of Coronary Artery Disease in Hypercholesterolemic Patients Treated with Statins: Sub-Analysis of the Japan EPA Lipid Intervention Study (JELIS). *J Atheroscler Thromb*. 2012;19(2):194–204.

18. Lavigne PM, Karas RH. The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression. *J Am Coll Cardiol*. 2013;61(4):440–446. doi:10.1016/j.jacc.2012.10.030.

19. Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 Fatty acids and cardiovascular outcomes: systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2012;5(6):808–818. doi:10.1161/CIRCOUTCOMES.112.966168.

20. ECRI Institute. AHRQ Healthcare Horizon Scanning System Status Update. (Prepared by ECRI Institute under Contract No. HHSA290201000006C) Rockville, MD: Agency for HEalthcare Research and Quality. July 2013. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

21. American Diabetes Association. Standards of medical care in diabetes--2013. *Diabetes Care*. 2013;36 Suppl 1:S11–66. doi:10.2337/dc13-S011.

22. Anderson TJ, Grégoire J, Hegele RA, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol*. 2013;29(2):151–167. doi:10.1016/j.cjca.2012.11.032.

23. Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). *Am J Cardiol*. 2011;108(5):682–690. doi:10.1016/j.amjcard.2011.04.015.

24. Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). *Am J Cardiol*. 2012;110(7):984–992. doi:10.1016/j.amjcard.2012.05.031.

25. Vascepa™ (icosapent ethyl) Capsules AMCP Dossier.pdf. 10/17/2012. Provided by Amarin Pharma Inc.

26. Amarin Pharma Inc. A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia and on Statin. The Primary Objective is to Evaluate the Effect of 4 g/Day AMR101 for Preventing the Occurrence of a First Major Cardiovascular Event. (REDUCE-IT). Available from: http://clinicaltrials.gov/ct2/show/study/NCT01492361. Accessed 2/7/13.

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

PHARMACOKINETICS[25,26]

Parameter	Result
Oral Bioavailability	Not described
Volume of distribution	88L
Protein Binding	>99%
Excretion	Not renally excreted,
Plasma elimination Half-Life	~89 Hours
Metabolism	Mainly hepatic via beta-oxidation with some minor Cyp 450
Time to peak plasma concentration	5 hours

DOSE & AVAILABILITY[25,26]

STRENGTH	ROUTE	FREQUENCY	DOSAGE FORM:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
1 Gram	By Mouth	2 capsule Twice daily	1 g oral liquid gel capsule	No dosage adjustments provided in manufacturer's labeling	No dosage adjustments provided in manufacturer's labeling	No studies have been conducted in children	Refer to adult dosing	Drug is not renally eliminated Monitoring of ALT and AST is recommended in patients with hepatic impairment.

DRUG SAFETY[25,26]

Contraindications: Hypersensitivity/anaphylactic reaction to ICP or any component of the formulation

Black Box Warning/REMS: N/A

Warnings and Precautions:

- Hypersensitivity reactions: Ethyl esters of EPA obtained from fish oil. Cross sensitivity to fish or shell fish is unknown. Use with caution in patients with these allergies

- Hepatic function impairment: monitor ALT and AST periodically
- Fertility impairment: ethyl EPA caused some infertility in rats but no human examples. BSA based dosing in rats was 7 times the human systemic exposure with 4 g per day. Pregnancy Category C. Lactation safety undefined-excreted in breast milk use caution.
- Children: Not defined
- Elderly: 33% of patients studied in clinical trials were 65 years old or greater and no difference in safety or effectiveness was observed in these patients.
- Concomitant use of drugs that may exacerbate hypertriglyceridemia should be avoided (i.e. beta blockers, thiazides, estrogen)
- Risk of prolonged bleeding time has been reported with omega-3 fatty acids therefore patients on drugs affecting platelet aggregation and coagulation should be closely monitored
- Appropriate use: ICP should be used as an adjunct to diet and exercise modifications and only in patients with TGs exceeding 500 mg/dL. Secondary causes of hypertriglyceridemia should be ruled out prior to initiating therapy.
- The effects of ICP risk of pancreatitis and CV morbidity and mortality in patients with severe hypertriglyceridemia is unknown.

Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Class Update: Parkinson's Drugs

Month/Year of Review: September 2013
PDL Class: Parkinson's Drugs
Literature Search End Date: July 2013

Date of Last Review: February 2012
Source Document: OSU College of Pharmacy

Current Preferred Agents	Current Non-Preferred Agents
Anticholinergics	
Benztropine tablets	
Trihexyphenidyl tablets/elixir	
COMT* Inhibitors	
Entacapone tablets	Tolcapone (Tamsar®) tablets
Dopaminergic Agents	
Carbidopa/Levodopa tablets	Carbidopa/Levodopa ER tablets
Dopamine Agonists	
Amantadine capsules/syrup/tablets	Bromocriptine (Parlodel®) tablets/capsules
Pramipexole DI-HCL tablets	Ropinirole (Requip®) IR and XL tablets
MAO- B** Inhibitors	
Selegiline capsules	Rasagaline (Azilect®) tablets
Combination Product	
	Carbidopa/Levodopa/Entacapone

*COMT = Catechol-O-methyl transferase; **MAO-B = Monoamine oxidase B

Previous Recommendations:

- Replace tolcapone with entacapone on the preferred drug list (PDL) due to reported liver toxicity with tolcapone.
- Evidence does not support a difference in efficacy/effectiveness
- Correct PDL to include amantadine as preferred.

PA Criteria: All non-preferred agents require prior authorization to cover preferred products when feasible for covered diagnosis (Appendix 1). OHP does not cover treatment for restless leg syndrome.

Recommendations:

- No further research or review needed at this time.
- Evaluate comparative costs in executive session.

Methods:
A MEDLINE OVID search was conducted using all treatments for Parkinson's Disease (PD) and limited to randomized controlled trials (RCTs) and meta-analysis, English language, and conducted in humans since the date of the literature search conducted for the previous OHA P & T review. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New drugs:
None

New FDA Indications:
None

New FDA safety alerts:
None

New Systematic Reviews:
Since the last review, there were two indirect meta-analyses conducted comparing rasagiline with selegiline by Jost WH et. al[4] and rasagiline versus placebo by Minguez-Minguez S et.al.[5](Appendix 3). Both of these relied entirely on indirect comparisons. Due to unknown quality of the trials, lack of information about the studies, the authors' conclusions should be interpreted with some caution.

The analysis by Jost WH et. al. compared the symptomatic efficacy and safety of selegiline vs. rasagiline in both mono- and combination therapy. Six randomized controlled studies on rasagiline and 15 on selegiline were included in the analysis. The analysis used a fixed effects model based on standardized mean differences for efficacy criteria and risk differences of safety outcomes. As outcomes, Unified Parkinson's Disease Rating Scale (UPDRS) (primary) and UPDRS motor functions, mental and Activity of Daily Life (ADL), the Schwab and England scale, the off-time as well as safety as secondary outcomes were used. Rasagiline showed a statistically significant advantage in the primary endpoint of UPDRS total scores (monotherapy: $p = 0.048$, sensitivity analysis: $p = 0.023$; pooled analyses: $p = 0.043$, sensitivity analysis $p = 0.014$) and the secondary endpoint UPDRS motor functions (monotherapy: $p = 0.049$, sensitivity analysis $p = 0.031$; pooled analyses: not significant, sensitivity analysis: $p = 0.046$). For the other secondary outcome parameters, a numerical advantage for rasagiline was found. Discontinuation rates due to adverse effects showed a tendency in favor of rasagiline, but not statistically significant. Risk for adverse events such as

dizziness, hallucinations, diarrhoea and syncope were lower with rasagiline than selegiline (each $p < 0.15$). As there were few trials with combination therapy available, and all had duration of 3 months, analysis of these studies was not conducted. The authors concluded rasagiline showed a statistically significant and clinically relevant advantage over selegiline in the primary endpoint. The superiority of rasagiline was further substantiated with advantages in tolerability and safety.

A Similar analysis by Minguez-Minguez S et.al. compared the efficacy of rasagiline versus placebo for decreasing Parkinson's Disease (PD) symptoms. UPDRS for rasagiline monotherapy and reduction in off-time for combined treatment were the outcomes assessed. Rasagiline monotherapy, in early stages of the disease, reduces the UPDRS score [-3.06 (95% CI -3.81 to -2.31, p<0.00001) with rasagiline 1mg/day]. In combination with levodopa, 1mg/day of rasagiline reduced off-time [-0.93h (95% CI -1.17 to -0.69, p<0.00001)]. However, although rasagiline reduces the UPDRS score [-0.89 (95% CI from -1.78 to 0, p=0.05)] in trials with a delayed-start design, authors found a disagreement between studies and doses, making it difficult to interpret this result. The authors concluded the results confirmed the efficacy of rasagiline in PD, but the clinical significance of these data remained to be established. Furthermore, the delayed-start study design did not establish with certainty the neuroprotective effect of rasagiline.

Guidelines:
National Guideline Clearinghouse (NGC) released treatment guidelines (Appendix 4) on early (uncomplicated) Parkinson's Disease. This guideline is an updated version of the therapeutic management of Parkinson's disease by the joint task force of the European Federation of Neurological Societies and the Movement Disorder Society-European Section.[6] Agents available in the US that carried **level A** recommendation for controlling PD's symptoms including Levodopa IR and CR, pramipexole, ropinirole IR and CR, selegiline and rasagliline. Levodopa also has **level A** recommendation as the most effective symptomatic antiparkinsonian drug, however after a few years of treatment, levodopa is frequently associated with the development of motor complications. As older patients are more sensitive to neuropsychiatric adverse reactions and are less prone to developing motor complications, the early use of levodopa is recommended in the older population (Good Practice Point). The early use of controlled release levodopa formulations is not effective in the prevention of motor complications (**Level A**). The guidelines also included the potential harms associated with each class of drugs. The guidelines recommended gradual discontinuation of anthicholinergics with caution due to abrupt withdrawal may lead to a rebound effect with marked deterioration of parkinsonism. COMT inhibitors increase levodopa bioavailability, so they can increase the incidence of dopaminergic adverse reactions, including nausea, and cardiovascular and neuropsychiatric complications. Side effects such as nausea, vomiting, orthostatic hypotension, confusion, psychosis, and somnolence may occur with administration of any of dopamine agonists and other active dopamine-mimetic medications. Peripheral leg edema is also commonly observed with most agonists. Hallucinations and somnolence are more frequent with some agonists than with levodopa, even in healthy subjects, in the case of somnolence. Side effects such as nausea, vomiting, orthostatic hypotension, confusion, psychosis, and somnolence may occur with administration of any of dopamine agonists and other active dopamine-mimetic medications. Peripheral leg edema is also commonly observed with most agonists. Hallucinations and somnolence are more frequent with some agonists than with levodopa, even in healthy subjects, in the case of somnolence. Impulse-control disorders have recently been identified as a common adverse drug reaction to dopamine agonists. Prevalence ranges between 5% and 15% depending on the author. The principal risk factor is treatment with dopamine agonists, although they can occur on levodopa as well. Personal traits, disturbed decision-making abilities, and younger age have also been implicated. Comorbidities, cognitive impairment, disease severity, and polytherapy are sometimes also mentioned. Up to the present there is no evidence about between-agonists difference in the frequency of these events.

New Trials:
A total of 124 citations resulted from initial literature search. After inclusion for further review, eight were evaluated further and 3 potentially relevant comparative randomized trials were identified through abstract review for appropriate medication, indication, study design, and outcomes (Appendix 4). These trials are briefly described in table 1:

Study	Comparison	Population	Primary Outcome	Results
Mizuno Y et al.[1], 2012	Pramipexole ER (N = 56) vs. pramipexole IR (N= 56)	Patients with modified Hoehn and Yahr stage of 2 to 4; on levodopa.	No predefined primary outcome; secondary outcomes include: unified Parkinson's Disease Rating Scale (UPDRS); percentage of off-time, actual off-time, and percentage of on-time without troublesome dyskinesia during waking hours; and L-dopa daily dose.	UPDRS parts II + III scores decreased significantly from baseline and to a similar degree with pramipexole ER and IR formulations. Both groups reported 83.9% reported adverse events, requiring withdrawal of 3 (5.4%) of ER pts and 2(3.6% IR patients
Chaudhuri R et al.[2], 2012	Ropinirole PR (N = 198) vs. placebo (N = 189)	Advanced PD; on levodopa.	Parkinson's Disease Sleep Scale (PDSS)	Pts with baseline PDSS ≤ 100 showed significant improvement with ropinirole PR vs. placebo in PDSS score from baseline to week 24 last observation carried forward (adjusted mean treatment difference 9.0% (95% CI: 2.76, 15.333; p = 0.0051); not significant in pts with baseline PDSS > 100.
Schapira, A. H. V et al.[3]	Pramipexole ER vs. pramipexole IR	Advanced PD; adjunctive therapy	Unified Parkinson's Disease Rating Scale; daily off-time.	At 32 weeks, the groups showed comparable improvements from DB baseline (pramipexole inception), including, on UPDRS II + III, adjusted mean (SE) changes of −14.8 (1.5) for IR-to-ER and −13.3 (1.6) for ER-to-ER. Rates of premature discontinuation owing to adverse events were 6.5% for IR-to-ER and 4.9% for ER-to-ER.

References:

1. Mizuno Y, Yamamoto M, Kuno S, et al. Efficacy and safety of extended- versus immediate-release pramipexole in Japanese patients with advanced and L-dopa-undertreated Parkinson disease: a double-blind, randomized trial. *Clin Neuropharmacol*. 2012;35(4):174–181. doi:10.1097/WNF.0b013e31825f77b9.

2. Ray Chaudhuri K, Martinez-Martin P, Rolfe KA, et al. Improvements in nocturnal symptoms with ropinirole prolonged release in patients with advanced Parkinson's disease. *European Journal of Neurology*. 2012;19(1):105–113. doi:10.1111/j.1468-1331.2011.03442.x.

3. Schapira AHV, Barone P, Hauser RA, et al. Success rate, efficacy, and safety/tolerability of overnight switching from immediate- to extended-release pramipexole in advanced Parkinson's disease. *European Journal of Neurology*. 2013;20(1):180–187. doi:10.1111/j.1468-1331.2012.03822.x.

4. Jost WH, Friede M, Schnitker J. Indirect meta-analysis of randomised placebo-controlled clinical trials on rasagiline and selegiline in the symptomatic treatment of Parkinson's disease. *Basal Ganglia*. 2012;2(4, Supplement):S17–S26. doi:10.1016/j.baga.2012.05.006.

5. Mínguez-Mínguez S, Solís-García Del Pozo J, Jordán J. Rasagiline in Parkinson's disease: A review based on meta-analysis of clinical data. *Pharmacol Res*. 2013;74C:78–86. doi:10.1016/j.phrs.2013.05.005.

6. National Guideline Clearinghouse | Early (uncomplicated) Parkinson's disease. Available at: http://www.guideline.gov/content.aspx?id=34899. Accessed July 17, 2013.

Appendix 1: Current PA Criteria

Anti-Parkinsons Agents

Goal(s):

- Cover preferred products when feasible for covered diagnosis. Preferred products are selected on evidence based reviews.
- OPH does not cover treatment for restless leg syndrome (Coverage line 624)

Length of Authorization: 12 months

Requires PA:

Non-preferred drugs

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis Parkinson's disease or another chronic neurological condition?	**Yes:** Go to #5.	**No:** Go to #3
3. Is the diagnosis Restless Leg Syndrome (ICD9-333.94)? *Baseline therapy is defined as being on ≥1 stable dose of an anti-epileptic(s) drug for at least 4 weeks.	**Yes:** Pass to RPH; Deny, (Not covered by OHP)	**No:** Go to #4
4. RPH only All other indications need to be evaluated as to whether they are above the line or below the line	**Above:** Go to #5	**Below:** Deny, (Not covered by the OHP)
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resources Commission (HRC).	**Yes:** Inform provider of covered alternatives in class.	**No:** Approve for the shorter of 1 year or length of prescription

DUR/P&T Board Action: 9/06/10 (DO)
Revision(s):
Initiated: 1/1/11

Appendix 2

1. **Jost WH, Friede M, Schnitker J. Indirect meta-analysis of randomised placebo-controlled clinical trials on rasagiline and selegiline in the symptomatic treatment of Parkinson's disease. *Basal Ganglia*. 2012;2(4, Supplement):S17–S26.**

Introduction: Selegiline and rasagiline are established in the treatment of Parkinson's disease. As no direct comparative randomised controlled trials on these drugs are available, an indirect meta-analysis was conducted.

Objective: Goal of the meta-analysis was to examine the clinical differentiation between rasagiline and selegiline based on efficacy and safety in Parkinson's disease.

Methods: Literature databases, study registries and references of relevant publications were the basis of our literature search. Studies were selected according to Jadad and Delphi criteria. The analysis used a fixed effects model based on standardised mean differences for efficacy criteria and risk differences of safety outcomes. As outcomes, UPDRS (primary) and UPDRS motor functions, mental and ADL, the Schwab and England scale, the off-time as well as safety as secondary outcomes were used.

Results: Rasagiline showed a statistically significant advantage in the primary endpoint UPDRS total scores (monotherapy: $p = 0.048$, sensitivity analysis: $p = 0.023$; pooled analyses: $p = 0.043$, sensitivity analysis $p = 0.014$) and the secondary endpoint UPDRS motor functions (monotherapy: $p = 0.049$, sensitivity analysis $p = 0.031$; pooled analyses: not significant, sensitivity analysis: $p = 0.046$). For the other secondary outcome parameters, a numerical advantage for rasagiline was found. Discontinuation rates due to adverse effects showed a tendency in favour of rasagiline. Risk for adverse events such as dizziness, hallucinations, diarrhoea and syncope were lower with rasagiline than selegiline (each $p < 0.15$).

Conclusion: This meta-analysis showed a statistically significant and clinically relevant advantage for rasagiline over selegiline in the primary endpoint. The superiority of rasagiline was further substantiated with advantages in tolerability and safety.

2. **Mínguez-Mínguez S, Solís-García Del Pozo J, Jordán J. Rasagiline in Parkinson's disease: A review based on meta-analysis of clinical data. *Pharmacol Res*. 2013;74C:78–86.**

Abstract: Rasagiline (Azilect®) is a selective and irreversible monoamine oxidase B inhibitor, which is well tolerated, safe, improves motor symptoms, and prevents motor complications in Parkinson's disease (PD). Rasagiline is effective in monotherapy and as an adjunct to levodopa-therapy, with beneficial effects on quality-of-life parameters in early and late stages of PD. In this review, we compare the efficacy of rasagiline versus placebo for decreasing PD symptoms. Major databases (Medline, the Cochrane Library) were systematically searched to identify and select clinical randomized control trials of rasagiline. The Unified Parkinson Disease *Rating Scale (UPDRS) for rasagiline monotherapy and reduction in off-time for combined treatment were the outcomes assessed. Rasagiline monotherapy, in early* stages of the disease, reduces the UPDRS score [-3.06 (95% CI -3.81 to -2.31, p<0.00001) with rasagiline 1mg/day]. In combination with levodopa, 1mg/day of rasagiline reduced off-time [-0.93h (95% CI -1.17 to -0.69, p<0.00001)]. However, although rasagiline reduces the UPDRS score [-0.89 (95% CI from -1.78 to 0, p=0.05)] in trials with a delayed-start design, we found a disagreement between studies and doses, making it difficult to interpret this result. In conclusion, our results confirm the efficacy of rasagiline in PD, but the clinical significance of these data remains to be established. Furthermore, the delayed-start study design did not establish with certainty the neuroprotective effect of rasagiline. It is advisable to carry out comparative trials with other drugs used in Parkinson's disease.

Appendix 3

National Guideline Clearinghouse | Early (uncomplicated) Parkinson's disease. February 20, 2012.

Major Recommendations:
The levels of evidence (Class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Point [GPP]) are defined at the end of the "Major Recommendations" field.

Early Untreated Patients

The optimal time frame for onset of therapy has not been clearly defined. Once parkinsonian signs start to have an impact on the patient's life, initiation of treatment is recommended. For each patient, the choice between the numerous effective drugs available is based on a subtle combination of subjective and objective factors. These factors include considerations related to the drug (efficacy for symptomatic control of parkinsonism/prevention of motor complications, safety, practicality, costs, etc.), to the patient (symptoms, age, needs, expectations, experience, co-morbidity, socioeconomic level, etc.), and to their environment (drug availability according to national markets in the European Union, variability in economic and health insurance systems, etc.). However, based on the available level of evidence alone, two main issues are usually considered when initiating a symptomatic therapy for early Parkinson's disease (PD): the symptomatic control of parkinsonism, and the prevention of motor complications (see table below).

Currently, there is no uniform proposal across Europe on initiating symptomatic medication for PD. Options include starting treatment with:

- *Monoamine oxidase isoenzyme type B (MAO-B inhibitor)*, like selegiline or rasagiline (**Level A**). The symptomatic effect is more modest than that of levodopa and (probably) dopamine agonists, but they are easy to administer (one dose, once daily, no titration), and well tolerated (especially rasagiline).
- *Amantadine or an anticholinergic* (**Level B**). The impact on symptoms is smaller than that of levodopa. Anticholinergics are poorly tolerated in the elderly and their use is mainly restricted to young patients.
- *Levodopa*, the most effective symptomatic antiparkinsonian drug (**Level A**). After a few years of treatment, levodopa is frequently associated with the development of motor complications. As older patients are more sensitive to neuropsychiatric adverse reactions and are less prone to developing motor complications, the early use of levodopa is recommended in the older population (**GPP**). The early use of controlled release levodopa formulations is not effective in the prevention of motor complications (**Level A**).
- *Orally active dopamine agonist*. Pramipexole, piribedil, and ropinirole immediate- or controlled-release are effective as monotherapy in early PD (**Level A**), with a lower risk of motor complications than levodopa for pramipexole or ropinirole (**Level A**). Older drugs like bromocriptine are supported by lower class evidence, giving a **Level B recommendation**. However, there is no convincing evidence that they are less effective in managing patients with early PD. The benefit of agonists in preventing motor complications (**Level A**, with data up to 5 years only) must be balanced with the smaller effect on symptoms and the greater incidence of hallucinations, impulse-control disorders, somnolence, and leg edema, as compared with levodopa. Patients must be informed of these risks (e.g., excessive daytime somnolence is especially relevant to drivers). Younger patients are more prone to developing levodopa-induced motor complications, and therefore initial treatment with an agonist can be recommended in this population (**GPP**). Ergot derivatives such as pergolide, bromocriptine, and cabergoline are not recommended as first-line medication because of the risk of fibrotic reactions. Rotigotine is administered transdermally using a patch and ropinirole controlled-release (CR) once daily orally, as opposed to the other agonists that are administered orally three times a day. Subcutaneous apomorphine is not appropriate at this stage of the disease. The early combination of low doses of a dopamine agonist with low doses of levodopa is another option, although the benefits of such a combination have not been properly documented.
- *Rehabilitation*. Due to the lack of evidence of the efficacy of physical therapy and speech therapy at the early stage of the disease, a recommendation cannot be made.

Table. Recommendations for the Treatment of Early PD

	Recommendation Level	
Therapeutic Interventions	**Symptomatic Control of Parkinsonism**	**Prevention of Motor Complications**
Levodopa	Effective (**Level A**)	Not applicable
Levodopa controlled release (CR)	Effective (**Level A**)	Ineffective (**Level A**)
Apomorphine	Not used[a]	Not used[a]
Bromocriptine[b]	Effective (**Level B**)	Effective (**Level B**)
Cabergoline[b]	Effective (**Level B**)	Effective (**Level A**)
Dihydroergocryptine[b]	Effective (**Level A**)	No recommendation[c]
Lisuride[b]	Effective (**Level B**)	Effective (**Level C**)
Pergolide[b*]	Effective (**Level A**)	Effective (**Level B**)
Piribedil	Effective (**Level C**)	No recommendation[c]
Pramipexole	Effective (**Level A**)	Effective (**Level A**)
Pramipexole CR[e]	Not available	Not available
Ropinirole	Effective (**Level A**)	Effective (**Level A**)
Ropinirole CR[e]	Effective (**Level A**)	No recommendation[c]
Rotigotine[f]	Effective (**Level A**)	No recommendation[c]
Selegiline	Effective (**Level A**)	Ineffective (**Level A**)
Rasagiline	Effective (**Level A**)	No recommendation[c]
Entacapone[d]	No recommendation[c]	No recommendation[c]
Tolcapone[d]	No recommendation[c]	No recommendation[c]
Amantadine	Effective (**Level B**)	No recommendation[c]
Anticholinergics	Effective (**Level B**)	No recommendation[c]
Rehabilitation	No recommendation[c]	No recommendation[c]
Surgery	Not used	Not used

[a]Subcutaneous apomorphine is not used in early PD.
[b]Pergolide*, bromocriptine, cabergoline and, precautionarily, other ergot derivatives, cannot be recommended as a first-line treatment for early PD because of the risk of valvular heart disorder (Rascol et al., "New concerns," 2004; Rascol et al., "Dopamine agonists," 2004).
[c]No recommendation can be made due to insufficient data .
[d]As catechol-O-methyltransferase (COMT) inhibitors, entacapone and tolcapone should always be given with levodopa. Due to hepatic toxicity, tolcapone is not recommended in early PD.
[e]Controlled-release.
[f]Transdermal patch delivery system.

***Note from the National Guideline Clearinghouse (NGC)**: On March 29, 2007, Permax (pergolide) was withdrawn from the market in the U.S. and worldwide due to safety concerns of an increased risk of cardiovascular events. See the U.S. Food and Drug Administration (FDA) Web site for more information.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment of early Parkinson's disease

Potential Harms

- The most commonly reported side effects of *anticholinergics* are blurred vision, urinary retention, nausea, constipation (rarely leading to paralytic ileus), and dry mouth. The incidence of reduced sweating, particularly in those patients on neuroleptics, can lead to fatal heat stroke. Impaired mental function (mainly immediate memory and memory acquisition) and acute confusional state are a well-documented central side effect that resolves after drug withdrawal. The abrupt withdrawal of anticholinergics may lead to a rebound effect with marked deterioration of parkinsonism. Consequently, anticholinergics should be discontinued gradually and with caution.
- As with any dopaminergic drug, *monoamine oxidase isoenzyme type B (MAO-B) inhibitors* can induce a variety of dopaminergic adverse reactions. At the daily doses of selegiline currently recommended, the risk of tyramine-induced hypertension (the 'cheese effect') is low. Concerns that the selegiline/levodopa combination increased mortality rates have been allayed.
- Side effects of *amantadine* are generally mild, most frequently including dizziness, anxiety, impaired coordination and insomnia (>5%), nausea and vomiting (5% to 10%), peripheral distal oedema (unresponsive to diuretics), and headache, nightmares, ataxia, confusion/agitation, drowsiness, constipation/diarrhoea, anorexia, xerostomia, and livedo reticularis (<5%). Less common side effects include psychosis, abnormal thinking, amnesia, slurred speech, hyperkinesia, epileptic seizures (rarely, and at higher doses), hypertension, urinary retention, decreased libido, dyspnoea, rash, and orthostatic hypotension (during chronic administration).
- Catechol-O-methyltransferase (COMT) inhibitors increase levodopa bioavailability, so they can increase the incidence of dopaminergic adverse reactions, including nausea, and cardiovascular and neuropsychiatric complications. Diarrhoea and urine discolouration are the most frequently reported non-dopaminergic adverse reactions.
- Peripheral side effects of *levodopa* include gastrointestinal and cardiovascular dysfunction. Central adverse effects include levodopa motor problems such as fluctuations, dyskinesia and dystonia, and psychiatric side effects such as confusion, hallucinations and sleep disorders. A meta-analysis found approximately 40% likelihood of motor fluctuations and dyskinesias after 4 to 6 years of levodopa therapy. Risk factors are younger age, longer disease duration, and levodopa. In individual studies, the percentage of fluctuations and dyskinesia may range from 10% to 60% of patients at 5 years, and up to 80% to 90% in later years. Neuropsychiatric complications occur in less than 5% of *de novo* patients on levodopa monotherapy.

- Side effects such as nausea, vomiting, orthostatic hypotension, confusion, psychosis, and somnolence may occur with administration of any of *dopamine agonists and other active dopamine-mimetic medications*. Peripheral leg edema is also commonly observed with most agonists. Hallucinations and somnolence are more frequent with some agonists than with levodopa, even in healthy subjects, in the case of somnolence. Though there is no convincing evidence that any agonist is better tolerated than bromocriptine, a recent meta-analysis suggested that while frequencies of somnolence, hallucination, or anxiety cases were higher with non-ergot dopamine agonists (DAs), incidence of vomiting, arterial hypotension, or depression was higher with ergots. The rare but severe risk of pleuropulmonary/retroperitoneal fibrosis is greater with ergot agonists than with non-ergot agonists. The same is true for valvular heart disorders. As pergolide and cabergoline have been the most frequently reported drugs at the present time, they are only used as a second-line alternative option, when other agonists have not provided an adequate response. If employed, regular monitoring of heart valves by ultrasound is mandatory. Impulse-control disorders have recently been identified as a common adverse drug reaction to dopamine agonists. Prevalence ranges between 5% and 15% depending on the author. The principal risk factor is treatment with dopamine agonists, although they can occur on levodopa as well. Personal traits, disturbed decision-making abilities, and younger age have also been implicated. Comorbidities, cognitive impairment, disease severity, and polytherapy are sometimes also mentioned. Up to the present there is no evidence about between-agonists difference in the frequency of these events.

Appendix 4:

1. **Mizuno Y, Yamamoto M, Kuno S, et al. Efficacy and safety of extended- versus immediate-release pramipexole in Japanese patients with advanced and L-dopa-undertreated Parkinson disease: a double-blind, randomized trial. *Clin Neuropharmacol*. 2012;35(4):174–181.**

Abstract

Objectives: To compare the efficacy, safety, tolerability, and trough plasma levels of pramipexole extended-release (ER) and pramipexole immediate-release (IR), and to assess the effects of overnight switching from an IR to an ER formulation, in L-dopa-treated patients with Parkinson disease (PD).

Methods: After a 1- to 4-week screening/enrollment, 112 patients who had exhibited L-dopa-related problems or were receiving suboptimal L-dopa dosage were randomized in double-blind, double-dummy, 1:1 fashion to pramipexole ER once daily or pramipexole IR 2 to 3 times daily for 12 weeks, both titrated to a maximum daily dose of 4.5 mg. Successful completers of double-blind treatment were switched to open-label pramipexole ER, beginning with a 4-week dose-adjustment phase.

Results: Among the double-blind treatment patients (n = 56 in each group), Unified Parkinson's Disease Rating Scale Parts II+III total scores decreased significantly from baseline and to a similar degree with pramipexole ER and IR formulations. In each group, 47 double-blind patients (83.9%) reported adverse events (AEs), requiring withdrawal of 3 ER patients (5.4%) and 2 IR patients (3.6%). Trough plasma levels at steady state (at the same doses and dose-normalized concentrations) were also similar with both formulations. Among open-label treatment patients (n = 53 from IR to ER), 83% were successfully switched (no worsening of PD symptoms) to pramipexole ER.

Conclusions: In L-dopa-treated patients, pramipexole ER and pramipexole IR demonstrated similar efficacy, safety, tolerability, and trough plasma levels. Patients can be safely switched overnight from pramipexole IR to pramipexole ER with no impact on efficacy.

2. **Ray Chaudhuri K, Martinez-Martin P, Rolfe KA, et al. Improvements in nocturnal symptoms with ropinirole prolonged release in patients with advanced Parkinson's disease. *European Journal of Neurology*. 2012;19(1):105–113.**

Background: The 24-week, double-blind Efficacy and Safety Evaluation in PD–Adjunct (EASE-PD Adjunct) study randomized patients with advanced Parkinson's disease (PD) suboptimally controlled with levodopa to once-daily placebo or adjunctive ropinirole prolonged release (2–24 mg/day). We investigated the effect of ropinirole prolonged release on nocturnal symptoms in these patients.

Methods: Total and grouped item PD Sleep Scale (PDSS) scores were analyzed *post hoc* in patients with baseline PDSS total scores ≤100 (troublesome nocturnal symptoms) and >100.

Results: Baseline PDSS total score was ≤100 in 93 of 198 (47%) and 89 of 189 (47%) patients receiving ropinirole prolonged release and placebo, respectively; this subgroup displayed evidence at baseline of greater daily awake 'off' time, reduced night-time sleep and worse quality of life, than the PDSS >100 subgroup. Significant improvements with ropinirole prolonged release versus placebo in PDSS score from baseline to Week 24 last observation carried forward were observed for those with baseline PDSS ≤100 [adjusted mean treatment difference 9.0 (95% CI: 2.76, 15.33; $P = 0.0051$)], but not >100. The PDSS ≤100 subgroup demonstrated treatment benefits for PDSS groupings of motor symptoms on waking and global quality of sleep. Changes in daytime sleepiness were similar between treatment groups. The PDSS >100 subgroup demonstrated significant treatment benefit for global quality of sleep. The unadjusted odds ratio for a positive response with ropinirole prolonged release relative to placebo, for the PDSS ≤100 subgroup, was 2.90 (95% CI: 1.42, 5.95, $P = 0.004$).

Conclusions: Once-daily ropinirole prolonged release improves nocturnal symptoms in patients with advanced PD not optimally controlled with levodopa who suffer troublesome nocturnal disturbance.

3. **Schapira AHV, Barone P, Hauser RA, et al. Success rate, efficacy, and safety/tolerability of overnight switching from immediate- to extended-release pramipexole in advanced Parkinson's disease. *European Journal of Neurology*. 2013;20(1):180–187.**

Background and purpose: For Parkinson's disease (PD), an extended-release (ER) pramipexole formulation taken once daily, has shown efficacy, safety, and tolerability resembling those of immediate-release (IR) pramipexole taken three times daily. The present study assessed, in advanced PD, the success of an overnight switch from adjunctive IR to ER.

Methods: Levodopa users experiencing motor fluctuations were randomized to adjunctive double-blind (DB) placebo, IR, or ER. Amongst completers of ≥18 weeks, ER recipients were kept on DB ER, whilst IR recipients were switched overnight to DB ER at unchanged daily dosage. After a DB week, switch success was assessed. During the next 5 weeks, all patients underwent ER titration to optimal open-label maintenance dosage.

Results: One week post-switch, 86.2% of 123 IR-to-ER and 83.8% of 105 ER-to-ER patients had ≤15% (or ≤3-point, for pre- switch scores ≤20) increase on UPDRS Parts II + III, and 77.9% (of 122) and 70.2% (of 104) had ≤1-h increase in daily OFF- time. At 32 weeks, the groups showed comparable improvements from DB baseline (pramipexole inception), including, on UPDRS II + III, adjusted mean (SE) changes of −14.8 (1.5) for IR-to-ER and −13.3 (1.6) for ER-to-ER. Rates of premature discontinuation owing to adverse events were 6.5% for IR-to-ER and 4.9% for ER-to-ER.

Conclusions: By OFF-time and UPDRS criteria, majorities of patients with advanced PD were successfully switched overnight from pramipexole IR to ER at unchanged daily dosage. During subsequent maintenance, pramipexole showed sustained efficacy, safety, and tolerability, regardless of formulation (IR or ER) in the preceding DB trial.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Disease Modifying Agents for Multiple Sclerosis

Month/Year of Review: September 2013
PDL Classes: Neurologic– MS Drugs (Disease modifying agents)
New Drug Evaluation: Dimethyl Fumarate
Manufacturer: Biogen Idec

Date of Last Review: Drug March 2012
Source Document: OSU College of Pharmacy
Brand Name: Tecfidera®
Dossier Received: Pending

Current Status of PDL Class:

- **Preferred Agents:** INTERFERON BETA-1A IM (AVONEX®/AVONEX PEN®, AVONEX ®ADMINISTRATION PACK), GLATIRAMER ACETATE (COPAXONE®)
- **Non-Preferred Agents:** INTEFERON BETA-1A SUBQ (REBIF®), INTERFERON BETA-1B SUBQ (BETASERON® AND EXTAVIA®), NATALIZUMAB IV (TYSABRI®), MITOXANTRONE IV, FINGOLIMOD (GILENYA®), TERIFLUNOMIDE (AUBAGIO®)

Current PA: Prior authorization criteria is currently in place for dalfampridine (Appendix 2) and the oral drugs, fingolimod and teriflunomide, to ensure appropriate drug use and limit its use to patient populations in which the drug has been shown to be effective and safe.

Research Questions:

- Is there any new comparative evidence for disease-modifying treatments, in long term clinical outcomes such as relapse and disease progression in adult patients being treated for multiple sclerosis (MS)?
- Is there any new evidence about comparative harms of disease-modifying treatments in adult patients being treated for MS?
- Are there subpopulations of patients with MS for which one disease-modifying treatment is more effective or associated with less harm?
- Is dimethyl fumarate more effective or safer than other disease modifying treatments in reducing relapse rate or slowing disease progression in patients with relapsing remitting multiple sclerosis (RRMS)?

Conclusions:

- There is low strength of evidence indicating dimethyl fumarate 720 mg daily reduced the risk of relapse (RR 0.75, 95% CI 0.59 to 0.96) and improved annualized relapse rate (rate ratio 0.69, 95% CI 0.51 to 0.96) compared with glatiramer 20mg. This was based on one fair quality 2-year, placebo-controlled trial comparing dimethyl fumarate and glatiramer with placebo. The study was not designed to directly compare dimethyl fumarate with glatiramer and there was no difference in preventing disability progression.
- There is insufficient evidence that dimethyl fumarate is more effective than other treatment options in slowing disability progression in patients with RRMS.
- Based on an indirect study, there is low quality evidence that dimethyl fumarate is associated with more adverse events than glatiramer, but no differences in serious adverse events or withdrawals due to adverse events.

- The evidence supports a benefit of interferon beta-1b SC over interferon beta-1a IM in relapse outcomes (1.51, 95% CI 1.11 to 2.07; NNT 6). There is conflicting evidence on disease progression outcomes
- Three head to head trials suggest a benefit of interferon beta-1a SC over interferon beta-1a IM in relapse outcomes, with no differences in disease progression.
- There is insufficient evidence to identify any differences between interferon beta-1b SC and interferon beta-1a SC.
- There is no head to head evidence available for teriflunomide and insufficient evidence to determine its efficacy and safety relative to other therapies.
- The efficacy and risk-benefit profile of all treatments remains uncertain beyond two years

Recommendations:
- Include dimethyl fumarate on the Oral MS drug Prior authorization criteria to ensure appropriate and safe drug use and limit to patients who have tried and failed first line agents including beta interferons and/or glatiramer.
- Include either interferon beta-1a subQ or interferon beta-1b SubQ as a preferred option due to evidence demonstrating improved efficacy compared to interferon beta-1a IM in relapse related outcomes.
- Evaluate costs in executive session for further decision-making.

Reason for review:
Since the last review in March 2012, the class of MS treatments has been changing rapidly. While current treatments may slow disease progression, the disease has no cure and there has been an attempt to develop more effective treatments, as well as expand the number of oral options for patients. There are now 3 disease modifying oral agents FDA approved for the treatment of MS; fingolimod, teriflunomide, and dimethyl fumarate. Dalfampridine (Ampyra®) is not a disease modifying treatment, but it may improve impairment of walking associated with MS. In addition, the Pacific Northwest Evidence-based Practice Center's Drug Effectiveness Review Project (DERP) has completed a draft drug class review evaluating disease-modifying drugs for MS and the Canadian Agency for Drugs and Technologies in Health (CADTH) has released draft guideline recommendation for the treatment of RRMS. The new evidence will be reviewed and synthesized here.

Previous Conclusions and Recommendation:
- Due to similar efficacy and potential differences in relapse outcomes between the interferon products, evaluate costs of interferon beta-1a SC (Rebif®, interferon beta-1b SC (betaseron® and Extavia®), and interferon beta-1a IM (Avonex®) for further decision making
- Include dalfampridine as a non-preferred agent on the PDL and include clinical criteria for use including:
    - Has a walking disability that requires the use of a walking aid.
    - Be able to complete the T25FW in 8-45 seconds
    - Does not have renal impairment or a history of seizure disorder or epileptiform activity on an EEG.
- Include fingolimod as a non-preferred disease modifying medication for MS and develop clinical criteria to restrict based on the following:
    - Prescribed by or in consultation with a neurologist
    - Patient has relapsing remitting MS
    - Is not currently on therapy with an injectable disease modifying drug
    - Has failed or cannot tolerate a full course of a first line interferon or glatiramer
- Designate interferon alfacon-1 as a non-preferred agent due to the lack of recommendations for use in current treatment guidelines.

Authors: Kala Berkey, Pharm.D. Candidate and M. Herink, Pharm.D.

- The evidence supporting teriflunomide efficacy is low. The strongest evidence is in affecting relapse rate and evidence is more robust for the 14 mg dose than the 7 mg dose. Teriflunomide comes with numerous safety concerns including hepatotoxicity and teratogenicity, considerable monitoring, and an accelerated elimination procedure. It may be an important option for patients unable to take injectables and fingolimod.
- Prior authorize teriflunomide to limit use to confirmed RRMS patients with documentation of prior failed use of an interferon for MS or glatiramer acetate. Documentation of compliance with requisite laboratory evaluation prior to prescribing.

Background:

Multiple sclerosis (MS) is a chronic, autoimmune disease of the central nervous system affecting approximately 250,000 to 400,000 people in the United States.[1] MS is usually diagnosed in patients between the ages of 15 and 45 years, with the peak incidence in the fourth decade of life. MS is a diagnosis of exclusion and presents in a variety of ways.[2] Diagnosis begins with patients presenting with neurological symptoms or signs suggestive of demyelination (such as optic neuritis and transverse myelitis) and should be clinically determined on the basis of history and examination.[3] Patients should be under the care of a specialized neurological doctor. The McDonald criterion is a tool used to help in differential diagnosis and is based upon number of clinical attacks, lesions, and dissemination in time and space.[4]

There are four main types of MS: relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing. About 85% of patients have RRMS at diagnosis of disease and is defined by acute relapsed of neurological symptoms followed by full or partial recovery.[1] Some patients with RRMS will develop secondary progressive MS, which is a progressive form of the disease.

Acute exacerbations or relapses of MS can be disabling. [2] Treatment of MS includes corticosteroids for acute relapse, symptom management, and disease modification.[1] Use of disease-modifying drugs (DMD) in patients with RRMS has been shown to have many beneficial effects including reducing annual relapse rate, lessening severity of relapses, and slowing progression of disability. [2] Treatment with these agents should not be delayed in patients with a definite diagnosis of MS with active, relapsing disease. [2] Goals of treatment include decreasing exacerbations, hospitalizations, slowing disease progression, and disability.[2] There are currently ten DMD's approved by the U.S. Food and Drug Administration (FDA) for use in RRMS.[5] These medications come in a variety of dosage forms, including injectable and oral agents.

Most of the currently available DMD's require regular and frequent parenteral administration, which is inconvenient to the patient.[5] Due to many patients not responding adequately to available treatments and drug side effects, there is a need for more treatment options, including oral agents. [5] The newest oral DMD is dimethyl fumarate (Tecfidera®), which was approved March 2013.[6] A variation of the drug was approved in Germany in 1994 for the treatment of psoriasis. This drug's proposed mechanism of action is activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway that is involved in the cellular response to oxidative stress and which reduces inflammation and promotes cytoprotection. [6] Previously approved oral DMD's have also been associated with serious side effects. Teriflunomide carries a black box warning of hepatotoxicity and major birth defects due to either the mother or father.[7] Fingolimod is associated with cardiovascular risk such as bradycardia upon first dose and its use requires extensive cardiac monitoring.

Progression of MS is measured by the disability caused by the disease. The Expanded Disability Status Scale (EDSS) is a single-item scale used to assess disability and progression of disability and frequently used to measure disability progression in clinical trials.[8] The scale ranges from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments based on eight function system scales (FSS).[8,9] This tool is used primarily in clinical trials and less frequently by clinicians. Limitations to this scale include difficulty interpreting change or group differences due to a 1-point difference in one part of the scale not representing the same interval as a 1-point difference in another part of the scale, and evidence that the EDSS lacks adequate sensitivity to fluctuations in MS-related

impairment. Additionally, this outcome may not accurately measure long-term and irreversible disease progression.[19] Due to treatment length "sustained disease progression" is often used instead of hitting a long-term disease progression milestone. [9] Sustained disease progression is an increase in EDSS score that is sustained over several months. In clinical trials, disability progression is often defined as at least 1 point EDSS increase or a 0.5 point increase if the EDSS was greater than or equal to 5.5.

A newer tool to assess disability is the Multiple Sclerosis Functional Composite (MSFC), which was developed by a special Task Force on Clinical Outcomes Assessment appointed by the National Multiple Sclerosis Society's Advisory Committee on Clinical Trials of New Agents in Multiple sclerosis in 1999.[10] This is a three-part, standardized, quantitative, assessment instrument. The MSFC can produce scores for each of the three individual measures as well as a composite score. In addition, there are a variety of ways to calculate scores depending on the nature of the study and sample. The MSFC has rarely been used as an outcome measure in clinical trials.

Relapse rate is a clinically relevant outcome to both the patient and provider. Since, RRMS is characterized by periods or relapse, the goal is to diminish any signs or symptoms of relapse. Confirmed relapse is defined as the occurrence of new symptoms or worsening of previously stable or improving symptoms and signs not associated with fever or infection that occurs at least 30 days after the onset of a preceding relapse and lasts more than 24 hours.[5] This is generally studied after one or more years of treatment. However, the frequency of relapses in the general population is highly variable.[12] According to data from the Marshfield Multiple Sclerosis Center in Wisconsin, 1,078 RRMS pts had a mean of 2.4 relapses per patient, with a range of 1-11 relapses over 1-15 years with an average follow-up of 7.4 years.[11]

MS causes demyelination of neuronal axons which form lesions of the central nervous system on a magnetic resonance imaging (MRI).[1] MRI assessment is used to assess lesions due to MS. MRI changes seen in MS are nonspecific. Therefore, the AAN recommends always using the information derived from imaging in the context of the specific clinical situation presented by an individual patient.[4] T2-weighted lesions at onset appear to correlate with the development of disability. Gadolinium contrast material enhances the lesions and help identify new lesions and disruption of the blood-brain barrier, but do not correlate well over time with progression of disability.[2] In July 2013, a meta-analysis explored the potential of MRI lesions being used as a surrogate for effect of treatment on relapses.[12] Results suggested that MRI lesions can accurately predict the effect of a treatment on relapses and will enhance further trials by reducing the number of patients needed in a study. In most cases, MRI alone adds little to the clinical outcomes.

Methods:

A Medline literature search beginning January 2013 (since the literature search from the recent DERP report) and ending August 2013 for new systematic reviews and randomized controlled trials (RCTs) that compared disease modifying medications for the treatment of MS was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic reviews:

Drug Effectiveness Review Project:
A recent systematic review from the Drug Effectiveness Review Project (DERP) compared the effectiveness and safety of disease-modifying drugs for the treatment of MS.[1] A streamlined approach was used which focused on only head to head studies and natalizumab and mitoxantrone were not included in the report. Intermediate MRI outcomes were not included as they are surrogate markers. After applying exclusion criteria, a total of 37 publications were included in the review; including 10 trials, 17 observational studies, and 4 systematic reviews. A following is a summary of the comparative evidence:

Alemtuzumab:
- There is moderate strength evidence that alemtuzumab 12mg is superior to interferon beta-1a SC in sustained disability at 6 months (RR 0.59, 95% CI 0.40 to 0.86), risk of relapse (RR 0.61, 95% CI 0.52 to 0.71), disease free survival (RR 1.38, 95% CI 1.23 to 1.54), and annualized relapse rate (rate ratio 0.42, 95% CI 0.31 to 0.56), and low strength evidence for alemtuzumab 24 mg.
- There was moderate strength evidence that treatment with alemtuzumab increased the risks of thyroid disease but decreased the probability of withdrawing from the study due to an adverse event (RR 0.31, 95% CI 0.17 to 0.55) compared with interferon beta-1a SC, and low strength evidence of reduced liver toxicity but increased risk of any infection (RR 1.32, 95% CI 1.10 to 1.58).

Dimetheyl fumarate
- There is low strength of evidence indicating dimethyl fumarate 720 mg daily reduced the risk of relapse (RR 0.75, 95% CI 0.59 to 0.96) and improved annualized relapse rate (rate ration 0.69, 95% CI 0.51 to 0.96) compared with glatiramer 20mg. This was based on one fair quality 2-year, placebo-controlled trial comparing dimethyl fumarate and glatiramer with placebo. The study was not designed to directly compare dimethyl fumarate with glatiramer and there was no difference in preventing disability progression.
- Low strength evidence indicates that treatment with dimethyl fumarate increased the risk of experiencing any adverse event compared with glatiramer (480mg: RR 1.09, 95% CI 1.04 to 1.14; 720mg: RR 1.06, 95% CI 1.01 to 1.12).

Teriflunomide
- There is no direct, head to head evidence available
- Moderate strength evidence indicated that teriflunomide reduced annualized relapse rate compared to placebo and low strength evidence that teriflunomide 14 mg reduced sustained disability progression (RR 0.74, 95% CI 0.57 to 0.96).
- There is moderate strength evidence that teriflunomide increases alanine aminotransferase levels compared to placebo (RR 1.58, 95% CI 1.05 to 2.37).

Fingolimod
- There is moderate strength evidence that fingolimod 0.5 mg daily and 1.25 mg daily resulted in lower annualized relapse rates than interferon beta-1a (0.16, 0.20, and 0.33 respectively; $p<0.001$), and in more patients having no confirmed relapse at 1 year compared with interferon beta-1a (82.5%, 80.5%, and 70.1% respectively). There was no difference in disease progression.
- The benefit of fingolimod over interferon beta-1a was greater in the subgroup of patients who had prior exposure to a disease-modifying drug than in patients who had no prior exposure.

- Fingolimod was associated with higher rates of increased alanine aminotransferase levels (RR 3.52, 95% CI 1.66 to 7.50) and herpes virus infections when compared to inferferon beta-1a, while interferon beta-1a was associated with higher rates of pyrexia, influenza-like illness, and myalgia.
- Discontinuations due to adverse events and serious adverse events occurred more frequently with fingolimod 1.25 mg than with fingolimod 0.5 mg or interferon beta-1a (RR 2.69, 95% CI 1.55 to 4.69; NNT 16).
- After the first dose of fingolimod, dose-dependent bradycardia and atrioventricular block occurred in the first 6 to 8 hours.

Glatiramer acetate

- There is low strength of evidence of no difference in relapse related outcomes comparing glatiramer and interferon beta-1a and 1b and moderate strength evidence that glatiramer results in similar disease progression as treatment with interferon beta-1b and interferon beta-1a.

Beta interferons

- The evidence supports a benefit of interferon beta-1b SC over interferon beta-1a IM in relapse outcomes (1.51, 95% CI 1.11 to 2.07; NNT 6). There is conflicting evidence on disease progression outcomes with only 1 trial finding a significant benefit of interferon beta-1b SC over interferon beta-1a IM (RR 0.44; 95% CI 0.25 to 0.79; NNT 6). Despite a trend toward benefit, there was no statistically significant difference in mean change in EDSS score.
- Three head to head trials suggest a benefit of interferon beta-1a SC over interferon beta-1a IM in relapse outcomes, with no differences in disease progression.
- There is insufficient evidence to identify any differences between interferon beta-1b SC and interferon beta-1a SC.
- Interferon beta-1a IM appeared to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 2% to 8.5% reported. Antibodies occurred somewhat later with interferon beta-1a SC with rates of immunogenicity as low as 12% and as high as 46%. Neutralizing antibodies appeared as early as 3 months with interferon beta-1b SC and in 30-40% of patients.
- Evidence indicated that consistent positive neutralizing antibody status with high titer adversely affected the impact of these drugs on relapse rates, by one half to two thirds on longer follow up (greater than 2 years). There is insufficient evidence to conclude that there is an impact on disease progression.
- Although generally well tolerated, differences in adverse events between the products were seeming.
- Based on pooled trial rates, there were 7.5% of discontinuations due to adverse events with interferon beta-1b SC, 6.1% with interferon beta-1alfa SC = and 3.6% with interferon beta-1a IM =
- Interferon beta-1a IM had higher rates of flu-like syndrome, fatigue, and depression, while interferon beta-1b SC = had higher rates of fever and overall withdrawal.

Cochrane Collaboration

In June 2013, a Cochrane systematic review was published that evaluated the relative efficacy of interferon beta-1b (Betaseron), interferon beta-1a (Rebif and Avonex), glatiramer, natalizumab, mitoxantrone, cyclophosphamide, azathioprine, and long-term corticosteroids to provide a ranking of the treatments according to their effectiveness and risk-benefit balance.[13] A total of 44 trial s contributed to results with interferon, glatiramer, and natalizumab evaluated in the majority of the studies. Of the included studies, 11% were considered low risk of bias, 48% had moderate risk of bias, and 41% had high risk of bias. The two primary outcomes considered were clinical relapses (proportion of participants who experienced new relapses over 12, 24, or 36 months) and disability progression (proportion of participants who experienced disability progression over 24 or 36 months).

Results of a meta-analysis demonstrated high quality evidence that natalizumab and interferon beta-1a were more effective than interferon beta-1a in recurrence of relapse at 24 months (OR 0.28, 95% CI 0.22 to 0.36; OR 0.19, 95% CI 0.06 to 0.60, respectively). There was insufficient evidence to compare glatiramer with interferon beta-1b or interferon beta-1a. Disability progression was based on surrogate markers in the majority of studies and beyond two to three years, disability outcome data were unavailable or dropouts compromised interpretation. For disability progression over 24 months, natalizumab and interferon beta-1b were significantly more effective (OR 0.62, 95% CI 0.49 to 0.78; OR 0.35, 95% CI 0.17 to 0.70, respectively) than interferon beta-1a for RRMS and mitoxantrone appeared to be the most effective agents at two years, but this was based on very low evidence. None of the agents were effective in preventing disability worsening over two or three years in patients with progressive MS. Compared to placebo, the most effective drug appeared to be natalizumab, followed by interferon beta-1a mitoxantrone, glatiramer, interferon beta-1b.A lack of strong efficacy data shows that interferon beta-1a,intravenous immunoglobulins, cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.

There were no significant differences in withdrawals in direct comparison trials of the interferons compared to each other or to glatiramer. Treatment with natalizumab is associated with an increased risk of progressive multifocal leukoencephalopathy (PML). The efficacy and risk-benefit profile of all treatments remains uncertain beyond two years for a disease of 30 to 40 years duration. More than 70% of included studies were sponsored by pharmaceutical companies. More studies on the long-term efficacy and safety of immunotherapies for MS are needed.

Horizon Scan:

A recent AHRQ Horizon Scan report identified 5 agents that are currently in Phase III trials for the treatment of MS.[14] Alemtuzumab (Lemtrada®) is a monoclonal antibody that will target a new mechanism of action for treating RRMS. FDA accepted the new drug application in January 2013 and there are completed phase III trials. This drug is given as a once-yearly intravenous treatment regimen. In addition, there are 3 other agents currently in Phase III trials; 1 oral tyrosine kinase inhibitor, 1 oral monoclonal antibody, and one IV treatment. [14] NICE guidance is currently in progress for teriflunomide and dimethyl fumarate.

New Guidelines:

Canadian Agency for Drugs and Technologies in Health

At the time of this report, a CADTH draft recommendations report on drug therapies for the management of relapsing-remitting multiple sclerosis was available for feedback from all interested stakeholders and alemtuzumab and teriflunomide were not approved by Health Canada for the treatment of RRMS.[15] The following is a summary of recommendations:

- The committee recommends glatiramer acetate or interferon beta-1b as the initial pharmacotherapies of choice for patients with RRMS.
- Patients who have failed to respond to, or have contraindications to, glatiramer as the initial treatment, be treated with interferon beta-1b and patients who have failed interferon-beta 1b as initial treatment, be treated with glatiramer.
    - Interferon beta-1b and glatiramer have similar efficacy based on the annualized relapse rate from direct and indirect evidence and are the most cost-effective initial therapies for the treatment of RRMS.
    - SubQ interferon beta-1b is available as more than one branded product, and choice should be based on price.
    - IM interferon beta-1a was considered to be less efficacious, as assessed by the annualized relapse rate, compared with interferons beta-1b and subQ beta-1a based on both direct and indirect evidence.
- Subsequent pharmacotherapies should be selected from dimethyl fumarate, fingolimod, and natalizumab. The selection should be based on cost and individual safety concerns.

- There was insufficient data to determine relative efficacy of sequential treatments.
- Evolving safety considerations may influence the choice of subsequent pharmacotherapies.

- Combination therapy for treatment of RRMS should not be used.

National Institute for Health and Clinical Excellence
Currently, NICE limits fingolimod as an option for the treatment of highly active RRMS, only if: they have unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, AND the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.[16]

New FDA Safety Alerts:
In July 2012, the FDA released a drug safety communication of the risk of seizures in patients with MS who are starting dalfampridine (Ampyra) based on postmarketing case reports. The majority of seizures happened within days to weeks after starting therapy and in patients without a history of seizures.[17] The communication also warned of the increased risk of seizures in those with kidney impairment as dalfampridine is eliminated from the body through the kidneys. Dalfampridine should not be used in patients with a history of seizures or who have moderate to severe renal impairment (CrCl less than or equal to 50 ml/min).

New drugs/formulations/indications:
Teriflunomide (Aubagio®) was FDA approved in September 2012 for the treatment of patients with RRMS. This was reviewed by the P&T committee in May and a prior authorization was implemented to limit its use to confirmed patients with documentation of prior failed use of an interferon for MS or glatiramer acetate. Only placebo controlled studies are available for teriflunomide and no direct, head to head evidence is available at this time. The recent DERP report concluded there was moderate strength evidence that teriflunomide reduced annualized relapse rate compared with placebo and low strength evidence that teriflunomide 14 mg reduced sustained disability progression and was not associated with worse EDSS scores compared with placebo. There was no difference in disability progression between teriflunomide 7 mg and placebo. This was based on 3 fair-quality published and 2 fair-quality unpublished placebo-controlled trials.

New Drug Evaluation: Dimethyl Fumarate (Tecfidera)

FDA approved indications: Dimethyl fumarate is indicated for the treatment of patients with relapsing forms of MS.[18]

Clinical Efficacy Data:
ClinicalTrials.gov identified seven dimethyl fumarate trials: one Phase I, two Phase II, one of which was published, and 2 published Phase III trials. There are two additional long-term studies that are ongoing.[19] Based on published studies, the FDA approved dimethyl fumarate with an initial dose of 120 mg orally twice daily for seven days, followed by maintenance dose of 240 mg twice a day.

In addition to the pivotal phase III trials included in the evidence table, a study by Kappos et al.[20] was a fair quality phase IIb, 24 week dose-ranging trial that randomized patients to dimethyl fumarate 120 mg once daily (n=64), 120 mg three times a day (n=64), 240 mg three times a day (n=63), and matching placebo (n=65). The primary endpoint was total number of new gadolinium enhancing (GdE) lesions on brain MRI scan, which is an intermediate outcome. In patients

treated with dimethyl fumarate 120 mg once daily, 120 mg three times daily, and 240 mg three times daily there were non-significant results in number of patient that relapsed by 24 weeks (17%, 31%, 19% vs 25% placebo). Interestingly, a trend toward increased relapse was seen in the 120 mg three times daily group. Furthermore, only the 240 mg three times daily group had a significantly lower number of new GdE lesions compared to placebo at 24 weeks (2.2 vs 4.2 placebo; p=0.0006).

Gold et al.[21] was a fair quality phase III trial (DEFINE) that randomized patients to 240 mg dimethyl fumarate twice daily (n=410), dimethyl fumarate 240 mg three times daily (n=416), and matching placebo (n=408). Fox et al.[22] was a fair quality phase III trial (CONFIRM) that randomized 359 patients to blinded 240 mg dimethyl fumarate twice daily, 345 patients to blinded 240 mg dimethyl fumarate three times a day, and 363 patients to matching placebo. Additionally, 350 patients were randomized to open-label glatiramer acetate, 20 mg subcutaneous daily injections, as a reference comparator. In both studies, all patients could switch to alternative MS therapy if they had completed 48 weeks of blinded treatment and experienced at least 1 confirmed relapse after 24 weeks, or at any time if they had experienced disability progression sustained for 12 weeks. Randomization and allocation concealment was adequate and described in both phase III trials. Overall attrition was high in both studies, 23% and 21.2%, respectively. However, all groups had similar attrition rates and was mostly due to adverse events in the study groups and withdrawal of consent in the control group. There is a low risk of detection bias in studies due to requiring separate study personnel to treat patients and assess drug efficacy. However, there was a possibility of unblinding in all 3 trials due to the high incidence of flushing associated with dimethyl fumarate. Authors corrected for this by having patients take the study drug at least 4 hours before study visit. However, the authors do not address the patient telling the care provider or how the patient is blinded from this side effect.

Relapse rate at 2 years was similar across studies and was significantly better in the dimethyl fumarate groups compared to placebo.[21,22] Relapse rate in patients treated with dimethyl fumarate 240 mg twice daily and three times daily was 27% and 26% vs. 46% placebo ($p<0.001$), giving an NNT of 5 for both comparisons in Gold et al.[21], compared to 29% and 24% vs. 41% ($p\leq0.01$, $p<0.001$), giving an NNT of 8 and 6, respectively, in Fox et al.[22] The glatiramer group had 32% of patients relapse at 2 years, with an NNT of 11 when compared to placebo. [22] This study was not designed to directly compare dimethyl fumarate to glatiramer. Disability progression with dimethyl fumarate 240 mg twice daily and three times daily was statistically significant in Gold et al. [21] (16%, 18% vs. 27% placebo; p=0.005 and p=0.01; NNT of 9 and 11), while Fox et al. [22] showed no significance (13% in both groups vs. 17% placebo; p-value not provided) compared to placebo or glatiramer.

Mean age range in all three trials was 37 years old and patients were primarily female, which is representative of the RRMS population. However, the study population was predominately white. At baseline, most study patients had an EDSS score of 2.0-2.5, which corresponds to minimal disability in one to two items of the FSS. Furthermore, in the Phase III trials only approximately one-third of patients had received prior treatment with any approved DMD. Therefore, it appears study population had less severe forms of RRMS, and study outcomes may not correspond to patients with further stages of RRMS. Published subgroup analyses of DEFINE and CONFIRM showed that the benefits of treatment were consistent across subgroups of patients, irrespective of demographics, treatment history, and disease characteristics at baseline.[23,24]

There is currently a 5-year extension study of the 2 phase 3 trials underway (A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two doses of BG12 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis [ENDORSE] trial).[25]

Clinical Safety:

According to the FDA Summary Review safety data of 3,424 subjects in clinical trials of healthy volunteers, MS patients, psoriasis, and RA were submitted by the sponsor.[6] Flushing and GI related side effects were most common, and occurred most frequently early in treatment. Flushing was not dose dependent. In patients treated with dimethyl fumarate 240 mg twice daily and three times daily flushing was reported in 38% and 32% vs. 5% placebo in Gold et al. [21], compared to 31% and 24% vs. 4% in Fox et al. [22] Flushing resulted in 3% of patients stopping therapy. GI effects included diarrhea (11%), vomiting (5%), and abdominal pain (10%).[10] Serious side effects had low occurrence. Labeling includes risk of lymphopenia, due to decrease in lymphocyte count during the first year, which is followed by a plateau. A decrease in the lymphocyte count occurred in approximately 6% of patients in clinical trials with a decrease of up to 30% during the first year of therapy, with levels remaining stable after that. However, no serious infections or opportunistic infections were reported. Likewise, increases in hepatic enzymes and proteinuria are included on labeling. Safety data is from relatively short-term clinical trials. Two studies are ongoing to assess long-term safety profile. [19]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Relapse Rate
2) Disability Progression
3) Withdrawals due to adverse events
4) Quality of Life

Primary Study Endpoint:

1) Relapse rate at 2 years
2) Annualized relapse rate
3) Total number of new GdE lesions on MRI scan (Phase IIb trial)

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns

DEFINE trial Gold R, et al Phase III, RCT, DB, PC	1:1:1 ratio to 1 of 3 groups: 1. 240 mg dimethyl fumarate BID 2. 240 mg dimethyl fumarate TID 3. placebo Duration: 2 years* *All pts could switch to alternative MS therapy if they had completed 48 weeks of blinded treatment and experienced at least 1 confirmed relapse after 24 weeks, or at any time if they had experienced disability progression sustained for 12 weeks.	198 sites in 28 countries January 2007 – February 2011 Mean age: 38 Age range: 18-56 yrs Females %: 73.4% White %: 78.5% <u>Inclusion Criteria:</u> age 18-55 yo; confirmed diagnosis of RRMS; baseline EDSS between 0.0-5.0; at least 1 relapse within the 12 months with a prior brain MRI demonstrating lesion(s) consistent with MS, or show evidence of Gd-enhancing lesion(s) of the brain on an MRI performed within 6 weeks prior to randomization <u>Exclusion Criteria:</u> progressive relapsing MS; history of malignancy, severe allergic or reactions; history of abnormal lab results; history of significant cardiovascular, pulmonary, GI, dermatologic, psychiatric neurologic disease; HIV; drug or alcohol abuse; MS relapse within 50 days; hepatits C or B; ALT, AST, or GGT ≥2x ULN, leukocytes <3500/mm^3, eosinophils >0.7 GI/L; proteinuria, hematuria; prior treatment with any monoclonal antibody; tx w/n 1 year with mitoxantrone or cyclophosphamide	1. n= 410 2. n=416 3. n=408	<u>Annualized relapse rate at 2 years (adjusted)</u> 1. 0.17 2. 0.19 3. 0.36 p=0.01 in both comparisons <u>Relapse by 2 years</u> 1. 111 (27%) 2. 108 (26%) 3. 188 (46%) p<0.001 in both comparisons <u>Disability progression (1.0 point increase on the EDSS sustained for at least 12 weeks)</u> 1. 65 (16%); p=0.005 2. 75 (18%); p=0.01 3. 110 (27%) <u>Mean number of Gadolinium-enhancing lesions</u> 1. 0.1 2. 0.5 3. 1.8 p=0.01 in both comparisons	N/A 1. ARR: 19% NNT: 5 2. ARR: 20% NNT: 5 1. ARR: 11% NNT: 9 2. ARR: 9% NNT: 11 N/A	<u>Serious adverse events</u> 1. 74 (18%); p=0.291 2. 65 (16%); p=0.048 3. 86 (21%) <u>D/c of study drug due to adverse event</u> 1. 65 (16%); p=0.374 2. 68 (16%); p=0.851 3. 55 (13%)	2. ARR: 5% NNH: 20 NS	Quality rating: Fair Internal validity: <u>Selection:</u> Randomization and allocation concealment were performed with the use of a centralized IVRS and was stratified according to site. Baseline characteristics were similar. <u>Performance:</u> low/moderate risk; Pts took the study drug at least 4 hours before study visit due to flushing side effect, which helped blind care givers. Did not address pt telling care provider about side effect. Unclear how patients were blinded from this side effect, may compromise blinding. Placebo drug packaged in the same manner as the study drug. <u>Detection:</u> low risk; each study center used separate examining and treating neurologist <u>Attrition:</u> moderate risk; Overall attrition was high at 23% (952/1237), however, all groups had similar attrition rates (1. 23.4%, 2. 23.1%, 3. 22.7%). A modified ITT was used that included all pts that received at least one dose (did not include 3 pts that underwent randomization). All data before patient switched to alternative medication was used in the analysis. For analysis of MRI in these patients after they switched a constant rate assumption was used. External validity: <u>Recruitment:</u> Not provided. <u>Patient characteristics:</u> Age range representative of general population. Primarily white pts (78%). Healthy pt population, most having minimal disability. Only 40% had received DMD for MS before study entry. <u>Setting:</u> Included 198 sites in 28 countries. Sponsored by Biogen Idec. <u>Outcomes:</u> Efficacy: clinically relevant endpoints Safety: relevant endpoints reported, did not include p-values or CI

CONFIRM trial Fox R, et al Phase III, RCT, DB, PC	1:1:1:1 ratio to 1 of 4 groups: 1. 240 mg dimethyl fumarate BID 2. 240 mg dimethyl fumarate TID 3. 20 mg glatiramer daily SC injections 4. placebo Duration: 2 years *All pts could switch to alternative MS therapy if they had completed 48 weeks of blinded treatment and experienced at least 1 confirmed relapse after 24 weeks, or at any time if they had experienced disability progression sustained for 12 weeks.	200 sites in 28 countries June 2007-August 2011 Mean age: 37 Females %: 70.1% White %: 84.1% Inclusion Criteria: same as previous trial Exclusion Criteria: same as previous trial, except for including pts with prior treatment with glatiramer	1. n= 359 2. n= 345 3. n= 350 4. n= 363	<u>Annualized relapse rate at 2 years</u> 1. 0.22; p<0.001 2. 0.20; p<0.001 3. 0.29; p<0.05 4. 0.40 <u>Proportion of patients with relapse at 2 years</u> 1. 104 (29%); p≤0.01 2. 83 (24%); p<0.001 3. 112 (32%); p≤0.01 4. 149 (41%) <u>Disability progression at 2 years (sustained for at least 12 weeks)</u> 1. 47 (13%); p=0.25 2. 45 (13%); p=0.20 3. 56 (16%); p=0.70 4. 62 (17%) <u>Gadolinium-enhancing lesions at 2 years</u> 1. 0.5 2. 0.4 3. 0.7 4. 2.0 p<0.001 in all comparisons	N/A 1. ARR: 12% NNT: 8 2. ARR: 17% NNT: 6 3. ARR: 9% NNT: 11 NS N/A	<u>Serious adverse events</u> 1. 61 (17%); p=0.110 2. 54 (16%); p=0.43 3. 60 (17%); p=0.130 4. 79 (22%) <u>D/c of study drug due to adverse event</u> 1. 44 (12%); p=0.483 2. 41 (12%); p=0.553 3. 35 (10%); p=0.902 4. 38 (10%)	NS NS	Quality rating: Fair Internal validity: <u>Selection:</u> Randomization and allocation concealment were performed with the use of a centralized IVRS and was stratified according to site. Baseline characteristics were similar. <u>Performance:</u> moderate risk; Pts took the study drug at least 4 hours before study visit due to flushing side effect, which helped blind care givers. Did not address pt telling care provider about side effect. Unclear how patients were blinded from this side effect, may compromise blinding. Glatiramer was open-label. Placebo drug packaged in the same manner as the study drug. <u>Detection:</u> low risk; each study center used separate examining and treating neurologist <u>Attrition:</u> moderate risk; Overall attrition was high at 21.2% (1127/1430), however, all groups had similar attrition rates (1. 21.5%, 2. 20.9%, 3. 18.9%, 4. 23.4%). A modified ITT was used that included all pts that received at least one dose (did not include 13 pts that underwent randomization). Analyses of endpoints were based on all observed data before patients switched to alternative MS medications, with missing MRI end points imputed using the constant-rate assumption. External validity: <u>Recruitment:</u> Not provided. <u>Patient characteristics:</u> Age range representative of general population. Primarily white pts (84.1%). Healthy pt population, most having minimal disability. Only 30% had received DMD for MS before study entry. <u>Setting:</u> Included 200 sites in 28 countries. Sponsored by Biogen Idec. <u>Outcomes:</u> Efficacy: clinically relevant endpoints Safety: relevant endpoints reported

Abbreviations: RCT=randomized controlled trial, DB=double blind, PC=placebo controlled, BID = twice daily, TID = three times daily, ARR= absolute risk reduction, NNT = number needed to treat, NS – non-significant, N/A = not applicable

References:

1. Selph S, Thakurta S, McDonagh M. Drug Class Review: Disease-modifying Drugs for Multiple Sclerosis. Draft Update 2 Report. *Drug Effectiveness Review Project Paciric Northwest Evidence-based Practice Center*. 2013.

2. Dipiro J. Multiple Sclerosis. In: *Pharmacotherapy*. 8th Edition. McGraw-Hill Companies; 2011:Ch 64.

3. National Institute for Health and Clinical Excellence (NICE). Multiple sclerosis: management of multiple sclerosis in primary and secondary care. London (UK): National Institute for Health and Clinical Excellence; 2003 November. Clinical guidelines; no 8). Available at: http://www.nice.org.uk/. Accessed August 6, 2013.

4. Frohman EM, Goodin DS, Calabresi PA, et al. The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61(5):602–611.

5. He D, Xu Z, Dong S, et al. Teriflunomide for multiple sclerosis. *Cochrane Database Syst Rev*. 2012;12:CD009882. doi:10.1002/14651858.CD009882.pub2.

6. Center for Drug Evaluation and Research. Dimethyl fumarate: Summary review. Application Number: 204063Orig1s000SumR. 2013. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed June 28, 2013.

7. National Multiple Sclerosis Society. The MS disease-modifying medications. 2013. Available at: nationalMSsociety.org/DMD.

8. National Multiple S. Functional systems score (FSS) and expanded disability status scale (EDSS).

9. Healy BC, Engler D, Glanz B, Musallam A, Chitnis T. Assessment of definitions of sustained disease progression in relapsing-remitting multiple sclerosis. *Mult Scler Int*. 2013;2013:189624. doi:10.1155/2013/189624.

10. National Multiple Sclerosis Society. Multiple sclerosis function composite (MSFC). Available at: http://www.nationalmssociety.org/ms-clinical-care-network/researchers/clinical-study-measures/msfc/index.aspx.

11. Bejaoui K, Rolak LA. What is the risk of permanent disability from a multiple sclerosis relapse? *Neurology*. 2010;74(11):900–902. doi:10.1212/WNL.0b013e3181d55ee9.

12. Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. *Lancet Neurol*. 2013;12(7):669–676. doi:10.1016/S1474-4422(13)70103-0.

13. Filippini G, Del Giovane C, Vacchi L, et al. Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2013;6:CD008933. doi:10.1002/14651858.CD008933.pub2.

14. ECRI Institute. AHRQ Healthcare Horizon Scanning System Status Update. (Prepared by ECRI Institute under Contract No. HHSA290201000006C) Rockville, MD: Agency for HEalthcare Research and Quality. July 2013. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

15. Canadian Agency for Drugs and Technologies in Health. CADTH Therapeutic Review. Recommendations for Drug Therapies for Relapsing-Remitting Multiple Sclerosis [DRAFT]. 2013. Available at: http://www.cadth.ca/en/products/therapeutic-reviews/relapsing-remit-multiple-sclerosis.

16. National Institute for Health and Clinical Excellence (NICE). Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis. London (UK): National Institute for Health and Clinical Excellence;2012 April. 55 p. (Technology appraisal guidance; no 254).

17. U.S. Food and Drug Administration. FDA Drug Safety Communication: Seizure risk of multiple sclerosis patients who take Ampyra (dalfampridine). 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm312846.htm.

18. Tecfidera (dimethyl fumarate). Prescribing Information. Biogen Idec. Available at: http://www.tecfidera.com/pdfs/full-prescribing-informationl/pdf.

Authors: Kala Berkey, Pharm.D. Candidate and M. Herink, Pharm.D.

19. U.S. National Institutes of Health. Dimethyl fumarate. Available at: http://clinicaltrials.gov.

20. Kappos L, Gold R, Miller DH, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. *Lancet*. 2008;372(9648):1463–1472. doi:10.1016/S0140-6736(08)61619-0.

21. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367(12):1098–1107. doi:10.1056/NEJMoa1114287.

22. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367(12):1087–1097. doi:10.1056/NEJMoa1206328.

23. Bar-Or A, Gold R, Kappos L, et al. Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the DEFINE study. *J Neurol*. 2013. doi:10.1007/s00415-013-6954-7.

24. Hutchinson M, Fox RJ, Miller DH, et al. Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the CONFIRM study. *J Neurol*. 2013. doi:10.1007/s00415-013-6968-1.

25. McCoyd M. Update on therapeutic options for multiple sclerosis. *Neurol Clin*. 2013;31(3):827–845. doi:10.1016/j.ncl.2013.03.010.

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[21]: The mechanism of action of dimethyl fumarate is unknown. Dimethyl fumarate and the metabolite, monomethyl fumarate (MMF), have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. MMF has been identified as a nicotinic acid receptor agonist in vitro.

PHARMACOKINETICS[21]

Parameter	Result
Oral Bioavailability	Unknown
Protein Binding	27-45%
Elimination	Exhalation of CO_2 (60%), renal (16%), fecal (1%)
Half-Life	1 hr
Metabolism	Rapid presystemic hydrolysis by esterases to active metabolite, monomethyl fumarate (MMF), which is further metabolized by the TCA cycle

DOSE & AVAILABILITY[21]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
120 mg and 240 mg	Delayed-release	Oral	Initial dose: 120 mg twice a day After 7 days: 240 mg twice a day	None	None	Unknown	Has not been studied in patients >55	▪ A high-fat, high-calorie meal did not affect the AUC, but decreased its Cmax by 40%. Tmax was delayed from 2.0 hours to 5.5 hours. Flushing was reduced by ~25% in the fed state. ▪ Do not chew, crush, or open capsule

DRUG SAFETY[21]

Serious (REMS, Black Box Warnings, Contraindications): None

Warnings and Precautions:

- *Mean lymphocyte counts decreased by approximately 30% during the first year of treatment and then remained stable. The incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar with dimethyl fumarate and placebo, respectively. Before initiating treatment, a recent CBC (within 6 months) should be available, and is recommended annually and as clinically indicated. Treatment should be withheld in patients with serious infections until infection is resolved.*
- *40% of dimethyl fumarate treated patients experienced flushing. Flushing begin soon after initiation and usually improve over time. Administration of dimethyl fumarate with food may decrease flushing.*

Unanswered safety Questions: Further evaluation in ongoing long-term safety studies

Look-alike / Sound-alike (LA/SA) Error Risk Potential: None identified

Adverse Reactions Table[21]

In clinical trials, the most commonly observed adverse reactions, incidence ≥2% higher than placebo, reported in the prescribing information.

Adverse Reaction	Placbo (n=771)	Dimethyl fumarate (n=769)
Flushing	6%	40%
Abdominal pain	10%	18%
Diarrhea	11%	14%
Nausea	9%	12%
Albumin urine present	4%	6%
Vomiting	5%	9%
AST increased	2%	4%
Dyspepsia	3%	5%
Pruritus	4%	8%
Rash	3%	8%
Erythema	1%	5%
Lymphopenia	<1%	2%

Allergies/Interactions:
Drug-Drug: Live vaccines
Food-Drug: None known

Appendix 2: PA criteria

Oral MS Drugs

Goal(s):

- To ensure appropriate and safe drug use drugs
- Promote preferred drugs

Length of Authorization: One year

Requires PA:

- **Fingolimod (Gilenya)**
- **Teriflunomide (Aubagio)**
- **Dimethyl Fumarate (Tecfidera)**

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of relapsing Multiple Sclerosis (ICD-9 340)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Will the prescriber consider a change to a Preferred MS product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	**Yes:** Inform Provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml	**No:** Go to #4
4. Has the patient failed or cannot tolerate a full course of interferon beta 1a or interferon beta 1b, and glatiramer?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny (medical appropriateness)
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6.	**No:** Pass to RPH; Deny (medical appropriateness)
6. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta-1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #7
7. Is the prescription for teriflunomide?	**Yes:** Go to #8	**No:** Go to #10

8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Approve for up to one year
9. Does the patient currently on a documented use of reliable contraception?	**Yes:** Approve up to one year	**No:** Pass to RPH; Deny (medical appropriateness)
10. Is the prescription for fingolimod?	**Yes:** Go to #11	**No:** Pass to RPH; Deny (medical appropriateness)
11. Does the patient have evidence of macular edema (ICD-9 362.07)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #12
12. Does the patient has preexisting cardiac disease, risk factors for bradycardia, or is on antiarrhythmics, beta-blockers, or calcium channel blockers?	**Yes:** Go to #13.	**No:** Approve up to one year
13. Has the patient had a cardiology consultation before initiation?	**Yes:** Approve up to one year	**No:** Pass to RPH; Deny (medical appropriateness)

Fingolimod Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for six hours after initial dose in a clinically appropriate area.
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with bradycardia risk factors (h/o MI, age >70 yrs, electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod with caution and cardiology evaluation should be done before considering treatment.
- Injectable disease modifying treatments remain first line agents in MS therapy.
- An ophthalmology evaluation should be repeated 3- 4 months after fingolimod initiation with subsequent evaluations based on clinical symptoms.

Teriflunomide Clinical Notes:

- Before starting Terinflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in women of childbearing potential, check BP, obtain a complete blood cell count within the 6 months prior to starting therapy, instruct patients receiving Terinflunomide to report symptoms of infections, and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting Terinfluomide, monitor ALT levels at least monthly for 6 months after, consider additional ALT monitoring when Terinflunomide is given with other potentially hepatotoxic drugs, consider stopping Teriflunomide if serum transaminase levels increase (>3 times the ULN), monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction, stop TER and start accelerated elimination in those with suspected TER-induced liver injury and monitor liver tests weekly until normalized, check BP periodically and manage elevated BP, check serum potassium level in TER-treated patients with hyperkalemia symptoms or acute renal failure, monitor for signs and symptoms of infection.
- Monitor for hematologic toxicity when switching from TER to another agent with a known potential for hematologic suppression, because systemic exposure to both agents will overlap.

Dalfampridine (Ampyra)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which the drug has been shown to be effective and safe.

Length of Authorization: One year.

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of Multiple Sclerosis (ICD-9 340)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Is the request for continuation of therapy? (Patient has completed two month trial)	**Yes:** Go to "Continuation of Therapy"	**No:** Go to #5
5. Does the patient have a history of seizures (ICD-9 345.00-345.51, 345.80, 345.81, 780.33-780.39)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #6
6. Does the patient have moderate to severe renal impairment (CrCl <50 ml/min)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #7
7. Is the patient ambulatory with a walking disability requiring use of a walking aid OR with moderate ambulatory dysfunction who do not require a walking aid AND • Is able to complete the baseline timed 25 foot walk between 8 and 45 seconds	**Yes:** Approve initial fill for 2 month trial.	**No:** Pass to RPH; Deny (medical appropriateness)

Continuation of Therapy

1. Has the patient been taking dalfampridine for 2 months or longer and has demonstrated that walking speed has improved while on dalfampridine (documentation of ≥20% improvement in timed 25 foot walk).	**Yes:** Go to #2	**No:** Pass to RPH; Deny (medical appropriateness)
2. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny (medical appropriateness)

Clinical Notes:

- Because fewer than 50% of MS patients respond to therapy and therapy has risks, a trial of therapy should be used prior to beginning ongoing therapy.
- The patient should be evaluated prior to therapy and then 4 weeks to determine whether objective improvements which justify continued therapy are present (i.e. at least a 20% improvement from baseline in timed walking speed).
- Dalfampridine is contraindicated in patients with moderate to severe renal impairment.
- Dalfampridine can increase the risk of seizures; caution should be exercised when using concomitant drug therapies known to lower the seizure threshold.

DUR Board Action: 3-29-2012
Revision(s):
Initiated:

Authors: Kala Berkey, Pharm.D. Candidate and M. Herink, Pharm.D.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Abbreviated Class Update: Long-Acting Opioids (LAOs)

Month/Year of Review: September 2013
New drug(s): tramadol ER (Ultram ER™, Conzip™, & generics)

End date of literature search: July 2013
Manufacturers: Janssen Pharmaceutical, Inc. Vertical Pharmaceuticals Inc., & various

Oregon PDL status	Drug	Trade name(s)	Forms evaluated in review	Recommended usual dosing frequency (times per day)
N	buprenorphine	Butrans™	ER transdermal film	Every 7 days
Y	fentanyl	Duragesic™	ER transdermal film	Every 72 hours
N	hydromorphone ER	Exalgo™	ER oral tablet	1
N	levorphanol	generic	Oral tablet	3-4
N	methadone	generic, Dolophine™	Oral tablet	2-3
N	morphine sulfate ER	generic	ER oral capsule	1
N		Avinza™	ER oral capsule	1
N		Kadian™	ER oral capsule	1-2
N		generic	ER oral capsule	1-2
Y		generic	ER oral tablet	2-3
Y		MS Contin™	ER oral tablet	2-3
N	morphine sulfate and naltrexone hydrochloride	Embeda™	ER oral capsule	1-2
N	oxycodone ER	OxyContin™	ER oral tablet	2
N	oxymorphone ER	Opana ER™	ER oral tablet	2
N	tapentadol ER	Nucynta ER™	ER oral tablet	2
	tramadol ER	generic	ER oral tablet	1
		Ultram ER™	ER oral tablet	1
		Conzip™	ER oral capsule	1

Abbreviations: ER, extended release; MS, morphine sulfate; SR, sustained release.

There is a maximum dose prior authorization (PA) required for doses greater than 120 morphine equivalent doses (MED) on all LAOs. Duplication of LAOs is not allowed except for cross-titration. Methadone carries an additional PA for initial doses above 20mg per day when prescribed for pain. Methadone for addiction treatment is covered via professional claims.

Research Questions:

- Is there any evidence about comparative effectiveness of tramadol extended release (ER) versus the different long-acting opioids, in reducing pain and improving functional outcomes in adult patients being treated for chronic non-cancer pain?
- Is there any new evidence about comparative harms (including addiction and abuse) of tramadol ER versus the different long-acting opioids in adult patients being treated for chronic non-cancer pain?
- Are there subpopulations of patients (specifically by race, age, sex, socioeconomic status type of pain, or comorbidities) with chronic non-cancer pain for which tramadol ER is more effective or associated with less harm?

Conclusions:

- There is insufficient comparative evidence to establish differences in effectiveness of tramadol ER versus the other LAOs.
- There is insufficient comparative evidence to establish differences in safety of tramadol ER versus the other LAOs.
- There is insufficient comparative evidence in subpopulations to differentiate tramadol ER from the other LAOs.

Recommendations:

- Tramadol ER should be evaluated in executive session for relative cost.
- Set maximum daily dose to 300mg per the drug label.

Reason for Review: Oregon reviewed the literature in this class in July 2013 and recommended adding tramadol extended release products to complete the class.

Previous P&T Conclusions:

- There continues to be insufficient comparative evidence to establish differences in effectiveness among the LAOs. Morphine and fentanyl have the most evidence of efficacy against placebo per DynaMed. Treatment guidelines consistently recommend morphine as first-line with fentanyl patches recommended for patients who cannot tolerate oral medications.
- There continues to be insufficient comparative evidence to establish differences in safety among the LAOs. All LAOs carry FDA Black Box warnings for increased risk of death and risk of abuse and misuse. However, methadone alone carries the warning of accumulation and was associated with more than 30% of opioid related deaths in Oregon.
- There is insufficient comparative evidence in subpopulations to differentiate drugs.

Background: Tramadol ER is a weak opioid μ-agonist and thus differs from the other drugs in this class which are strong opioid μ-agonists. It also weakly inhibits norepinephrine and serotonin reuptake. It is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of pain for an extended period of time (at least 3 to 6 months).[1,2] Tramadol ER is recommended after non-opioids have failed and prior to initiation of full opioid μ-agonists by the Canadian Pain Society,[3,4] the National Institutes if Clinical Excellence[5] guidelines and the World Health Organization's (WHO) "analgesic ladder."[6] Potential off-label uses include premature ejaculation[7] and restless leg syndrome.[8]

Methods:
A Medline literature search ending July 2013 for new systematic reviews and randomized controlled trials (RCT's) that compared tramadol to long-acting opioids in head to head trials for chronic pain was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. After review of the citations from Medline and the manual searches, three systematic reviews[9,10,11] comparing tramadol to opioid treatments and two updated chronic pain treatment guidelines[3,4,5] were included in this review.

Systematic Reviews:
The DynaMed[9] review notes that not only is the comparative evidence lacking for this class but, that evidence of efficacy of the individual opioids is weak overall, with the best evidence for morphine ER tablets and transdermal fentanyl. DynaMed reports Level 1 Evidence (likely reliable) based upon a single Cochrane Review[12] that tramadol provides small degree of pain relief in osteoarthritis of knee and/or hip over placebo but insufficient evidence of benefit over active controls. Another Cochrane review provided Level 2 Evidence (mid-level) tramadol was effective over placebo for neuropathic pain but there was insufficient evidence against morphine.

A Clinical Evidence review of postherpetic neuralgia treatments found low-quality evidence that tramadol was likely be beneficial when compared to placebo (n=149).[10]

Another Clinical Evidence review of opioids in people with cancer-related pain found insufficient evidence to assess the equivalence, in terms of analgesic benefit and adverse effects, of morphine compared with codeine, dihydrocodeine, fentanyl, hydromorphone, methadone, oxycodone, or tramadol.[11]

New Guidelines:

The National Institute of Clinical Excellence published guidance on the use of strong opioids for pain in palliative care in 2012 and recommends they only be used for patients not controlled on codeine or tramadol.[5]

The Canadian guidelines[3,4] for chronic nonmalignant pain were updated and published in 2011. The guidelines include recommendations on opioid indications, selection, titration, precautions and monitoring. Only selection recommendations are reported here. After a failed trial of either codeine or tramadol, morphine is recommended for patients without renal impairment.

References:

1. ULTRAM ER (TRAMADOL HYDROCHLORIDE) TABLET, EXTENDED RELEASE [JANSSEN PHARMACEUTICALS, INC.]. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=039f9e7c-97f5-4062-8656-6f355c82008e. Accessed August 21, 2013.

2. CONZIP (TRAMADOL HYDROCHLORIDE) CAPSULE, EXTENDED RELEASE [VERTICAL PHARMACEUTICALS INC.]. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=2347726f-7755-7026-426c-6f7741776179#section-1. Accessed August 21, 2013.

3. Kahan M, Mailis-Gagnon A, Wilson L, Srivastava A, National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: general population. *Can Fam Physician*. 2011;57(11):1257–1266, e407–418.

4. Kahan M, Wilson L, Mailis-Gagnon A, Srivastava A, National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations. *Can Fam Physician*. 2011;57(11):1269–1276, e419–428.

5. Bennett MI, Graham J, Schmidt-Hansen M, Prettyjohns M, Arnold S, Guideline Development Group. Prescribing strong opioids for pain in adult palliative care: summary of NICE guidance. *BMJ*. 2012;344:e2806.

6. World Health Organization. WHO | WHO's pain ladder for adults. *WHO*. Available at: http://www.who.int/cancer/palliative/painladder/en/index.html. Accessed June 19, 2013.

7. Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. *J Clin Psychopharmacol*. 2006;26(1):27–31.

8. Hening WA, Allen RP, Earley CJ, Picchietti DL, Silber MH, Restless Legs Syndrome Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep*. 2004;27(3):560–583.

9. DynaMed. DynaMed: Opioids for chronic pain. *DynaMed*. 2013. Available at: http://web.ebscohost.com.liboff.ohsu.edu/dynamed/detail?vid=3&sid=66448eff-e5db-4c50-ab49-3cc13d4f51d7%40sessionmgr113&hid=113&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=361112. Accessed June 17, 2013.

10. Watson PN. Postherpetic neuralgia. *Clinical evidence*. 2010;2010. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3217735/. Accessed August 21, 2013.

11. Quigley C. Opioids in people with cancer-related pain. *Clinical evidence*. 2008;2008. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907984/. Accessed August 21, 2013.

12. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. *Cochrane Database of Systematic Reviews*. 2009;(1). Available at: http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD005522.pub2/abstract. Accessed August 21, 2013.

Appendix 1: Specific Drug Information

PHARMACOKINETICS[1,2]

Parameter	Result
Oral Bioavailability	85-90%
Protein Binding	20%
Elimination	Renally excreted: 30% unchanged and 60% as metabolites
Half-Life	10-11 hours
Metabolism	P450 CYP2D6, 3A4 and conjugation

DOSE & AVAILABILITY[1,2]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
100mg, 200mg, 300mg	PO	Q24H	Initially 100mg Q24H, with titration of 50mg Q5D to desired effect or maximum dose of 300mg Q24H	Not recommended if Cr. Clearance is <30ml/min	Do not use in patients with severe hepatic impairment (Child-Pugh class C)	The use of tramadol in children is not recommended.	On Beers watch list but no adjustments in label for normal renal and hepatic function	ADEs experienced at higher frequency in elderly.

DRUG SAFETY[1,2]

Serious (REMS, Black Box Warnings: No Black Box Warnings or REMS

Warnings and Precautions: Seizures have been reported within the normal dose range. Concomitant use with drugs affecting the serotonin system or in patients with increased seizure risk is not recommended. Serotonin syndrome may occur. Do not prescribe for patients who are suicidal or addiction prone.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

TraMADol may be confused with tapentadol, Toradol, Trandate, traZODone, Voltaren

Ultram may be confused with Ultane, Ultracet, Voltaren

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: September 2013
PDL Classes: Antivirals – Hepatitis C agents

Date of Last Review: Drug January 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- **Preferred Agents:** BOCEPREVIR CAPSULES (VICTRELIS®) PEGINTERFERONE ALFA-2B (PEGINTRON REDIPEN®), PEGINTERFERON ALFA-2B (PEGINTRON®) KIT, RIBAVIRIN CAPSULES AND TABLETS, TELAPREVIR (INCIVEK®) TABLETS
- **Non-Preferred Agents:** PEGINTERFERON ALFA-2A (PEGASYS PROCLICK®, PEGASYS®), RIBAVIRIN DOSE-PACK (RIBAPAK®)

Current PA: Prior authorization criteria is currently in place for oral protease inhibitors (Appendix 1) to ensure that they are used in appropriate patients and in consultation with a hepatologist, and for pegylated interferons and ribavirins (Appendix 2) to support preferred alternatives.

Research Questions:

- Is there any new evidence about comparative effectiveness of antiviral regimens, in long term clinical outcomes such as mortality and hepatitis C complications or in sustained virologic response (SVR) in adult patients being treated for chronic Hepatitis C virus (HCV)?
- Is there any new evidence about comparative harms of antiviral regimens in adult patients being treated for chronic HCV?
- Are there subpopulations of patients with HCV for which one antiviral regimen is more effective or associated with less harm?

Conclusions:

- There is moderate strength evidence from a recent AHRQ report of a lower chance of achieving an SVR with dual therapy with pegylated interferon alfa-2b plus ribavirin compared to dual therapy with pegylated interferon alfa- 2a (pooled RR 0.87, 95% CI 0.80 to 0.95; I^2=27.4%), with an absolute difference in SVR rates of 8 percentage points, while dual therapy with interferon alfa-2b is associated with a lower risk of serious adverse events than dual therapy with interferon alfa-2a (pooled RR 0.76, 95% CI 0.71 to 0.88; I^2=0.0%) with no differences in withdrawals due to adverse events (pooled RR 1.1, 95% CI 0.73 to 1.7, I^2=42%).
- There is high quality evidence that triple therapy with either boceprevir or telaprevir produces a higher likelihood of achieving SVR as compared to dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin.
- There is insufficient direct comparative evidence between boceprevir (BOC) and telaprevir (TVR) on long term clinical outcomes.

Recommendations:

- There are multiple new drugs in the pipeline that are expected to change the course of therapy. No further research or review needed until available.
- Recommend to maintain either one or both of peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (PegIntron®) as preferred pegylated interferon products.

- Consider removing criteria #9 of current PA criteria, requiring denial for patients with HIV coinfection.
- Evaluate comparative costs in executive session.

Previous Conclusions and Recommendation:

- Recommend to maintain either one or both of peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (PegIntron®) as preferred pegylated interferon products. These two agents are recommended in the current guidelines and have been shown to be similar in efficacy and safety.
- Designate interferon alfacon-1 as a non-preferred agent due to the lack of recommendations for use in current treatment guidelines.
- Prior authorize the oral protease inhibitors (boceprevir [BOC] and telaprevir [TVR]) for use in patients with genotype 1 chronic hepatitis c in combination with pegylated interferon and ribavirin and other drug specific criteria (Appendix 1).

Methods:

A Medline literature search beginning August 2012 (since the most recent AHRQ report) and ending July 2013 for new systematic reviews and randomized controlled trials (RCTs) that compared antiviral regimens and oral protease inhibitors, including boceprevir (BOC) and telaprevir (TVR) was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic reviews:

1. An AHRQ comparative effectiveness review evaluated the comparative benefits and harms of current antiviral treatment regimens for chronic HCV in treatment-naïve adults.[1] A total of 90 RCTs and observational studies were included from a literature search up to August 2012. There was no direct evidence comparing current regimens on long-term clinical outcomes. However, results from 5 trials provided moderate strength evidence that SVR rates were substantially higher in patients with HCV genotype 1 infection who were on triple therapy with pegylated interferon, ribavirin, and an oral protease inhibitor (boceprevir or telaprevir) compared with dual therapy with pegylated interferon plus ribavirin (absolute increase in SVR rates of 22-31%). Triple therapy with boceprevir was associated with increased risk of hematological effects while therapy with telaprevir was associated with an increased risk of anemia and severe rash compared to dual therapy. There was insufficient evidence to compare effectiveness of triple therapy to dual therapy based on fibrosis state.

   There was a difference in absolute SVR of about 8%, and moderate strength evidence of a slightly lower chance of achieving an SVR with dual therapy with pegylated interferon alfa-2b compared to dual therapy with pegylated interferon alfa- 2a (pooled RR 0.87, 95% CI 0.80 to 0.95; I2=27.4%). The largest study found no difference in SVR rates for dual therapy between the interferons. There was no difference in risk of withdrawals due to adverse events, but dual therapy with interferon alfa-2b was associated with a lower risk of serious adverse events than dual therapy with interferon alfa-2a (pooled RR 0.76, 95% CI

0.71 to 0.88; I2=0.0%). A large cohort study found that patients who achieved an SVR had a lower risk of all-cause mortality than patients who did not (Hazard ratio ranging from 0.51 to 0.71, depending on genotype).

2. The DynaMed review[2] notes that for patients with genotype 1, optimal therapy is protease inhibitor (boceprevir or telaprevir) plus peginterferon alfa and ribavirin based on increased virologic response rates. The same level of evidence is given for both protease inhibitors. It cites level 3 (low) evidence that boceprevir is as effective as telaprevir for reducing relapse and improving SVR when used with peginterferon alfa plus ribavirin.

3. A meta-analysis evaluated for the efficacy and tolerability of TVR in genotype 1 HCV.[3] Five RCT's evaluating TVR with peginterferon-alfa2b and ribavirin were identified and included. Trials were assessed for quality using the Cochrane methodology and the included trials generally were at a low risk of bias. The pooled estimates showed that the proportion of patients achieving SVR was significantly higher in the TVR group than the dual therapy group (OR 3.40; 95% CI 1.92-6.00, p<00001, I^2 =87%).[3] This was true for both the previously untreated subgroup (OR 2.25, 95% CI 1.35-3.77; p=0.002; i^2=77%) and in the previously treated subgroup (OR 6.70, 95% CI 3.35-13.41; p<0.002, I^2=71%). In addition, the incidence of drug discontinuations due to adverse events was significantly higher in the TVR group (OR 2.24, 95% CI 1.43-3.50; p<0.001; I^2=37%), with the most common being rash and anemia. This review included a small number of trials with significant heterogeneity. [3]

4. Another meta-analysis of RCTs compared the efficacy and safety of the addition of TVR to a standard regimen of peginterferon and ribavirin to the standard regimen alone.[4] Six RCTs were included in this meta-analysis and assessment of study quality was done using the Jadad system. Significant heterogeneity was observed between the included studies (I^2=80.5%, p<0.001). Overall, there was a significantly greater SVR rate in the TVR group compared to the standard group (66.5% vs. 35.8%, respectively, OR 3.81, 95% CI 2.43-5.96). This was similar in the subgroup of previously treated patients (OR 8.17, 95% CI 5.61-11.92) and untreated (OR 2.90, 95% CI 2.36-3.56). [4]

5. An indirect comparison of TVR and BOC in treatment-naïve and treatment-experienced genotype 1 CHC patients was conducted, using a Bayesian network meta-analysis framework.[5] A literature review identified all RCTs through July 2011; no head to head trials were available. Each trial was assessed for quality using the Cochrane metholodogy. A total of 11 studies were of acceptable quality and included in the meta-analysis. The analysis showed both BOC (OR 2.99; 95% CI 2.23-4.01) and TVR (3.80; 95% CI 2.78-5.22) to be superior to conventional dual therapy. Based on indirect comparisons, a meta-analysis suggests better efficacy for TVR than BOC in both treatment-naïve (OR 1.42, 95% CI 0.89-5.22) and treatment-experienced patients (OR 2.45; 95% CI 1.02-5.80). [5]

6. A systematic review with indirect comparisons included 13 RCTs evaluating direct-acting protease inhibitors in patients with HCV genotype 1 infection.[6] Six trials evaluated pegylated interferon alfa-2a plus ribavirin vs. pegylated interferon alfa-2b plus ribavirin. Three trials compared TVR plus peginterferonalpha-2a plus ribavirin to pegineterferon alfa-2a plus ribavirin and 4 trials compared BOC plus peginterferon alpha-2b plus ribavirin to opeginterferon alpha-2b plus ribavirin. Using indirect comparisons, TVR and BOC were statistically comparable in achieving SVR (OR 1.11; 95% CI 0.23-5.68) and relapse (OR 1.09; 95% CI 0.19-4.83). In treatment-experienced patients TVR and BOC were also comparable in achieving SVR (OR 1.45; 95% CI 0.70-3.08), relapse (OR 0.35; 95 % CI 0.13-1.02), and in discontinuations due to adverse events (OR 0.44; 95% CI 0.11 to 1.63). Triple therapy with either BOC or TVR achieved higher SVR rates, lower relapse rates, and higher discontinuation rates than dual therapy. There was a higher incidence of rash in patients treated with TVR compared with BOC (OR 3.09; 95% CI 1.45-6.65) and for treatment-experienced patients, all adverse event rates were higher with TVR.

7. Another mixed treatment comparisons looked at the differences in efficacy between BOC and TVR in the treatment of HCV genotype 1.[7] A literature search up to September 2012 identified 10 studies, 6 in treatment-naïve patients and 4 in treatment-experienced. Most of the studies had a low risk of bias. In treatment-naïve patients, there was insufficient evidence to detect a difference between TVR and BOC (OR 1.06, 95% CI 0.75-1.47). In the overall treatment experienced population (n=1495), there was also insufficient evidence to detect a difference in SVR between the two agents when added to standard of care (OR 1.27, 95% CI 0.71-2.30). When including only those patients with a prior treatment relapse (n=841), there was a significant difference in efficacy, favoring TVR (OR 2.61, 95% CI 1.24-5.52).

8. A meta-analysis evaluated if there were any differences in dual therapy with peginterferon alfa-2b vs. peginterferon alfa-2a in SVR, relapse, and treatment discontinuation.[8] Twenty-one trials were included for peginterferon alpha-2a plus ribavirin and fourteen trials included peginterferon alpha-2b plus ribavirin. Five were direct head-to-head evaluations. Among treatment naïve patients, the pooled estimate of SVR was 47% for those treated with peginterferon alpha-2a plus ribavirin and 40% for peginterferon alpha-2b plus ribavirin. For treatment-experienced patients, 12% on peginterfron alpha-2a achieved a SVR compared to 16% on peginterferon alpha-2b. The subgroup of head-to-head trials showed no significant differences between the two treatments.

9. Another meta-analysis of RCTs was performed to evaluate the efficacy and tolerability of peginterferon alfa-2a and peginterferon alfa-2b, both plus ribavirin.[9] A literature search through August 30, 2012 included 7 trials after review and exclusion. The methodological quality of the studies was assessed according to the Cochrane Collaboration's tool. In total, 1845 and 1823 patients were randomly treated with peginterferon alfa-2a and peginterferon alfa-2b, respectively. The overall SVR rates for patients treated with peginterferon alfa-2a plus ribavirin were 46.7% compared to 42.4% of patients treated with peginterferon alfa-2b (OR 1.20, 95% CI 1.04-1.38, p=0.01). A subgroup analysis found that SVR rate was significantly higher in the peginterferon alfa-2a group compared to peginterferon alfa-2b in treatment naïve patients (47.9% vs. 43.5%, OR 1.20, 95% CI 1.04-1.39, p=0.01). Meta-analysis by a random-effects model revealed similar discontinuation rates, while meta-analysis by a fixed-effects model demonstrated that peginterferon alfa-2a had a significantly lower discontinuation rate than peginterferon alfa-2b (27.9% vs. 33.9%, OR 0.71, 95% CI 0.61-0.84; p<0.0001).

10. A meta-analysis of data from 22 phase II and III trials compared 24 and 48 week SVR and adverse events between TVR and BOC regimens in the treatment of chronic HCV.[10] Both agents were compared to control therapy (peginterferon plus ribavirin) and indirectly compared to each other in a simple pairwise comparison. The indirect comparison favored TVR for 24-233k SVR in treatment-naïve patients (OR 1.78, 95% CI 1.39-2.28; p<0.0001) but there was no difference at 48 weeks (OR 0.82, 95% CI 0.6-1.11; p=0.2). TVR and BOC were similar in discontinuations due to adverse events (OR 1.23, 95% CI 0.95-1.6; p=0.11). Both agents showed improved SVR compared to dual therapy while increasing adverse events. [10]

New drugs/formulations/indications:
None

Horizon Scan:
A recent AHRQ Horizon Scan report identified 10 antiviral agents that are currently in Phase III trials for the treatment of chronic HCV.[11] Many of these agents are being studied as an interferon-free regimen and many have been granted fast-track status by the FDA. In particular, the drug sofosbuvir, is expected to have

high potential to address significant unmet needs for HCV treatment due to its high efficacy and being well-tolerated, as well as a shorter and simpler dosing regimen.[12] In June of this year, FDA granted sofosbuvir priority review with a Prescription Drug User Fee Act date of December 8, 2013. [12]

New FDA Safety Alerts:

In December 2012, the FDA released a drug safety communication of reports of serious skin reactions, some fatal, in patients taking telaprevir in combination with peginterferon and ribavirin.[13] Some patients died when they continued treatment after developing a worsening, or progressive rash and systemic symptoms. A boxed warning was added to the drug label that telaprevir combination treatment must be immediately stopped in patients experiencing a rash with systemic symptoms or a progressive severe rash.

New Guidelines:

The World Gastroenterology Organization updated their guideline on diagnosis, management and prevention of hepatitis.[14] The following are the main recommendations:

- All chronic hepatitis C patients with compensated liver disease should be considered for treatment.
- Treatment is strongly recommended for patients with moderate to advanced fibrosis
- Patients with mild disease should be considered for treatment on an individual basis, taking into account their age, gender, metabolic syndrome, symptoms, and motivation.
- Naïve CHC HCV genotype 1 patients with non-CC +Il28B and fibrosis F3-F4 should be treated with triple therapy for 48 weeks.
- Naïve patients with CC genotype IL28B and f1-f2 receive standard of care greamtnet (dual therapy) for 48 weeks, achive the same SVR rate.
- Special caution is needed in the treatment of patients with clinically apparent cirrhosis. Triple therapy is poorly tolerated and is associated with a 2% mortality rate.
- All patients in whom dual therapy treatment has failed, relapsers, partial responders, and null responders should be treated with triple therapy.

The U.S. preventive Services Task Force (USPSTF) recommend screening for HCV infection in persons at high risk for infection.[15] They also recommend offering 1-time screening for HCV infection to adults born between 1945 and 1964 (B recommendation). This recommendation came from 2 AHRQ systematic reviews used to update the screening recommendations. These reviews focused on evidence gaps identified in the previous recommendations.

The Department of Veterans Affairs (VA) Hepatitis C Resource Center Program/National Hepatitis C Program Office (HCRC/HCV) updated the recommendations on management and treatment of hepatitis C virus infection.[16] A grading system for recommendations was adapted from the AASLD guidelines. Major recommendations are as followed:

- IL28B genotype testing can be performed before pegylated interferon plus ribavirin, with or without a protease inhibitor, if the information on the probability of treatment response or duration would alter treatment decisions (Class IIa, Level B).
- Peggylated interferon and ribavirin, in combination with boceprevir or telaprevir is the standard of care for most treatment-naïve genotype 1-infected patients (Class I, Level A).
- For patients who previously failed PegIFN – RBV, retreatment with BOC or TVR, and PegIFN – RBV may be considered, particularly in patients who were relapsers (Class I, Level A).

- PegIFN alfa and RBV doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin, or platelets, as outlined in **Table 5** (Class I, Level A).
- If RBV is stopped for 7 days or more in patients who are concomitantly receiving BOC or TVR, then the PI also should be permanently discontinued (Class I, Level A).
- HCV PIs should be either continued at full dose or discontinued (Class I, Level A).
- Initial management of HCV treatment-related anemia should consist of RBV dose reduction in a symptomatic patientwith a hemoglobin < 10g/ dl, or as clinically indicated. Erythropoietin may be administered in patients with symptomatic anemia related to PegIFN – RBV therapy with or without BOC / TVR to limit anemia-related RBV dose reductions or dose disconinuations (Class II, LEVEL C)
- Initial management of HCV treatment-related neutropenia should consist of PegIFN dose reduction for an ANC < 750, or as clinically indicated. Granulocyte colony-stimulating factor should not be given as primary therapy to prevent PegIFN alfa dose reductions (Class I, Level C).

Guidance from NICE[17] recommends telaprevir in combination with peginterferon alfa and ribavirin as an option for genotype 1 CHC in adults with compensated liver disease:

- Who are previously untreated OR
- In whom previous treatment with interferon alfa alone or in combination with ribavirin has failed, including relapsers, partial responders, or non-responders.

Guidance from NICE[18] recommends boceprevir in combination with peginterferon alfa and ribavirin as an option for genotype 1 CHC in adults with compensated liver disease:

- Who are previously untreated OR
- In whom previous treatment has failed

Randomized Controlled Trials: A summary of the identified trials are in Table 1 below and the abstracts are in Appendix 3.

Study	Comparison	Population	Primary Outcome	Results
Flamm et al.[19] DB,RCT	BOC + pegenterferon alfa-**2a** + ribavirin vs. peginterferon alfa-2a + ribavirin	Adults with genotype-1 HCV with previously responsiveness to peginterferon and ribavirin but failure to achieve SVR N=201	SVR at 24 weeks	<u>% achieving SVR</u> BOC: 64% Peg/rib: 21% P<0.0001 Similar results as previous studies using BOC in combination with peginterferon alfa-2b
Gane et al.[20] Randomized, open-label	Sofosbuvir + ribavirin x 12 weeks vs. sofosbuvir + ribavirin + 4 wk, 8wk, or 12 wk of peginterferon	19 years or older Chronic HCV w/o cirrhosis Genotype 1, 2, and 3 N=95	SVR at 24 weeks	The presence or absence of peginterferon alfa-2a appeared to have no effect on rate of SVR

	alfa-2a			
Kowdley et al[21] Randomized, open-label	Sofosbuvir 200mg/day vs. sofosbuvir 400mg/day vs. placebo	18-70 years with previously untreated CHC (genotype 1)	SVR at 24 weeks	<u>SVR at 12 weeks</u> 90% (p=0.001) 91% (p=0.0005) 58%
Sulkowski et al.[22] Subanalysis of Sprint-2[23]	BOC + peginterferon + ribavirin who developed anemia vs. those who did not develop anemia	Previously untreated patients with chronic HCV genotype 1 N=1097	Relationship between SVR and treatment-associated anemia and its management	<u>SVR rate</u> Anemia: 72% No anemia: 58% <u>SVR based on anemia management:</u> EPO: 74% RBV Reduction: 72% Both: 70% Neither: 73%

References:

1. Chou R, Hartung D, Rahman B, Wasson N, Cottrell E, Fu R. *Treatment for Hepatitis C Virus Infection in Adults*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012. Available at: http://www.ncbi.nlm.nih.gov/books/NBK115347/. Accessed July 18, 2013.

2. DynaMed. Hepatitis C. *DynaMed*. 2013. Available at: http://web.ebscohost.com/dynamed/results?sid=fdd7778f-60ad-424a-b86b-d135104a2f63%40sessionmgr115&vid=6&hid=127&bquery=hepatitis+AND+c&bdata=JnR5cGU9MCZzaXRlPWR5bmFtZWQtbGl2ZSZzY29wZT1zaXRl.

3. Kong Y, Wang X, Shang Y, et al. Efficacy and tolerability of telaprevir for chronic hepatitis virus C genotype 1 infection: a meta-analysis. *PLoS ONE*. 2012;7(12):e52158. doi:10.1371/journal.pone.0052158.

4. Yang D, Liang HJ, Li D, Wei X, Ma L, Jia Z. The efficacy and safety of telaprevir-based regimens for treating chronic hepatitis C virus genotype 1 infection: a meta-analysis of randomized trials. *Intern Med*. 2013;52(6):653–660.

5. Cure S, Diels J, Gavart S, Bianic F, Jones E. Efficacy of telaprevir and boceprevir in treatment-naïve and treatment-experienced genotype 1 chronic hepatitis C patients: an indirect comparison using Bayesian network meta-analysis. *Curr Med Res Opin*. 2012;28(11):1841–1856. doi:10.1185/03007995.2012.734798.

6. Cooper C, Lester R, Thorlund K, et al. Direct-acting antiviral therapies for hepatitis C genotype 1 infection: a multiple treatment comparison meta-analysis. *QJM*. 2013;106(2):153–163. doi:10.1093/qjmed/hcs214.

7. Kieran J, Schmitz S, O'Leary A, et al. The relative efficacy of boceprevir and telaprevir in the treatment of hepatitis C virus genotype 1. *Clin Infect Dis*. 2013;56(2):228–235. doi:10.1093/cid/cis880.

8. Druyts E, Mills EJ, Nachega J, O'Regan C, Cooper CL. Differences in clinical outcomes among hepatitis C genotype 1-infected patients treated with peginterferon alpha-2a or peginterferon alpha-2b plus ribavirin: a meta-analysis. *Clin Exp Gastroenterol*. 2012;5:11–21. doi:10.2147/CEG.S28253.

9. Yang Z, Zhuang L, Yang L, Chen X. Efficacy and Tolerability of Peginterferon α -2a and Peginterferon α -2b, Both plus Ribavirin, for Chronic Hepatitis C: A Meta-Analysis of Randomized Controlled Trials. *Gastroenterol Res Pract*. 2013;2013:739029. doi:10.1155/2013/739029.

10. Sitole M, Silva M, Spooner L, Comee MK, Malloy M. Telaprevir versus boceprevir in chronic hepatitis C: a meta-analysis of data from phase II and III trials. *Clin Ther*. 2013;35(2):190–197. doi:10.1016/j.clinthera.2012.12.017.

11. ECRI Institute. AHRQ Healthcare Horizon Scanning System Status Update. (Prepared by ECRI Institute under Contract No. HHSA290201000006C) Rockville, MD: Agency for HEalthcare Research and Quality. July 2013. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

12. ECRI Institute. AHRQ Healthcare HOrizon Scanning System Potential High-Impact Interventions: Priority Area 09: Infectious Disease Including HIV/AIDS. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. June 2013. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

13. Food and Drug Administration. FDA Drug Safety Communication: Serious skin reactions after combination treatment with the Hepatitis C drugs Incivek (telaprevir), peginterferon alfa, and ribavirin. 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm332731.htm.

14. World Gastroenterology Organisation Global Guidelines. Diagnosis, management and prevention of hepatitis C. 2013.

15. Moyer VA, on behalf of the U.S. Preventive Services Task Force*. Screening for Hepatitis C Virus Infection in Adults: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2013. doi:10.7326/0003-4819-159-5-201309030-00672.

16. Yee HS, Chang MF, Pocha C, et al. Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. *Am J Gastroenterol*. 2012;107(5):669–689; quiz 690. doi:10.1038/ajg.2012.48.

17. National Institute for Health and Clinical Excellence. Telaprevir for the treatment of genotype 1 chronic hepatitis C. 2012.

18. National Institute for Health and Clinical Excellence. Boceprevir for the treatment of genotype 1 chronic hepatitis C. 2012.

19. Flamm SL, Lawitz E, Jacobson I, et al. Boceprevir with peginterferon alfa-2a-ribavirin is effective for previously treated chronic hepatitis C genotype 1 infection. *Clin Gastroenterol Hepatol*. 2013;11(1):81–87.e4; quiz e5. doi:10.1016/j.cgh.2012.10.006.

20. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med*. 2013;368(1):34–44. doi:10.1056/NEJMoa1208953.

21. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet*. 2013;381(9883):2100–2107. doi:10.1016/S0140-6736(13)60247-0.

22. Sulkowski MS, Poordad F, Manns MP, et al. Anemia during treatment with peginterferon Alfa-2b/ribavirin and boceprevir: Analysis from the serine protease inhibitor therapy 2 (SPRINT-2) trial. *Hepatology*. 2013;57(3):974–984. doi:10.1002/hep.26096.

23. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364(13):1195–1206. doi:10.1056/NEJMoa1010494.

Appendix 1: PA criteria

Hepatitis C Oral Protease Inhibitors/Triple Therapy

Goal(s) :

- Approve treatments of chronic hepatitis C which are supported by the medical literature

Length of Authorization

- Initial trial of 6-10 weeks (depending on regimen)
- Continuation of therapy up to 48 weeks of total therapy

Requies PA:

- Telaprevir
- Boceprevir

Approval Criteria		
1. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #2	**No:** Pass to RPh, Deny For Appropriateness
2. Does the patient have documented HCV genotype 1? Record Genotype:	**Yes:** Go to #3	**No:** Pass to RPh, Deny For Appropriateness
3. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin and has been granted prior authorization or meets criteria for pegylated interferon-alfa and ribavirin?	**Yes:** Go to #4	**No:** Pass to RPh, Deny For Appropriateness
4. Is the request for continuation of therapy? (Patient has been on triple therapy with a oral antiviral agent in preceding 6 weeks)	**Yes**: Go to "Continuation of Therapy	**No**: Go to #5
5. Does the patient have a Child-Pugh score < 7 (compensated liver disease)?	**Yes:** Go to #6	**No:** Pass to RPh, Deny For Appropriateness
6. Is the medication being prescribed by or in consultation with a specialist in the field of gastroenterology, infectious disease, or hepatitis C?	**Yes:** Go to #7	**No:** Pass to RPh, Deny For Appropriateness
7. If the patient has been treated with peginterferon and ribavirin before, do they have documented compliance/adherence to their previous treatment?	**Yes:** Go to #8	**No:** Pass to RPh, Deny For Appropriateness
8. Does the patient have a biopsy to indicate moderate to severe fibrosis (stage 2 or greater) OR radiologic, laboratory, or clinical evidence of cirrhosis? OR has extrahepatic manifestations (vasculitis, glomerulonephritis, cryoglobulins).	**Yes:** Go to #9	**No:** Pass to RPh, Deny For Appropriateness
9. Does the patient have a HIV coinfection?	**Yes:** Pass to RPh, Deny For Appropriateness	**No:** Go to #10
10. Has the patient previously been treated with boceprevir or telaprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #11

11. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks?	**Yes:** Approve for 6 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks	**No:** Go to #12 (If dose is different pass to RPh for appropriateness)
12. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon?	**Yes:** Approve for 10 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response	**No:** Pass to RPh; Deny for appropriateness

Continuation of Therapy- Telaprevir		
1. Is the patient treatment-naïve or a prior relapse patient and has undetectable HCV RNA or measured at 4 and 12 weeks?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
2. Is the patient treatment-naïve or a prior relapse patient and has detectable (1000 IU/mL or less) at Weeks 4 and/or 12	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
3. Is the patient a prior partial or null responder?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness)
4. Is the patient treatment-naïve with documented cirrhosis that has undetectable HCV-RNA at weeks 4 and 12?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
***TREATMENT FUTILITY RULES** Week 4 or Week 12: HCV-RNA greater than 1000 IU/mL: Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks) Week 24: Detectable Discontinue peginterferon and ribavirin. If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued		

Continuation of Therapy- Boceprevir		
1. Is the patient treatment-naïve and have undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
2. Is the patient treatment-naïve and have detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
3. Is the patient a previous partial responder or relapser and has undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir for total treatment duration of 36 weeks (4 week lead-in, 32 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
4. Is the patient a previous partial responder or relapser and has detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
5. Does the patient have documented cirrhosis or is documented as a null responder and does not meet the futility rules at treatment weeks 8, 12, and 24?	**Yes:** Approve as follows: • Continue triple therapy with boceprevir for a total treatment duration of 48 weeks (4 week lead-in, 44 weeks triple therapy).	**No:** DENY (Medical Appropriateness)
***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.		

Appendix 2: Interferon/ribavirin PA criteria

Interferons and Ribavirins

Goal(s):

Cover drugs only for those clients where there is medical evidence of effectiveness and safety

Length of Authorization: 16 weeks plus 12-36 additional weeks or 12 months

Requires pa: All drugs in HIC3 = W5G

Preferred Alternatives: See PDL list at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Is peginterferon requested preferred?	**Yes:** Go to #4	**No:** Go to #2.
2. Will the prescriber consider a change to a preferred product? Message: - Preferred products are evidence-based reviewed for comparative effectiveness & safety Oregon Pharmacy and Therapeutics (P&T) Committee	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.	**No:** Go to #3.
3. If the request is for interferon alfacon-1, does the patient have a documented trial of a pegylated interferon?	**Yes:** Go to #4.	**No:** Deny; Pass to RPH (Medical Appropriateness)
4. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code: (571.40; 571.41; 571.49)	**Yes:** Go to #5.	**No:** Go to #11
5. Is the request for continuation of therapy? (Patient has been on HCV treatment in the preceding 12 weeks according to the Rx profile)	**Yes:** Go to "Continuation of Therapy"	. **No:** Go to #6
6. Does the patient have a history of treatment with previous pegylated interferon-ribavirin combination treatment? Verify by reviewing member's Rx profile for PEG-Intron or Pegasys, PLUS ribavirin history. Does not include prior treatment with interferon monotherapy or non-pegylated interferon.	**Yes:** Forward to DMAP Medical Director	**No:** Go to #7
7. Does the patient have any of the following contraindications to the use of interferon-ribavirin therapy?	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #8

• severe or uncontrolled psychiatric disorder • decompensated cirrhosis or hepatic encephalopathy • hemoglobinopathy • untreated hyperthyroidism • severe renal impairment or transplant • autoimmune disease • pregnancy • unstable CVD		
8. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months?	**Yes:** Go to #9	**No:** Deny; Pass to RPH (Medical Appropriateness)
9. Does the patient have a detectable HCV RNA (viral load) > 50IU/mL? Record HCV RNA and date:	**Yes:** Go to #10	**No:** Deny; Pass to RPH (Medical Appropriateness)
10. Does the patient have a documented HCV Genotype? Record Genotype:	**Yes:** Approve for 16 weeks with the following response: Your request for has been approved for an initial 16 weeks. Subsequent approval is dependent on documentation of response via a repeat viral load demonstrating undetectable or 2-log reduction in HCV viral load. Please order a repeat viral load after 12 weeks submit lab results and relevant medical records with a new PA request for continuation therapy. Note: For ribavirin approve the generic only	**No:** Deny; Pass to RPH (Medical Appropriateness)
11. Is the request for Pegasys and the treatment of confirmed, compensated Chronic Hepatitis B?	**Yes:** Go to #11	**No:** Deny; Pass to RPH (Medical Appropriateness)
12. Is the patient currently on LAMIVUDINE (EPIVIR HBV), ADEFOVIR (HEPSERA), ENTECAVIR (BARACLUDE), TELBIVUDINE (TYZEKA) and the request is for combination Pegasys-oral agent therapy?	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #12
13. Has the member received previous treatment with pegylated interferon?	**Yes:** Deny; Pass to RPH (Medical Appropriateness) Recommend: LAMIVUDINE (EPIVIR HBV) ADEFOVIR (HEPSERA)	**No:** Approve Pegasys #4 x 1ml vials or #4 x 0.5 ml syringes per month for 12 months (maximum per lifetime).

Continuation of Therapy- HCV

<table>
<tr>
<td>1. Does the client have undetectable HCV RNA or at least a 2-log reduction (+/- one standard deviation) in HCV RNA measured at 12 weeks?</td>
<td>Yes: Approve as follows:

Approval for beyond quantity and duration limits requires approval from the medical director.

<table>
<tr><th>Genotype</th><th>Approve for</th><th>Apply</th></tr>
<tr><td>1 or 4</td><td>An additional 36 weeks or for up to a total of 48 weeks of therapy (whichever is the lesser of the two).</td><td>Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose =1200 mg).</td></tr>
<tr><td>2 or 3</td><td>An additional 12 weeks or for up to a total of 24 weeks of therapy (whichever is the lesser of the two).</td><td>Ribavirin quantity limit of 200 mg tab QS# 120 / 25 days (for max daily dose = 800 mg).</td></tr>
<tr><td>For all genotypes and HIV co-infection</td><td>An additional 36 weeks or for up to a total of 48 weeks of therapy (whichever is the lesser of the two)</td><td>Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose = 1200 mg).</td></tr>
</table>
</td>
<td>No: DENY
(Medical Appropriateness)

Treatment with pegylated interferon-ribarvirin does not meet medical necessity criteria because there is poor chance of achieving an SVR.</td>
</tr>
</table>

Clinical Notes:

- Serum transaminases: Up to 40 percent of clients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels, even when tested on multiple occasions.
- RNA: Most clients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 (10^5) and 10,000,000 (10^7) copies per ml. Expressed as IU, these averages are 50,000 to 5 million IU. Rates of response to a course of peginterferon-ribavirin are higher in clients with low levels of HCV RNA. There are several definitions of a “low level” of HCV RNA, but the usual definition is below 800,000 IU (~ 2 million copies) per ml.(5)
- Liver biopsy: Not necessary for diagnosis but helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage and for ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, or iron overload.
-

Stage is indicative of fibrosis:			**Grade is indicative of necrosis:**	
Stage 0	No fibrosis			
Stage 1	Enlargement of the portal areas by fibrosis		Stage 1	None
Stage 2	Fibrosis extending out from the portal areas with rare bridges between portal areas		Stage 2	Mild
Stage 3	Fibrosis that link up portal and central areas of the liver		Stage 3	Moderate

Stage 4	Cirrhosis		Stage 4	Marked

The following are considered investigational and/or do not meet medical necessity criteria:

- ✓ Treatment of HBV or HCV in clinically decompensated cirrhosis
- ✓ Treatment of HCV or HBV in liver transplant recipients
- ✓ Treatment of HCV or HBV > 48 weeks
- ✓ Treatment of advanced renal cell carcinoma
- ✓ Treatment of thrombocytopenia
- ✓ Treatment of human papilloma virus
- ✓ Treatment of multiple myeloma

Appendix 3: RCT Abstracts

BACKGROUND & AIMS:

The addition of boceprevir to therapy with peginterferon alfa-2b and ribavirin results in significantly higher rates of sustained virologic response (SVR) in previously treated patients with chronic hepatitis C virus (HCV) genotype-1 infection, compared with peginterferon alfa-2b and ribavirin alone. We assessed SVR with boceprevir plus peginterferon alfa-2a-ribavirin (PEG2a/R) in patients with identical study entry criteria.
METHODS:

In a double-blind, placebo-controlled trial, 201 patients with HCV genotype-1 who had relapsed or not responded to previous therapy were assigned to groups (1:2) and given a 4-week lead-in phase of PEG2a/R, followed by placebo plus PEG2a/R for 44 weeks (PEG2a/R) or boceprevir plus PEG2a/R for 44 weeks (BOC/PEG2a/R). The primary end point was SVR 24 weeks after therapy ended.
RESULTS:

The addition of boceprevir after 4 weeks of lead-in therapy with PEG2a/R significantly increased the rate of SVR from 21% in the PEG2a/R group to 64% in the BOC/PEG2a/R group (P < .0001). Among patients with poor response to interferon therapy (<1-log(10) decline in HCV RNA at week 4), 39% in the BOC/PEG2a/R group had SVRs, compared with none of the patients in the PEG2a/R group. Among patients with good response to interferon (≥1-log(10) decline), 71% in the BOC/PEG2a/R group had SVRs, compared with 25% in the PEG2a/R group. A ≥1-log(10) decline in HCV RNA at treatment week 4 was the strongest independent predictor of SVR, exceeding that of IL-28B genotype. Among 8 patients who began the study with HCV amino acid variants associated with boceprevir resistance, 3 (38%) achieved SVRs. Fifty percent of patients in the BOC/PEG2a/R group developed anemia (hemoglobin <10.0 g/dL), compared with 27% in the PEG2a/R group; 43% vs 21%, respectively, developed neutropenia (neutrophil count <750/mm(3)).
CONCLUSIONS:

The addition of boceprevir after 4 weeks of lead-in therapy with PEG2a/R caused significantly higher rates of SVR in previously treated patients with chronic HCV genotype-1 infection, compared with patients given only PEG2a/R. ClinicalTrials.gov Identifier: NCT00845065.

BACKGROUND:

The standard treatment for hepatitis C virus (HCV) infection is interferon, which is administered subcutaneously and can have troublesome side effects. We evaluated sofosbuvir, an oral nucleotide inhibitor of HCV polymerase, in interferon-sparing and interferon-free regimens for the treatment of HCV infection.
METHODS:

We provided open-label treatment to eight groups of patients. A total of 40 previously untreated patients with HCV genotype 2 or 3 infection were randomly assigned to four groups; all four groups received sofosbuvir (at a dose of 400 mg once daily) plus ribavirin for 12 weeks. Three of these groups also received peginterferon alfa-2a for 4, 8, or 12 weeks. Two additional groups of previously untreated patients with HCV genotype 2 or 3 infection received sofosbuvir monotherapy for 12 weeks or sofosbuvir plus peginterferon alfa-2a and ribavirin for 8 weeks. Two groups of patients with HCV genotype 1 infection received sofosbuvir and ribavirin for 12 weeks: 10 patients with no response to prior treatment and 25 with no previous treatment. We report the rate of sustained virologic response 24 weeks after therapy.
RESULTS:

Of the 40 patients who underwent randomization, all 10 (100%) who received sofosbuvir plus ribavirin without interferon and all 30 (100%) who received sofosbuvir plus ribavirin for 12 weeks and interferon for 4, 8, or 12 weeks had a sustained virologic response at 24 weeks. For the other patients with HCV genotype 2 or 3 infection, all 10 (100%) who received sofosbuvir plus peginterferon alfa-2a and ribavirin for 8 weeks had a sustained virologic response at 24 weeks, as did 6 of 10 (60%) who received sofosbuvir monotherapy. Among patients with HCV genotype 1 infection, 21 of 25 previously untreated patients (84%) and 1 of 10 with no response to previous therapy (10%) had a sustained virologic response at 24 weeks. The most common adverse events were headache, fatigue, insomnia, nausea, rash, and anemia.
CONCLUSIONS:

Sofosbuvir plus ribavirin for 12 weeks may be effective in previously untreated patients with HCV genotype 1, 2, or 3 infection.

BACKGROUND:

The uridine nucleotide analogue sofosbuvir is a selective inhibitor of hepatitis C virus (HCV) NS5B polymerase. We assessed the safety and efficacy of sofosbuvir in combination with pegylated interferon alfa-2a (peginterferon) and ribavirin in non-cirrhotic treatment-naive, patients with HCV.
METHODS:

For this open-label, randomised phase 2 trial, we recruited patients from 42 centres in the USA and Puerto Rico between March 23, 2011, and Sept 21, 2011. Patients were eligible for inclusion if they had chronic HCV infection (genotypes 1, 4, 5, or 6), were aged 18 years or older, and had not previously received treatment for HCV infection. Using a computer-generated randomisation sequence, we randomly assigned patients with HCV genotype-1 to one of three cohorts (A, B, and C; in a 1:2:3 ratio), with randomisation stratified by IL28B (CC vs non-CC allele) and HCV RNA (<800,000 IU/mL vs ≥800,000 IU/mL). Patients received sofosbuvir 400 mg plus peginterferon and ribavirin for 12 weeks (cohort A) or for 24 weeks (cohort B), or 12 weeks of sofosbuvir plus peginterferon and ribavirin followed by 12 weeks of either sofosbuvir monotherapy or sofosbuvir plus ribavirin (cohort C). We enrolled patients with all other eligible genotypes in cohort B. The primary efficacy endpoint was sustained virological response at post-treatment week 24 (SVR24) by intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT01329978.
RESULTS:

We enrolled 316 patients with HCV genotype-1: 52 to cohort A, 109 to cohort B, and 155 to cohort C. We assigned 11 patients with HCV genotype-4 and five patients with genotype-6 to cohort B (we detected no patients with genotype 5). In patients with HCVgenotype-1, SVR24 was achieved by 46 patients (89%, 95% CI 77-96) in cohort A, 97 patients (89%, 82-94) in cohort B, and by 135 (87%, 81-92) in cohort C. We detected no difference in the proportion of patients achieving SVR24 in cohort A compared with cohort B (p=0·94), or in cohort C (p=0·78). Nine (82%) of 11 patients with genotype-4 and all five with genotype-6 achieved SVR24. Seven patients, all with genotype-1 infection, relapsed after completion of assigned treatment. The most common adverse events that led to the discontinuation of any study drug--anaemia and neutropenia--were associated with peginterferon and ribavirin treatment. Three (6%) patients in cohort A, 18 (14%) patients in cohort B, and three (2%) patients in cohort C discontinued treatment because of an adverse event.
INTERPRETATION:

Our findings suggest that sofosbuvir is well tolerated and that there is no additional benefit of extending treatment beyond 12 weeks, but these finding will have to be substantiated in phase 3 trials. These results lend support to the further assessment of a 12 week sofosbuvir regimen in a broader population of patients with chronic HCV genotype-1 infection, including those with cirrhosis.

Boceprevir (BOC) added to peginterferon alfa-2b (PegIFN) and ribavirin (RBV) significantly increases sustained virologic response (SVR) rates over PegIFN/RBV alone in previously untreated adults with chronic hepatitis C genotype 1. We evaluate the relationship of incident anemia with triple therapy. A total of 1,097 patients received a 4-week lead-in of PegIFN/RBV followed by: (1) placebo plus PegIFN/RBV for 44 weeks (PR48); (2) BOC plus PegIFN/RBV using response-guided therapy (BOC/RGT); and (3) BOC plus PegIFN/RBV for 44 weeks (BOC/PR48). The management of anemia (hemoglobin [Hb]<10 g/dL) included RBV dose reduction and/or erythropoietin (EPO) use. A total of 1,080 patients had ≥1 Hb measurement during treatment. The incidence of anemia was 50% in the BOC arms combined (363/726) and 31% in the PR48 arm (108/354, P<0.001). Among BOC recipients, lower baseline Hb and creatinine clearance were associated with incident anemia. In the BOC-containing arms, anemia was managed by the site investigators as follows: EPO without RBV dose reduction, 38%; RBV dose reduction without EPO, 8%; EPO with RBV dose reduction, 40%; and neither RBV dose reduction nor EPO, 14%. SVR rates were not significantly affected by management strategy (70%-74%), and overall patients with anemia had higher rates of SVR than those who did not develop anemia (58%). Serious and life-threatening adverse events (AEs) and discontinuations due to AEs among BOC-treated patients did not differ by EPO use.
CONCLUSION:

With BOC/PR therapy, SVR rates in patients with incident anemia were higher than nonanemic patients and did not vary significantly according to the investigator-selected approach for anemia management. Prospective studies are needed to confirm this observation.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: September 2013 **Date of Last Review:** December 2009
PDL Classes: Topical Androgens **Source Document:** Provider Synergies

Current Status of PDL Class:
- Preferred Agents: TESTOSTERONE GEL (TESTIM®), TESTOSTERONE TRANSDERMAL PATCH (ANDRODERM®), AND TESTOSTERONE CYPIONATE IM (DEPO-TESTOSTERONE®) AND TESTOSTERONE ENANTHATE IM
- Non-Preferred Agents: TESTOSTERONE TRANSDERMAL GEL (ANDROGEL® 1%/ANDROGEL® 1.62%/ANDROGEL PUMP®/ FORTESTA®), TESTOSTERONE BUCCAL (STRIANT®), TESTOSTERONE TRANSDERMAL SOLUTION (AXIRON®), PATCH, AND TESTOSTERONE PELLET IMPLANT (TESTOPEL®)

Previous Conclusions and Recommendation:
- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Consider including at least one gel formulation
- Consider PA criteria for coverage only for:
    - Classic hypogonadism- clinically documented with verified low testosterone levels and no contraindications. Maintenance of bone density during prolonged corticosteroid therapy
    - Maintenance of muscle mass to prevent wasting in HIV

PA Criteria: A prior authorization criterion is currently in place for androgens to cover only for covered diagnosis and for medically appropriate conditions (Appendix 1). Use for body building and sexual dysfunction is not covered.

Conclusions and Recommendations:
- There is no new evidence that there is a difference in efficacy between the different testosterone products.
- Testosterone patches are associated with a higher incidence of adverse reactions related to administration.
- There is new low quality evidence that there is a potential increased risk of cardiovascular-related events associated with testosterone therapy, and caution should be used in older men where cardiovascular disease is common.
- There is insufficient evidence that the new formulations (Axiron®, Androgel® 1.62%, and Fortesta®) have improved efficacy or safety than other available agents.
- No further review or research needed at this time.
- Evaluate comparative costs in executive session.

Methods:
A Medline OVID search for randomized controlled trials (RCTs) was conducted with the following search terms: testosterone, testosterone congeners, testosterone propionate, testosterone cypionate, low testosterone, steroids, anabolic agents, androgens, hypogonadism, weight gain, and osteoporosis. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to July week one 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:
A systematic review and meta-analysis on the effect of androgen-replacement therapy on prostate growth was conducted by Cui, et al.[1] A literature review identified 16 RCTs with a total of 1030 patients. The quality of the RCTs was assessed using the Jadad scale, and all of the included trials were deemed to have a low risk of bias. For the 5 short term trials, 3 evaluated injected treatments compared to placebo on prostate growth (SMD 0.50, 95% CI -0.04 to 1.05; p=0.07), 2 compared transdermal application (SMD 0.30, 95% CI 0.07 to 0.54; p=0.002) and one study

evaluated oral treatment (SMD -0.02, 95% CI -0.62 to 0.60; p=0.95). For short term use, androgen replacement therapy was more likely to result in increased PSA levels than treatment with placebo when administered transdermally. Results also showed that regardless of administration method, there was no significant difference in prostate volume changes between androgen replacement therapy and placebo. Nine long term RCT's further clarified this conclusion (SMD 0.31, 95% CI -0.35 to 0.98). [1]

A systematic review and meta-analysis was conducted of placebo-controlled RCTs of testosterone therapy in men to evaluate for cardiovascular-related events.[2] A total of 27 articles were included in the systematic review and demonstrated that testosterone therapy increases composite cardiovascular-related events among men (OR 1.54, 95% CI 1.09 to 2.18, I2=7.8%). Results were similar when restricted to serious events only (OR 1.61, 95% CI 1.01 to 2.56). Previous systematic reviews have shown a non-significant increase in cardiovascular related events. The risk of cardiovascular-related events was shown to vary based on the source of funding (p=0.03) but not with baseline testosterone (p=0.70). There was not a significant increase in events in the subgroup of studies funded by the pharmaceutical industry (OR 0.89, 95% CI 0.50 to 1.60) while there was a higher risk in the subgroup of studies not funded by the pharmaceutical industry (OR 2.06, 95% CI 1.34 to 3.17). [2]

Guidelines:

The updated guidelines from the Endocrine Society for treatment of hypogonadism[3] evaluate the treatment of androgen deficiency syndromes in men. They recommend testosterone therapy for symptomatic men with classical androgen deficiency syndromes and recommend against therapy in patients with breast or prostate cancer. They give no specific recommendations based on which administration to use and recommend choice should be based on patient's preference, consideration of pharmacokinetics, treatment burden, and cost. They also recommend that clinicians consider short-term testosterone therapy as an adjunctive therapy in HIV-infected men with low testosterone levels and weight loss to promote muscle strength. Lastly, there is a level 2 recommendation that clinicians offer testosterone therapy to men receiving high doses of glucocorticoids who have low testosterone levels to promote preservation of lean body mass and bone mineral density.

New guidelines on the treatment of male hypogonadism were released by the European Association of Urology in 2012.[4] Levels of evidence were assessed based on their level of scientific evidence and guideline recommendations were graded in accordance with the Oxford Centre for Evidence-Based Medicine levels of evidence. A Grade A recommendation is one based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial, a Grade B study is based on well-conducted clinical studies, but without randomized clinical trials, and a Grade C recommendations I made despite the absence of directly applicable clinical studies of good quality.

The guidelines recommend testosterone replacement therapy in patients with:

- A decline in muscle mass and strength (Grade A recommendation, level of evidence 1b)
- Reduced bone mideral density at the lumbar spine (Grade A recommendation, level of evidence 1a)

Decreased libido and erection (Grade B recommendation, level of evidence 3)

The following recommendations are included regarding choice of treatment:

- The patient should be fully informed about expected benefits and side effects of each treatment option. The selection of the preparation should be a joint decision by an informed patient and the physician (Grade A recommendation, level of evidence 1a)
- Short-acting preparations may be preferred to long-acting depot administration when starting the initial treatment (Grade B recommendation, level of evidence 3).
- hCG treatment can only be recommended for hypogonadal patients with simultaneous fertility treatment (Grade B recommendation, level of evidence 1b).

No specific recommendations are given for a preferred method of delivery for testosterone therapy.

The updated guidelines for osteoporosis in men were reviewed.[5] No changes regarding the use of medications were found.

New drugs:
None

New Formulations/Indications:

FDA approved Fortesta® is a 2% strength gel available in a pump and applied to the upper thighs.[6] In an unpublished 90-day open label trial in 149 men with hypogonadism, application of Fortesta led to testosterone concentrations in the normal range in 78% of patients. [6] Skin reactions at the site of application were the most common adverse effects.

Axiron, a 2% testosterone solution, is available as a pump and is administered to the axillae, or armpit area, with an applicator.[7] This site of action theoretically minimizes the risk of transferring the drug to a family member or sexual partner. An open-label, 120 day study evaluated its use in 155 men with hypogonadism.[8] At day 120, the proportion of patients with testosterone levels within the eugonadal range was 84.1% (116/138) and significant changes from baseline were seen in sexual desire, sexual activity, positive mood and negative mood. Skin reactions were the most commonly reported adverse events.

An extension study up to 180 days was continued to assess skin safety and included a total of 71 patients.[9] Overall, 17% of patients had at least one new skin reaction and 3 patients discontinued due to a adverse skin reaction. The skin reaction events were often reported as a transidet stinging or burning sensation occurring immediately after application.All three products are indicated for androgen replacement therapy in adult men with primary or hypogonadotropic hypogonadism.

Testosterone gel 1.62% (Androgel) is a new strength of testosterone gel approved in 2011 for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone due to primary or secondy hypogonadism.[10] Dosing and administration differ from Androgel 1% and are not interchangeable. Androgel 1.62% may not be applied to the abdomen.

Testosterone gel 1.62% was studied in a single randomized, double-blind, parallel group, placebo-controlled study through 182 days.[11] Of the 274 patients randomized, 196 completed the double-blind period. The most common adverse events leading to discontinuation was increased PSA which was prespecified as a discontinuation criterion. Results demonstrated that 82% of patients demonstrated restoration of testosterone levels and achieved an average serum testosterone level within the normal range on day 112 compared to 37% of patients on placebo ($P<0.0001$). The most common adverse events were increased PSA (9.8%), upper respiratory infection (4.7%), back pain (3.0%), headache (3%), insomnia, and hypertension (2.6%). An open label period followed to establish 1 year data.[12] On days 266 and 364, the proportion of responders for the continuing active agent group was 78.4 and 77.9%, suggesting continued efficacy for up to 1 year.

New FDA safety alerts:
None

New Trials (Appendix 1):
A total of 94 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below in addition to the trials supporting the new formulation approvals above. Please see Appendix 1 for the full abstracts.

Fennell et al conducted a small crossover study to compare the subcutaneous implant with injectable testosterone in adult males with primary or secondary hypogonadism.[13] Patients (n=38) were randomized to receive injectable or implanted testosterone for 24 to 30 weeks and then switched without a washout period to the alternative formulation. Primary endpoints were pharmacokinetic and pharmacodynamic differences between formulations.

Secondary outcomes were improvement in quality of life as measured by patient questionnaire. No statistical difference was seen in peak concentrations at week two between the two products; however, testosterone injections showed a significant drop at week four ($p < 0.001$) compared with the implant. Both formulations showed similar changes in increased hemoglobin ($p = 0.78$) and prostate specific antigens ($p = 0.44$), and decreased urea ($p = 0.15$). No differences were seen in subjects' pulse, blood pressure, or fat and lean body mass. Subjects using injectable testosterone showed a significant increase in total body weight ($p = 0.035$), while subjects using the implant had a significant increase in grip strength ($p = 0.023$). For quality of life measures, both products increased perceptions of functioning, vitality, mood, and sexual satisfaction. No statistical difference was seen between the two products for these quality of life measures. This was a poor quality trial with unclear clinical outcomes where blinding was absent, and randomization and allocation concealment were not discussed.

Aversa et al compared the efficacy of two different formulations of testosterone undecanoate in adult men with primary or secondary hypogonadism and metabolic syndrome.[14] Subjects (n = 52) were randomized to one of three parallel treatment arms: transdermal placebo gel, intramuscular (IM) or oral testosterone for six months. The primary outcomes were change from baseline in several laboratory and clinical markers including total and free testosterone, blood glucose, lipids, blood pressure and body mass index (BMI). At six months, IM testosterone subjects had significantly higher free and total testosterone compared with baseline. Oral testosterone and placebo subjects showed no significant change in concentration. No treatment showed a statistical improvement in Hbg A1c, total cholesterol, or triglycerides. IM testosterone (105 vs. 101 cm; $p < 0.0001$) showed a significant decrease in waist circumference at six months compared with baseline. No significant change was seen in blood pressure or BMI for any group. At the end of six months the oral testosterone subjects were switched to IM treatment and the trial continued for an additional six months. This was a poor quality study. Comparisons were not made between testosterone or placebo treatments but instead each arm was compared with their baseline average. Allocation concealment, randomization and blinding were not described and not all results (i.e. testosterone concentration values) were included in the published article.

References:

1. Cui Y, Zhang Y. The Effect of Androgen-replacement Therapy on Prostate Growth: A Systematic Review and Meta-analysis. *Eur Urol*. 2013. doi:10.1016/j.eururo.2013.03.042.

2. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*. 2013;11:108. doi:10.1186/1741-7015-11-108.

3. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95(6):2536–2559. doi:10.1210/jc.2009-2354.

4. Dohle G, Arver S, Bettocchi C, Kliesch S, Punab M, de Ronde W. Guidelines on Male Hypogonadism. European Association of Urology. 2012.

5. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(6):1802–1822. doi:10.1210/jc.2011-3045.

6. Foresta (testosterone gel). Prescribing Information. Endo Pharmaceuticals Inc. Malvern, PA. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021015s036lbl.pdf.

7. Axiron (testosterone topical solution). Prescribing Information. Lilly USA, LLC. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022504s000lbl.pdf.

8. Wang C, Ilani N, Arver S, McLachlan RI, Soulis T, Watkinson A. Efficacy and safety of the 2% formulation of testosterone topical solution applied to the axillae in androgen-deficient men. *Clin Endocrinol (Oxf)*. 2011;75(6):836–843. doi:10.1111/j.1365-2265.2011.04152.x.

9. Muram D, Melby T, Alles Kingshill E. Skin reactions in a phase 3 study of a testosterone topical solution applied to the axilla in hypogonadal men. *Curr Med Res Opin*. 2012;28(5):761–766. doi:10.1185/03007995.2012.681034.

10. Androgel (testosterone gel 1.62%). Prescribing information. AbbVie pharmaceuticals. Available at http://www.rxabbvie.com/pdf/ANDRGEL1_62_PI.pdf.

11. Kaufman JM, Miller MG, Garwin JL, Fitzpatrick S, McWhirter C, Brennan JJ. Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. *J Sex Med*. 2011;8(7):2079–2089. doi:10.1111/j.1743-6109.2011.02265.x.

12. Kaufman JM, Miller MG, Fitzpatrick S, McWhirter C, Brennan JJ. One-year efficacy and safety study of a 1.62% testosterone gel in hypogonadal men: results of a 182-day open-label extension of a 6-month double-blind study. *J Sex Med*. 2012;9(4):1149–1161. doi:10.1111/j.1743-6109.2011.02630.x.

13. Fennell C, Sartorius G, Ly LP, et al. Randomized cross-over clinical trial of injectable vs. implantable depot testosterone for maintenance of testosterone replacement therapy in androgen deficient men. *Clin Endocrinol (Oxf)*. 2010;73(1):102–109. doi:10.1111/j.1365-2265.2009.03744.x.

14. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest*. 2010;33(11):776–783. doi:10.3275/6903.

Appendix 1

Hormones - Testosterone

Goal(s):

- Cover only for covered diagnosis and for medically appropriate conditions.
- Use for body building is not covered.
- Use for sexual dysfunction is not covered.

Length of Authorization: 6 months

Preferred Alternatives: After coverage verified refer to the PDL for preferred alternatives: http://www.orpdl.org/

Requires PA: **All testosterones require PA for coverage verification**

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Does the diagnosis for the medication requested include any of the following? - Ovarian failure (256.31, 256.39) - Testicular Hypofunction (257.2) - Hypopituitarism and related disorders (253.2, 253.4, 253.7, 253.8) - AIDS-related cachexia (253.2)	**Yes**: Go to #3	**No**: Pass to RPh. RPh go to #4
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml. Approve for 6 months.	**No**: Go to #4
4. RPH only All other indications need to be evaluated to see if they are above the line or below the line.	**If above the line or clinic provides supporting literature:** approve for length of treatment.	**If below the line:** Deny, (Not Covered by the OHP).

P&T/DUR Action: 2/23/12 (TDW)

Appendix 2: Abstracts of Randomized Control Trials

Fennell C, Sartorius G, Ly LP, et al. Randomized cross-over clinical trial of injectable *vs.* implantable depot testosterone for maintenance of testosterone replacement therapy in androgen deficient men. *Clinical Endocrinology*. 2009. doi:10.1111/j.1365-2265.2009.03744.x.

Background Life-long testosterone replacement therapy (TRT) for younger men with organic androgen deficiency is best provided by depot testosterone (T) products. This study compared directly the two long-acting depot T products, subdermal T implants (TI) and injectable T undecanoate (TU) for maintenance of TRT.

Design, setting and participants Men with organic androgen deficiency (n = 38) undergoing regular TRT at an academic Andrology centre were recruited for a two period, randomized sequence, cross-over clinical trial without intervening wash-out period of TRT maintenance.

Outcomes For both depot T products, their pharmacokinetics and pharmacodynamics were evaluated using a range of androgen sensitive clinical, laboratory and quality of life measures as well as preference for ongoing treatment after experience of both products.

Results The two depot T products had distinct pharmacokinetics and were not bioequivalent. However, there were no consistent clinical differences in a comprehensive range of pharmacodynamics measures reflecting androgen effects on biochemistry and haematology, muscle mass and strength, and quality of life, mood and sexual function. The majority (91%) of participants chose TU over TI at study completion.

Conclusion Despite significant pharmacokinetic differences, the two depot T products are clinically interchangeable allowing for choice dependent on patient and physician delivery preference in practice but most patients preferred the injectable over the implantable form.

Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest*. 2010;33(11):776–783. doi:10.3275/6903.

Aim: To investigate efficacy and safety of two different preparations of testosterone undecanoate (tu) in 52 hypogonadal men [mean age 57 yr and mean testosterone (t) < 320 ng/dl] with metabolic syndrome (ms).

Subjects and methods: Randomized, double-blind, double-dummy study with three parallel treatment arms [oral tu; transdermal placebo gel (p); im tu] administration for 12 months (mo). Each subject was randomized (1:1:3) to receive either oral tu (2 capsules of 40 mg/twice per day at breakfast and dinner, equalling a total dose of 160 mg/day; no.=10) for 6 mo and continued with im tu for further 6 mo, or p (3-4 g/day; no.=10) and im tu (1000 mg/12 weeks from week 6; no.=32) for 12 mo.

Results: After 6 mo, im tu increased t and free- t levels ($p<0.0001$), and improved metabolic parameters [reduction in homeostasis model assessment (homa) index, $p<0.0001$; waist circumference and fat mass, $p<0.001$, respectively], in international index of erectile function-5 and aging males' symptoms scores ($p<0.01$, respectively). After 12 months, im tu produced further increases in t and free- t levels ($p<0.0001$) and metabolic parameters (reduction in homa-index, $p<0.0001$; waist circumference $p<0.0001$; fat mass, $p<0.001$). No major adverse event due to t treatment occurred.

Conclusions: Clinical efficacy of t replacement therapy in hypogonadal men with ms is reached when its plasmatic levels approach into the medium-high range of normality (>5 ng/ml), although subjective threshold values may be different. Administration of im tu was more effective than oral tu to reach the target for t levels and to improve ms parameters. Tu was safe over 12 months and discontinuation rates were similar to placebo.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: September 2013 **Date of Last Review:** May 2012
PDL Classes: Topical Antiparasitics **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: PERMETHRIN CREAM, PERMETHRIN LIQUID, PIP BUTOX/PYRETHRINS/PERMETH KIT, PIPERONYL BUTOXIDE/PYRETHRINS GEL, PIPERONYL BUTOXIDE/PYRETHRINS KIT, PIPERONYL BUTOXIDE/PYRETHRINS LIQUID, PIPERONYL BUTOXIDE/PYRETHRINS SHAMPOO , SPINOSAD 0.9% (NATROBA®) SUSPENSION
- Non Preferred: BENZYL ALCOHOL 5 % LOTION, CROTAMITON 10 % CREAM, CROTAMITON 10 % LOTION, LINDANE 1 % LOTION, LINDANE 1 % SHAMPOO, MALATHION 0.5 % LOTION, POTASS HYD/GLYCO/PQ10/HE-CELL GEL, IVERMECTIN 0.5% LOTION (SKLICE®)

Previous Conclusions and Recommendation:

- There is insufficient evidence of superiority of either spinosad 0.9% topical suspension or ivermectin 0.5% lotion over permethrin.
- There is insufficient evidence that either spinosad 0.9% topical suspension or ivermectin 0.5% lotion are safer than permethrin.
- No unique patient groups or situations were identified where either spinosad 0.9% topical suspension or ivermectin 0.5% lotion are safer or more effective than permethrin.
- For patients that have failed permethrin or malathion, there is moderate evidence from one good quality RCT that oral ivermectin is more effective than malathion 0.5% lotion. However, oral ivermectin is not FDA approved for this indication and the malathion lotion studies is not available in the same vehicle in the US.
- Continue to include permethrin as preferred to assure adequate coverage for scabies.

Conclusions and Recommendations:

- There is no new clinical evidence for efficacy or safety that disputes permethrin as first-line therapy for the treatment of lice.
- No further review or research needed at this time
- Evaluate comparative costs in executive session.

Methods:

A Medline OVID search was conducted with the following search terms: permethrin, piperonyl butoxide, pyrethrins, spinosad, lindane, crotamiton, malathion, benzoyl alcohol, ivermectin, topical antiparasitic, lice, scabies, pediculosis capitis, pediculocide and scabicide. The search was limited to English language articles of controlled trials conducted on humans published from March 2012 to July week three 2013. The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

None

Guidelines:

The International Journal of STD and AIDs published the 2010 European guidelines for treatment of scabies.[1] Levels of evidence were assessed based on their level of scientific evidence and guideline recommendations were graded in accordance with the Oxford Centre for Evidence-Based Medicine levels of evidence. A Grade A recommendation is one based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial, a Grade B study is based on well-conducted clinical studies, but without randomized clinical trials, and a Grade C recommendations is made despite the absence of directly applicable clinical studies of good quality.

The recommendations for the treatment of scabies:

- Permethrin cream 5% is considered effective and well-tolerated (level of evidence Ib; grade A recommendation)
- Benzyl benzoate lotion (10 to 25%) is also effective but requires application on more than one day (level of evidence III; grade B recommendation)
- Ivermectin can be given orally as a repeated dose (200 mg/kg) two weeks apart. Comparisons with lindane and benzyl benzoate show conflicting results with regard to efficacy (level of evidence Ib; grade A recommendation)
- A foam-based preparation of synergized pyrethrins is available in some countries and may be as effective as permethrin (level of evidence II; grade B recommendation)

The 2010 updated recommendations from the Center of Disease Control (CDC) for the treatment of scabies were reviewed. [2] The CDC guidelines are developed by the CDC staff, and public and private sector experts on sexually transmitted diseases (STD). These individuals reviewed literature for inclusion in the guideline based on four questions: 1) treatment of infection based on microbiologic eradication, 2) alleviation of signs and symptoms, 3) prevention of sequelae, and 4) prevention of transmission. Evidence quality was not analyzed.

For the treatment of scabies, the CDC recommends:

- Permethrin cream 5% applied to all areas of the body from the neck down and washed off after 8 to 14 hours

Or

- Ivermectin 200 µg/kg taken orally, repeat in two weeks

Alternative

- Lindane 1% one ounce of lotion (or 30 g of cream) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after 8 hours

New Trials (Appendix 1):

A total of 19 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, 4 relevant clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Burgess et al compared topical dimeticone gel with permethrin cream rinse for the eradication of head lice.[3] Subjects (n = 90) were randomized to one application of dimeticone or two applications of permethrin in this open label controlled trial. The endpoint was measured after two weeks. Dimeticone treated subjects were significantly more likely to be lice-free than the permethrin subjects (69.8% vs. 14.9%; 95% CI 4.69 to 37.07). This was a fair quality trial with detailed explanations of study procedures.

Three recent trials compared ivermectin and permethrin for the treatment of scabies. Goldust et al conducted a trial to examine the efficacy of treating scabies with permethrin versus ivermectin.[4] Subjects (n= 242) with a scabies infection and their households (aged three to 78 years old) were randomized to either a single dose of oral ivermectin or two applications of topical permethrin. The primary outcome was eradication of scabies after two weeks defined as the absence of new lesions and all old lesions healed. At week two the difference between the two treatments was nonsignificant: 92.5% of permethrin and 85.9% of ivermectin subjects were scabies-free (p = 0.42). This was a poor quality trial. Because of the differences in administration and lack of double dummy, the impartiality of the investigators seems questionable. Randomization and allocation concealment were not described and the results were not analyzed

as intention-to-treat.

Chhaiya et al also examined the comparative efficacy of ivermectin and permethrin for treatment of scabies infections in an open label controlled trial.[5] Patients (n = 315) were randomized to a single application of one of three treatments: oral ivermectin, topical permethrin or topical ivermectin. Subjects were followed for four weeks, if no evidence of a cure was seen at week one, two or three an additional or application was given. Patients in the oral ivermectin group had a significantly lower cure rate than either topical preparation at week one: 74.8% in permethrin group, 30% in oral ivermectin group, and 69.3% in topical ivermectin group ($P < 0.05$). The same trend continued at the end of second week: 99% in permethrin group, 63% in oral ivermectin group, and 100% in topical ivermectin group ($P < 0.05$). There was no statistical difference between topical ivermectin and permethrin. At the end of the third week there was no statistical difference between the three groups and a 100% cure rate was observed in both the permethrin and topical ivermectin group while 99% in the oral ivermectin group ($P = 0.367$). This was a poor quality study with little information provided concerning randomization and allocation concealment. Study treatment regimens did not follow standard clinical practice for either medication.

Two multisite, randomized, double-blind studies (n=289) compared a single application of 0.5% ivermectin lotion with a vehicle control for the eliminations of infestations in patients 6 months of age or older.[6] The final visit was on day 15 and if any live lice were present at this visit, the study treatment was considered to have failed. The primary efficacy end point was the number of index patients who were louse-free by day 2 and remained louse-free through days 8 and 15. Significantly more patients in the ivermectin group than in the vehicle-control group were free of live lice on day 2 (94.9% vs. 31.3%; $p<0.001$, NNT 2) and at subsequent observations through day 15 (73.8% vs. 17.6%; $p<0.001$, NNT 2). Pruritus, excoriation, and erythema were the most common adverse events (1% in vehicle-control group and less than 1% in the ivermectin group). In this population, the use of an active comparator group would have been more relevant. In addition, trials that use single-dose treatment may not fully evaluate the true effectiveness of lice treatments since repeat treatment is typically required.[7]

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
None

References:

1. Scott GR, Chosidow O. European guideline for the management of scabies, 2010. *International Journal of STD & AIDS*. 2011;22(6):301–303. doi:10.1258/ijsa.2011.011112.

2. Workowski KA, Berman S, Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1–110.

3. Burgess IF, Brunton ER, Burgess NA. Single application of 4% dimeticone liquid gel versus two applications of 1% permethrin creme rinse for treatment of head louse infestation: a randomised controlled trial. *BMC Dermatology*. 2013;13(1):5. doi:10.1186/1471-5945-13-5.

4. Goldust M, Rezaee E, Hemayat S. Treatment of scabies: Comparison of permethrin 5% versus ivermectin. *The Journal of Dermatology*. 2012;39(6):545–547. doi:10.1111/j.1346-8138.2011.01481.x.

5. Chhaiya SB, Patel VJ, Dave JN, Mehta DS, Shah HA. Comparative efficacy and safety of topical permethrin, topical ivermectin, and oral ivermectin in patients of uncomplicated scabies. *Indian J Dermatol Venereol Leprol*. 2012;78(5):605–610.

6. Pariser DM, Meinking TL, Bell M, Ryan WG. Topical 0.5% ivermectin lotion for treatment of head lice. N Engl J Med. 2012 Nov;367(18):1687-93.

7. Gunning K, Pippitt K, Kiraly B, Sayler M. Pediculosis and scabies: treatment update. Am Fam Physician. 2012 Sep 15;86(6):535-41.

Appendix 1: Abstracts of Randomized Control Trials

Goldust M, Rezaee E, Hemayat S. Treatment of scabies: Comparison of permethrin 5% versus ivermectin. *The Journal of Dermatology*. 2012;39(6):545–547. doi:10.1111/j.1346-8138.2011.01481.x.

Scabies is an ectoparasitic, highly contagious skin disease caused by a mite called Sarcoptes scabiei. The insecticides ivermectin and permethrin are commonly used for treatment of scabies. This study aimed at comparing the efficacy of oral ivermectin with topical permethrin in treating scabies. Two hundred and forty-two patients with scabies attending the dermatology outpatient department of Sina Hospital, Tabriz University of Medical Sciences were admitted. Patients were divided into two groups randomly. The first group and their family contacts received 5% permethrin cream and the other received oral ivermectin. Treatment was evaluated at intervals of 2 and 4 weeks. A single dose of ivermectin provided a cure rate of 85.9% at a 2-week interval, which increased to 100% after crossing over to the permethrin group at a 4-week interval. Twice application of permethrin with a 1-week interval was effective in 92.5% of patients, which increased to 94.2% after crossing over to the ivermectin group at a 4-week interval. Permethrin-treated patients recovered earlier. Twice application of permethrin with a 1-week interval is superior to a single dose of ivermectin. The temporal dissociation in clinical response suggests that ivermectin may not be effective against all the stages in the life cycle of the parasite.

Burgess IF, Brunton ER, Burgess NA. Single application of 4% dimeticone liquid gel versus two applications of 1% permethrin creme rinse for treatment of head louse infestation: a randomised controlled trial. *BMC Dermatology*. 2013;13(1):5. doi:10.1186/1471-5945-13-5.

Background: A previous study indicated that a single application of 4% dimeticone liquid gel was effective in treating head louse infestation. This study was designed to confirm this in comparison with two applications of 1% permethrin.

Methods: We have performed a single centre parallel group, randomised, controlled, open label, community based trial, with domiciliary visits, in Cambridgeshire, UK. Treatments were allocated through sealed instructions derived from a computer generated list. We enrolled 90 children and adults with confirmed head louse infestation analysed by intention to treat (80 per-protocol after 4 drop outs and 6 non-compliant). The comparison was between 4% dimeticone liquid gel applied once for 15 minutes and 1% permethrin creme rinse applied for 10 minutes, repeated after 7 days as per manufacturer's directions. Evaluated by elimination of louse infestation after completion of treatment application regimen.

Results: Intention to treat comparison of a single dimeticone liquid gel treatment with two of permethrin gave success for 30/43 (69.8%) of the dimeticone liquid gel group and 7/47 (14.9%) of the permethrin creme rinse group (OR 13.19, 95% CI 4.69 to 37.07) ($p < 0.001$). Per protocol results were similar with 27/35 (77.1%) success for dimeticone versus 7/45 (15.6%) for permethrin. Analyses by household gave essentially similar outcomes.

Conclusions: The study showed one 15 minute application of 4% dimeticone liquid gel was superior to two applications of 1% permethrin creme rinse ($p < 0.001$). The low efficacy of permethrin suggests it should be withdrawn.

Chhaiya SB, Patel VJ, Dave JN, Mehta DS, Shah HA. Comparative efficacy and safety of topical permethrin, topical ivermectin, and oral ivermectin in patients of uncomplicated scabies. *Indian J Dermatol Venereol Leprol*. 2012;78(5):605–610. doi:10.4103/0378-6323.100571.

Background: Ivermectin has opened a new era in the management of scabies as orally effective drug. However, topical route has been little explored for ivermectin.
Aims: To compare the efficacy and safety of topical permethrin, oral ivermectin, and topical ivermectin in the treatment of uncomplicated scabies.
Methods: This was an open-label, randomized, comparative, parallel clinical trial conducted in 315 patients, randomly allocated to 3 groups. First group received permethrin 5% cream as single application, second group received tablet ivermectin 200 mcg/kg as single dose, and third group received ivermectin 1% lotion as single application. All the patients received anti-histaminic for pruritus. The patients were followed up at intervals of 1, 2, 3, and 4 weeks. If there were no signs of cure, the same intervention was repeated at each follow up. Primary efficacy variable was clinical cure of lesions. Statistical analysis was done by chi square test and one way ANOVA test using SPSS version 12.
Results: At the end of first week, cure rate was 74.8% in permethrin group, 30% in oral ivermectin group, and 69.3% in topical ivermectin group ($P < 0.05$). At the end of second week, cure rate was 99% in permethrin group, 63% in oral ivermectin group, and 100% in topical ivermectin group ($P < 0.05$). At the end of third week, 100% cure rate was observed in permethrin and topical ivermectin group while 99% in oral ivermectin group ($P = 0.367$). No serious adverse events were observed.
Conclusions: Permethrin and topical ivermectin were equally effective against scabies while oral ivermectin was significantly less effective up to 2 weeks. Topical ivermectin can be used as an alternative to permethrin.

Pariser DM, Meinking TL, Bell M, Ryan WG. Topical 0.5% ivermectin lotion for treatment of head lice. N Engl J Med. 2012 Nov;367(18):1687-93.
Background:The emergence of resistance to treatment complicates the public health problem of head-louse infestations and drives the need for continuing development of new treatments. There are limited data on the activity of ivermectin as a topical lousicide.
Methods: In two multisite, randomized, double-blind studies, we compared a single application of 0.5% ivermectin lotion with vehicle control for the elimination of infestations without nit combing in patients 6 months of age or older. A tube of topical ivermectin or vehicle control was dispensed on day 1, to be applied to dry hair, left for 10 minutes, then rinsed with water. The primary end point was the percentage of index patients (youngest household member with ≥3 live lice) in the intention-to-treat population who were louse-free 1 day after treatment (day 2) and remained so through days 8 and 15.
Results:A total of 765 patients completed the studies. In the intention-to-treat population, significantly more patients receiving ivermectin than patients receiving vehicle control were louse-free on day 2 (94.9% vs. 31.3%), day 8 (85.2% vs. 20.8%), and day 15 (73.8% vs. 17.6%) (P<0.001 for each comparison). The frequency and severity of adverse events were similar in the two groups.
Conclusions: A single, 10-minute, at-home application of ivermectin was more effective than vehicle control in eliminating head-louse infestations at 1, 7, and 14 days after treatment. (Funded by Topaz Pharmaceuticals [now Sanofi Pasteur]; ClinicalTrials.gov numbers, NCT01066585 and NCT01068158.).

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Chronic Obstructive Pulmonary Disease (COPD)

Month/Year of Review: July 2013 **Date of Last Review: February 2012**

PDL Classes: Beta$_2$ Agonists, Inhaled Corticosteroids, Anticholinergics **Source Document: OSU College of Pharmacy**

Current Status of PDL Class:

- **Preferred Agents:** IPRATROPIUM BROMIDE HFA AER AD, IPRATROPIUM BROMIDE SOLUTION, IPRATROPIUM/ALBUTEROL SULFATE AMPUL-NEB, TIOTROPIUM BROMIDE(SPIRIVA®) CAP W/DEV, BECLOMETHASONE DIPROPIONATE(QVAR®) AER W/ADAP, CICLESONIDE (ALVESCO®) HFA AER AD, FLUTICASONE PROPIONATE(FLOVENT DISKUS®) DISK W/DEV, FLUTICASONE PROPIONATE(FLOVENT HFA®) AER W/ADAP, FLUTICASONE/SALMETEROL (ADVAIR DISKUS®) DISK W/DEV, FLUTICASONE/SALMETEROL (ADVAIR HFA®) HFA AER AD, FORMOTEROL FUMARATE (FORADIL®) CAP W/DEV, SALMETEROL (SEREVENT®) DISKUS
- **Non-Preferred Agents:** BUDESONIDE, BUDESONIDE/FORMOTEROL, BUDESONIDE (PULMICORT®), BUDESONIDE (PULMICORT®) FLEXHALER, MOMETASONE (ASMANEX®) TWISTHALER, MOMETASONE/FORMOTEROL (DULERA®), OMALIZUMAB (XOLAIR®), AFORMOTEROL (BROVANA®), FORMOTEROL (PERFOROMIST), IPRATROPIUM/ALBUTEROL (COMBIVENT®) RESPIMAT, ROFLUMILAST (DALIRESP®), INDACATEROL (ARCAPTA®) NEOHALER, ACLIDINIUM (TUDORZA®) PRESSAIR

Current PA Criteria: Prior Authorization (PA) criteria is in place for long-acting beta(2)-agonists (LABAs) and inhaled corticosteroid (ICS) inhalers (Appendix 1) to ensure that they are being prescribed for appropriate diagnoses and therapy. Combination Short Acting Bronchodilator Inhalers (Appendix 2) require step therapy with a short acting beta agonist (SABA) or an inhaled short acting anticholinergic agent ensure appropriate drug use. Roflumilast (Appendix 3) requires a PA to ensure appropriate therapy for patients with severe Chronic Obstructive Pulmonary Disease (COPD) with a history of chronic exacerbations or prior exacerbations while being treated with a long-acting bronchodilator.

Research Questions:

- Is there new comparative evidence that there is a meaningful difference in LABAs, long-acting antimuscarinic agents (LAMAs), and ICSs or combinations thereof in long term clinical outcomes or safety that could justify changes in current PDL management?
- Is there any new relevant evidence to change current policy?

Recommendations:

- Recommend evaluating comparative costs in executive session.
- Bring back more detailed drug review of fluticasone furoate/vilanterol inhalation powder (Breo Ellipta®) at upcoming meeting.

Previous Conclusions and Recommendations:

- There is insufficient comparative effectiveness evidence between inhaled corticosteroids and inhaled anticholinergics.
- There is no evidence demonstrating clinical superiority of aclidinium bromide over tiotropium, recommend making it non-preferred.
- There is moderate quality evidence that ipratropium bromide/albuterol Respimat inhaler is non-inferior to ipratropium bromide/albuterol MDI on lung function in the treatment of moderate to severe COPD.
- Make Combivent Respimat and Combivent MDI non-preferred and require a step through therapy with either component (short acting beta agonist OR a short acting anticholinergic). Grandfather current utilizers.
- Due to limited long term effectiveness or safety evidence compared to multiple alternatives, recommend making indacaterol a nonpreferred LABA.

- Recommend maintaining roflumilast as a non-preferred agent and include clinical PA criteria necessary for approval to ensure it is only used in the appropriate patient population:
    - Patient has severe or very severe COPD with chronic bronchitis and frequent exacerbation
    - Patient has documented failure with an ICS or ICS combination product or tiotropium
    - Patient is on a concurrent long acting controller medication (LABA or LAMA) as monotherapy or in combination with other therapies.

Methods:

A Medline literature search ending July 2013 for new systematic reviews and randomized controlled trials (RCT's) comparing ipratropium, tiotropium, beclomethasone, ciclesonide, fluticasone, salmeterol, formoterol,budesonide, mometasone, aformoterol, roflumilast, indacaterol, and aclidinium . The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials (RCTs) will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, seven systematic reviews, one guideline update and three head to head RCTs were identified.

Systematic reviews:

A new Cochrane Collaboration systematic review by Chong et al[1] evaluated the use of tiotropium versus LABAs. This review included seven randomized trials with 12,223 participants. All studies were of good methodological quality. However, there was a high amount of heterogenicity among the trials. The primary objective was to compare the relative clinical effects of tiotropium alone versus a LABA alone in quality of life, exacerbations, lung function and serious adverse events in people with chronic stable COPD. Tiotropium reduced the number of participants experiencing one or more exacerbations compared to the LABA (OR 0.86, 95% Confidence Interval (CI) 0.79 to 0.93). There was no difference seen among the different LABAs. Tiotropium was associated with a reduction in the number of COPD exacerbations leading to hospitalization compared to LABA treatment (OR 0.87; 95% CI 0.77 to 0.99), but the difference in overall hospitalizations or mortality. Symptom improvement and changes in lung function were similar between the two groups. There is not enough data to demonstrate clinical superiority of either tiotropium or LABAs.

Cope at al[2] evaluated the use of indacaterol 75 µg versus fixed-dose combinations of an ICS and LABA for the treatment of COPD. Fifteen randomized, placebo-controlled trials including COPD patients were evaluated. All trials were analyzed simultaneously using a Bayesian network meta-analysis and relative treatment effects between all regimens were obtained. Outcomes of interest were trough FEV_1 and transitional dyspnea index at 12 weeks. Indacaterol resulted in greater improvement in FEV_1 at 12 weels compared with budesonide/formoterol 160/9 ug (change from baseline 0.09L; 95% CI 0.04 to 0.13), budesonide/formoterol 320/9 ug (change from baseline 0.07L; 95% CI 0.03 to 0.11), fluticasone/salmeterol 250/50 ug (change from baseline 0.00L; 95% CI -0.07 to 0.07), and fluticasone/salmeterol 500/50 ug (change from baseline 0.01L; 95% CI -0.04 to 0.05). Based on the results of a network meta-analysis with and without covariates, indacaterol 75 µg is expected to be at least as efficacious to budesonide/formoterol and comparable to fluticasone/salmeterol with respect to lung function, but the results of effects on dypsnea are inconclusive with available data.

Dong et al[3] evaluated the overall safety and cardiovascular death for inhaled medications in patients with COPD. Forty-two trials with 52,516 subjects were included. A mixed-treatment comparison meta-analysis with a fixed effect model indicated tiotropium Soft Mist Inhaler was associated with a universally increased risk of overall death compared with placebo (OR 1.51; 95% CI 1.06 to 2.19), tiotropium HandiHaler (OR 1.65; 95% CI 1.13 to 2.43), LABA (OR 1.63; 95% CI

1.10 to 2.44) and LABA-ICS (OR 1.90; 95% CI 1.28 to 2.86). The risk was more evident for cardiovascular death, in patients with severe COPD, and at higher daily doses. LABA-ICS was associated with the lowest risk of death among all treatments. No excess risk was noted for tiotropium Handihaler or LABA.

Karner et al[4] evaluated the use of LABA and tiotropium versus either tiotropium or a LABA for the Cochrane Collaboration. Five trials were included in this review, mostly recruiting participants with moderate or severe COPD. All of them compared tiotropium in addition to LABAto tiotropium alone, but only one trial additionally compared a combination of the two types of bronchodilator with LABA(formoterol) alone. Two studies (moderate quality evidence) used the LABA indacaterol, two used formoterol and one used salmeterol. Compared to tiotropium alone (3263 patients), treatment with tiotropium plus LABA resulted in a slightly larger improvement in the mean health-related quality of life (St George's Respiratory Questionnaire (SGRQ) MD -1.61; 95% CI -2.93 to -0.29). In the control arm, tiotropium alone, the SGRQ improved by falling 4.5 units from baseline and with both treatments the improvement was a fall of 6.1 units from baseline (on average). There were no significant differences in the other primary outcomes (hospital admission or mortality).The secondary outcome of pre-bronchodilator FEV(1) showed a small mean increase with the addition of LABA (MD 0.07 L; 95% CI 0.05 to 0.09) over the control arm, which showed a change from baseline ranging from 0.03 L to 0.13 L on tiotropium alone. None of the other secondary outcomes (exacerbations, symptom scores, serious adverse events, and withdrawals) showed any statistically significant differences between the groups. The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and LABA compared to tiotropium alone, but it is not clear how clinically important this mean difference may be.

Nannini et al[5] evaluated the efficacy of ICS and LABA in a single inhaler with mono-component LABA alone for the Cochrane Collaborative. Fourteen studies were included, randomizing 11,794 people with COPD. Ten studies assessed fluticasone plus salmeterol and four assessed budesonide plus formoterol. All studies were well designed with a low risk for bias for randomization and blinding, but had high rates of attrition. There was low quality evidence that exacerbation rates in people using LABA/ICS inhalers were lower in comparison to those with LABA alone, from nine studies which randomized 9921 participants (rate ratio 0.76; 95% CI 0.68 to 0.84). This corresponds to one exacerbation per person per year on LABA and 0.76 exacerbations per person per year on ICS/LABA. When analyzed as the number of people experiencing one or more exacerbations over the course of the study, FPS lowered the odds of an exacerbation with an odds ratio (OR) of 0.83 (95% CI 0.70 to 0.98, 6 studies, 3357 participants). With a risk of an exacerbation of 47% in the LABA group over one year, 42% of people treated with LABA/ICS would be expected to experience an exacerbation. There was no significant difference in the rate of hospitalizations (rate ratio 0.79; 95% CI 0.55 to 1.13, very low quality evidence). There was no significant difference in mortality between people on combined inhalers and those on LABA, from 10 studies on 10,680 participants (OR 0.92; 95% CI 0.76 to 1.11, moderate quality evidence). Pneumonia occurred more commonly in people randomized to combined inhalers, from 12 studies with 11,076 participants (OR 1.55; 95% CI 1.20 to 2.01, moderate quality evidence) with an annual risk of around 3% on LABA alone compared to 4% on combination treatment. There were no significant differences between the results for either exacerbations or pneumonia from trials adding different doses or types of inhaled corticosteroid. Data were inconclusive as to the superiority of ICS/LABA over LABA alone in preventing COPD exacerbations. There was moderate quality evidence that combination therapy increased risk of pneumonia.

Rodrigo et al[6] explored the efficacy and safety of indacaterol in comparison with tiotropium or twice-daily dosed LABAs for the treatment of moderate to severe COPD. Five trials were included. Compared with tiotropium, indacaterol showed statistically and clinically significant reductions in the use of rescue medication and dyspnea(43% greater likelihood of achieving a minimal clinically important difference [MCID] in the transitional dyspnea index [TDI]; number needed to treat (NNT) = 10). Additionally, the MCID in health status was more likely to be achieved with indacaterol than with tiotropium (OR = 1.43; 95% CI, 1.22–1.68; P = .00001; NNT = 10). Trough FEV1 was statistically significantly higher at the end of treatment with indacaterol than with TD-LABAs (80 mL, p = .00001). Similarly, indacaterol significantly improved dyspnea (61% greater likelihood of achieving an MCID in TDI, p = .008) and health status (21% greater likelihood of achieving an MCID in St. George’s Respiratory Questionnaire, p = .04) than TD-LABA. Indacaterol showed

similar levels of safety and tolerability to both comparators. There was moderate quality evidence showing indacaterol may be a useful alternative to tiotropium or twice-daily dosed LABAs.

Rodrigo et al[7] evaluated the use of tiotropium plus a LABA ("dual" therapy), LABA/ICS ("combined" therapy), tiotropium plus a LABA/ICS ("triple" therapy), and tiotropium monotherapy in the maintenance treatment of moderate to severe COPD. Twenty trials (6803 participants) were included. "Dual" therapy showed significant improvements in FEV1, health-related quality of life (HRQoL), and dyspnea. However, it failed to reduce the risk of COPD exacerbations. Compared with tiotropium, "combined" therapy presented modest but significant effects on FEV1, HRQoL, and dyspnea. Again, there was no significant difference in exacerbations, but it was associated with a significant increase of serious adverse effects (SAE) (number need to harm = 20; 95% CI: 11-119). Finally, "triple therapy" increased FEV1, improved HRQoL (both benefits exceeded minimal important differences) and decrease COPD exacerbations in anon-significant way. (Odds ratio [OR] = 0.57; 95% CI: 0.24 to 1.37, p = 0.21). While treatments with tiotropium plus a LABA and tiotropium plus a LABA/ICS look promising, there is no data to support a recommendation of either therapy over the other. More studies are needed to examine long-term safety and efficacy of these combinations.

New drugs:

FDA approved the combination of fluticasone furoate and vilanterol inhalation powder (Breo Ellipta®)[8] in May 2013 for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations. Approval was based on two pivotal trials studying Breo Ellipta to fluticasone alone, vilanterol alone, or placebo. The primary efficacy variable was mean change from baseline in weighted mean FEV1 0-4 hour on day 168. Breo 100/25 (difference from placebo 0.17; 95% CI 0.12 to 0.22; p <0.001) was statistically significant from placebo, as was fluticasone 100mg alone (difference from placebo 0.05; 95% CI 0.00 to 0.10; p=0.04) and vilanterol alone (difference from placebo 0.10; 95% CI 0.05 to 0.15; p <0.001).There was not an active comparator.

FDA approved aclidinium bromide (Tudorza Pressair®)[9] in July 2012 (P&T reviewed this drug in January 2013). It is currently non-preferred due to a lack of evidence demonstrating clinical superiority of aclidinium bromide over tiotropium.

New Formulations

Ipratropium/albuterol (Combivent®) Respimat[10] inhalation spray was approved in October 2011 (P&T reviewed this drug in January 2013). Generic Combivent Inhalation Aerosol (ipratropium/albuterol sulfate) is currently a preferred inhaler on the preferred drug list. Evidence demonstrated that ipratropium/albuterol (Combivent®) Respimat inhaler is non-inferior to ipratropium bromide/albuterol (Combivent®) MDI on lung function as measured by FEV1 in the treatment of moderate to severe COPD. Ipratropium/albuterol Respimat is a new version of Combivent without chlorofluorcarbons and will be replacing the previous MDI inhaler. It will be the only product available as of January 1, 2014. Combivent Respimat and Combivent MDI are non-preferred and require a step through therapy with either component (short acting beta agonist or a short acting anticholinergic).

New FDA Safety Alerts:
None.

New Guidelines:

An update to the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines was released in 2013.[11] This update redefines COPD as a mixture of airflow obstruction, alveolar destruction and chronic inflammation. Previous GOLD guidelines classified COPD severity by post-bronchodilator FEV1 alone. Grading was updated to include grades A-D

based upon a combination of clinical symptoms, most notably dypsnea, FEV1 and number of yearly exacerbations. Drug therapy options for COPD were addressed. Indacaterol was included as a therapeutic option superior to salmeterol and formeterol, with similar efficacy to tiotropium (level A evidence). Roflumilast was included in the 2011 guidelines, but was again supported with level A evidence for its proven efficacy in reducing exacerbations in patients with severe COPD. Aclidinium was not added to the guidelines.

Randomized Controlled Trials

A total ofsix RCT's were identified in the literature search. Of these, there are three potentially relevant head to head clinical trials. Abstracts of these trials are located in Appendix 4.

Study	Comparison	Population	Primary Outcome	Results
Fuhr et al[12]	Aclidinium 400 ug BID with placebo and tiotropium (1:1:1)	Moderate to severe COPD N=30	Mean change from baseline in FEV1 AUC on day 15	Mean change from baseline in FEV1 at day 15 was significantly greater for aclidinium and tiotropium over placebo (p<0.0001)
Sharafkheneh et al[13]	BID budesonide/formoterol pMDI 320/9 ug, budesonide/formoterol pMDI 160/9 ug, or formoterol dry powder inhaler 9 ug (1:1:1)	COPD patients aged >= 40 years with an exacerbation history discontinued medications except ICSs N=1219	Exacerbation rates (number per patient-treatment year)	Budesonide/formoterol 320/9 ug and 160/9 ug reduced exacerbation rates by 34.6% and 25.9%, respectively, versus formoterol (p<= 0.002
Zhong et al[14]	Budesonide/formoterol 320/9 ug BID or budesonide 400 ug BID	Moderate to very severe COPD in Chinese population N=308	FEV1 change from baseline after 24 weeks	Budesonide/formoterol FEV1 improved by 0.18L vs 0.03L in budesonide alone group (p<0.001)

References

1. Chong, J., Karner, C. & Poole, P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* (2012). at <http://summaries.cochrane.org/CD009157/tiotropium-versus-long-acting-beta2-agonists-labas-in-the-management-of-copd>
2. Cope, S., Kraemer, M., Zhang, J., Capkun-Niggli, G. & Jansen, J. P. Efficacy of indacaterol 75 µg versus fixed-dose combinations of formoterol-budesonide or salmeterol-fluticasone for COPD: a network meta-analysis. *Int J Chron Obstruct Pulmon Dis* **7,** 415–420 (2012).
3. Dong, Y.-H. *et al.* Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. *Thorax* **68,** 48–56 (2013).
4. Karner, C. & Cates, C. J. Long-acting beta(2)-agonist in addition to tiotropium versus either tiotropium or long-acting beta(2)-agonist alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* **4,** CD008989 (2012).
5. Nannini, L. J., Lasserson, T. J. & Poole, P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* **9,** CD006829 (2012).
6. Rodrigo, G. J. & Neffen, H. Comparison of indacaterol with tiotropium or twice-daily long-acting β -agonists for stable COPD: a systematic review. *Chest* **142,** 1104–1110 (2012).
7. Rodrigo, G. J., Plaza, V. & Castro-Rodríguez, J. A. Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review. *Pulm Pharmacol Ther* **25,** 40–47 (2012).
8. Breo Ellipta Label Information. *Label and Approval History: Breo Ellipta* (2013). at <www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist>
9. Tudorza Label Information. *Label and Approval History: Tudorza* (2013). at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist>
10. Combivent Respimat Label Information. *Label and Approval History: Combivent Respimat* (2013). at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist>
11. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. (2013). at <http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf>
12. Fuhr, R. *et al.* Efficacy of aclidinium bromide 400 µg twice daily compared with placebo and tiotropium in patients with moderate to severe COPD. *Chest* **141,** 745–752 (2012).
13. Sharafkhaneh, A., Southard, J. G., Goldman, M., Uryniak, T. & Martin, U. J. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. *Respir Med* **106,** 257–268 (2012).
14. Zhong, N. *et al.* Efficacy and safety of budesonide/formoterol via a dry powder inhaler in Chinese patients with chronic obstructive pulmonary disease. *Curr Med Res Opin* **28,** 257–265 (2012).

Current PA (Appendix 1):

LABA/ICS Inhalers

Goal(s):

- *Approve LABA/ICS only for covered diagnosis (e.g. COPD or Asthma and on concurrent controller medication)*
- *LABA are only indicated for use in clients with Asthma already receiving treatment with an asthma controller medication (e.g. Inhaled corticosteroids or leukotriene receptor antagonists).*

Initiative: LABA/ICS Step Therapy

Length of Authorization: 6 months - 1 year

Covered alternatives that DO NOT require a PA:
See PDL list at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Step Therapy Required prior to coverage:

Asthma: oral corticosteroid inhalers (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml),

COPD: short and long-acting beta-agonist inhalers, anticholinergics and inhaled corticosteroids (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml), DO NOT require prior authorization.

Requires PA: All combination inhaled corticosteroid/long-acting beta-agonist inhalers.

Approval Criteria		
1. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)?	**Yes:** Go to **2**	**No:** Go to **3**
2. Has patient: • failed an inhaled corticosteroid or other controller medication OR • Had ≥2 exacerbations requiring oral systemic corticosteroids in the past year, OR • Is there documentation of step 3 asthma or higher OR • Is there a hospital admission or ER visit related to asthma or reactive airway disease within last 60 days?	**Yes**: Document the following: Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	**No**: **PASS TO RPH DENY (Medical Appropriateness).**
3. Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.) and/or emphysema (492.xx)?	**Yes:** Go to **4**	**NO: PASS TO RPH DENY (Medical Appropriateness).** *Need a supporting diagnosis. If prescriber believes diagnosis appropriate inform them of the provider reconsideration process for Medical Director Review.*
4. Has patient failed a combination of **short acting** (ipratroprium or	**Yes:** Document the following: Date of trial, drug, reason(s) for failure or contraindications in the	(**No:** Pass to RPH; Deny, (Medical Appropriateness). *Gold*

ipratroprium/albuterol) **and** **long-acting** (salmeterol, formoterol and/or tioptropium) inhaled bronchodilators?	PA record**.** Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	*guidelines recommend addition of inhaled corticosteroid if disease severity persistent despite use of combination of short acting and long-acting bronchodilators. http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf*

Appendix 2:

Combination Short Acting Bronchodilator Inhalers

Goal(s):

- *Promote preferred drugs that are selected based on evidence based reviews.*
- *To ensure appropriate drug use .*

Initiative: Short Acting Bronchodilator Step Therapy

Length of Authorization: 1 year

Covered alternatives that DO NOT require a PA:
See PDL list at http://www.orpdl.org/

Step Therapy Required prior to coverage:

Requires PA: non-preferred combination short acting bronchodilators

Approval Criteria		
1. What diagnosis is being treated?	**Record ICD9 code**	
2. Does the patient have COPD (ICD-9 496)?	**Yes**: Go to #3	**No**: Pass to RPh; Deny (Medical Appropriateness).
3. Will the prescriber change to a preferred product?	**Yes:** Inform provider of covered alternatives in class	**NO:** Go to #4
4. Has patient failed an inhaled Short acting beta agonist (albuterol) OR An inhaled short acting anticholinergic agent (ipratropium)?	**Yes:** Approve for one year	**No:** Pass to RPh, Deny (medical appropriateness)

P&T/DUR Action: 1/31/2013 (MH)
Revision(s): 7/1/2013
Initiated: 9/1/2013

Roflumilast

Goal(s):

- Decrease the number of COPD exacerbations in patients with severe COPD and chronic bronchitis and a history of prior exacerbations.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3.	**No:** Pass to RPh, Deny for OHP Coverage.
3. Does the patient have documented severe or very severe (Stage III or Stage IV) COPD?	**Yes:** Go to #4	**No:** Deny (medical inappropriateness)
4. Does the patient have a history of chronic bronchitis AND Prior COPD exacerbations?	**Yes:** Go to #5	**No:** Deny (medical inappropriateness)
5. Is the patient currently on a long-acting bronchodilator?	**Yes:** Go to #6	**No:** Deny. Recommend trial of preferred long-acting bronchodilators
6. Has the patient tried an inhaled corticosteroid (ICS), and ICS combination, or tiotropium (LAMA)?	**Yes:** Approve up to 1 year	**No:** Deny. Recommend trial of preferred long-acting ICS or LAMA

Appendix 4: RCT Abstracts

Furh, R., H. Magnussen, et al. (2012). "Efficacy of aclidinimium bromide 400 ug twice daily compared with placebo and tiotropium in patients with moderate to severe COPD." Chest **141**(3): 745-752.

BACKGROUND: The efficacy and safety of aclidinium bromide bid, a novel, long-acting, muscarinic antagonist, was assessed in patients with moderate to severe COPD.

METHODS: In this phase IIa randomized, double-blind, double-dummy, crossover trial, patients with moderate to severe COPD received aclidinium 400 ug bid, tiotropium 8 ug once daily, and placebo for 15 days, with a 9- to 15-day washout between treatment periods. Treatments were administered through the Genuair or HandiHaler dry powder inhalers. The primary end point was mean change from baseline in FEV(1) AUC(0-12 /12h)(area under the curve where the numbers represent the time period for which data were collected divided by the number of hours over which the data are averaged [eg, 0-12 h postdose divided by 12h]) on day 15. Secondary end points were changes from baseline in FEV(1) AUC(12-24/12h), FEV(1) AUC(0-24/24h), morning predose FEV(1), peak FEV(1), and COPD symptom scores.

RESULTS: Thirty patients with COPD were randomized, and 27 completed the study. Mean change from baseline in FEV(1) AUC(12-24/12h) at day 15 was significantly greater for aclidinium and tiotropium over placebo (P < .0001). Mean changes from baseline in FEV(1) AUC(12-24/12h), FEV(1) AUC(0-24/24h), morning predose FEV(1), and peak FEV(1) at day 15 were significantly greater for aclidinium and tiotropium over placebo (P < .0001 for all except P <.001 for FEV(1) AUC(12-24/12h) tiotropium vs placebo). Improvements were significantly greater with aclidinium vs tiotropium on day 1 for all of the normalized AUC values of FEV(1) as well as on day 15 for FEV(1) AUC(12-24/12h) (P < .05 for all). COPD symptoms were significantly improved from baseline with aclidinium vs placebo (P < .05) but not with tiotropium.

CONCLUSIONS: In patients with COPD, aclidinium 400 ug bid compared with placebo provided clinically meaningful improvements in 24-h bronchodilation that generally were comparable to tiotropium 18 ug daily but with significant differences in favor of aclidinium observed in the average nighttime period. Larger studies with longer treatment duration are ongoing to confirm the efficacy of aclidinium 400 ug bid on bronchodilation and COPD symptoms. Trial registry: ClinicalTrials.gov; No.: NCT00868231; URL: www.clinicaltrials.gov.

Sharafkhaneh, A., J. G. Southard, et al. (2012). "Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study." Respiratory Medicine **106**(2):257-268.

BACKGROUND: Treatment of an inhaled corticosteroid (ICS) and long-acting bronchodilator is recommended for severe/very severe chronic obstructive pulmonary disease (COPD) patients with repeated exacerbations This randomized, double-blind, double-dummy, parallel-group, 12-month multicenter study evaluated the effect of budesonide/formoterol pressurized metered-dose inhaler (pMDI) on COPD exacerbations.

METHODS: Following a 2-week run-in during which COPD patients aged >=40 years with an exacerbation history discontinued medications except ICSs, 1219 patients were randomized 1:1:1 to twice-daily budesonide/formoterol pMDI 320/9 ug, budesonide/formoterol 160/9 ug, or formoterol dry powder inhaler 9 ug. An exacerbation was defined as COPD worsening requiring oral corticosteroids and/or hospitalization. A post hoc analysis, with antibiotic treatment added to the exacerbation definition, was also performed.

RESULTS: Budesonide/formoterol 320/9 and 160/9 rediced exacerbation rates (number per patient-treatment year) by 34.6% and 25.9%, respectively, versus formoterol (p ,= 0.002). Budesonide/formoterol320/9 prolonged time to first exacerbation versus formoterol, corresponding to a 21.2% reduction in hazard ration (0.788 [95% CI: 0.639, 0.972]; p = 0.026). Exacerbation rates (number per patient-treatment year) including antibiotic treatment (post hoc analysis) were reduced by 25.9% and 18.7% with budesonide/formoterol 320/9 and 160/9, respectively, versus formoterol (p <= 0.023). Both budesonide/formoterol 320/9, 160/9 and formoterol groups.

CONCLUSIONS: Over 12 months, both budesonide/formoterol doses reduced the exacerbation rate (defined with or without antibiotic treatment) versus formoterol. Budesonide/formoterol pMDI is an appropriate treatment for reducing exacerbations in COPD patients with a history of exacerbations. (NTC00419744).

Zhong, N., J. Zheng, et al. (2012). "Efficacy and safety of budesonide/formoterol via a dry powder inhaler in Chinese patients with chronic obstructive pulmonary disease. Current Medical Research & Opinion 28**(2):** 257-265**.**

OBJECTIVE: To evaluate the efficacy and safety of budesonide (BUD)/formoterol (FORM) compared with BUD, both administered by way of a dry powder inhaler (Turbuhaler).

METHODS: This was a 6-month, multicenter, randomized, parallel-group, double-blind, double-dummy design study (NCT 00421122). Patients were randomized to either BUD/FORM 160/9 twice daily or BUD 400 ug, twice daily. Improvement of lung function, daily symptoms, reliever use and health-related quality-of-life (St. George's Respiratory Questionaire [SGRQ] score) were compared between the two treatment groups.

RESULTS: A total of 308 patients with moderate to very severe COPD from 12 centers in China were randomized to BUD/FORM (n=156) or BUD (n=152). The primary endpoint, 1-hour post-dose forced expiratory volume in 1 second (FEV1), in the BUD/FORM group improved by 0.18L (from 0.83L at baseline to 1.01L) and this was significantly better (p<0.001) than the small increase (0.03L) observed in the BUD group after 24 weeks' treatment. Increases in pre-dose and 15-min post-does FEV(1) together with 1-hour post-dose forced vital capacity were also significantly larger with BUD/FORM than BUD (p<0.001 for all). Compared with BUD alone, BUD/FORM improved COPD total symptom scores (-1.04+/-0.16 vs -0.55+/-0.17; p=0.03), reduced reliever use (-0.85+/-0.16 puffs/day vs -0.31+/-0.16 puffs/day; p=0.012) and improved health-related quality-of-life (mean change of total SGRQ score -4.5 points (p=0182). Overall, both treatment groups were well tolerated.

CONCLUSIONS: In Chinese patients with moderate to very severe COPD, fixed combination treatments with BUD/FORM resulted in clinically meaningful improvements in lung function, health-related quality-of-life, COPD symptoms and a reduction in reliever use, compared with BUD use alone and both treatments were well tolerated. Treatment of BNUD/FORM for milder patients with COPD and head to head comparison of Chinese and Caucasians in future studies will be helpful to expand upon the findings of the current clinical trial.

Appendix 5: Abstracts of Meta Analyses

Chong M. J., C. Karner, et al. (2102). "Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease." ¨Cochrane Database of Systemic Reviews 9: CD009157.

BACKGROUND: Tiotropium and long-acting beta(2)-agonists (LABAs) are both accepted in the routine management for people with stable chronic obstructive pulmonary disease (COPD). There are new studies which have compared tiotropium with LABAs, including some that have evaluated recently introduced LABAs.

OBJECTIVES: To compare the relative clinical effects of tiotropium bromide alone versus LABA alone, upon measures of quality of life, exacerbations, lung function and serious adverse events, in people with stable COPD. To critically appraise and summarize current evidence on the costs and cost-effectiveness with tiotropium compared to LABA in people with COPD.

SEARCH METHODS: We identified randomized controlled trials (RCTs) from the Cochrane Airwasys Group Specialised Register of trials and economic evaluations from searching NHS EED and HEED (date of last search February 2012). We found additional trials from web-based clinical trial registers.

SELECTION CRITERIA: We included RCTs and full economic evaluations if they compared effects of tiotropium alone with LABAs alone in people with COPD. We allowed co-administration of standard COPD therapy.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed studies for inclusion, then extracted data on study quality and outcomes .We contacted study authors and trial sponsors for additional information. We analyzed data using the Cochrane Review Manager (RevMan 5.1) software.

MAIN RESULTS: Seven clinical studies totaling 12,223 participants with COPD were included in the review. The studies used similar designs and were generally of good methodological quality. Inclusion criteria for RCTs were similar across the included studies, although studies varied in terms of smoking history and COPD severity of participants. They compared tiotropium (which was delivered by HandiHaler in all studies) with salmeterol (four studies, 8936 participants), formoterol (one study, 431 participants) and indacaterol (two studies, 2856 participants). All participants were instructed to discontinue anticholinergic or LABAbronchodilators during treatment, but could receive inhaled corticosteroids (ICS) at a stable dose. Study duration ranged from 3 to 12 months. We extracted data for 11,223 participants. In general, the treatment groups were well matched at baseline. Overall, the risk of bias across the included RCTs was low. In the analysis of the primary outcomes in this review, a high level of heterogenicity amongst studies meant that we did not pool data for St. George's Respiratory Questionnaire quality of life score. Subgroup analyses based on the type of LABA found statistically significant differences among effects on quality of life depending on whether tiopropium was compared with salmeterol, formoterol, or indacaterol. Tiotropium reduced the number of participants experiencing one or more exacerbations compared with LABA (odds ratio (OR) 0.86; 95% confidence interval (CI) 0.79 to 0.93). For this outcome, there was no difference seen among the different types of LABA. There was no statistical difference in mortality observed between the treatment groups. For secondary outcomes, tiotropium was associated with a reduction in the number of COPD exacerbations leading to hospitalisation compared with LABA treatment (OR 0.87; 95% CI 0.77 to 0.99), but not in the overall rate of all-cause hospitalizations. There was no statisticallysignificant difference in forced expiratory volume in one second FEV(!) or symptom score between tiotropium and LABA-treated participants. There was a lower rate of non-fatal serious adverse events recorded with tiotropium compared with LABA (OR 0.88; 95% CI 0.78 to 0.99). The tiotropium group was also associated with a lower rate of study withdrawals (OR 0.89; 95% CI 0.81 to 0.99). We identified six full economic evaluations assessing the cost and cost-effectiveness of tiotropium and salmeterol. The studies were based on an economic model or empirical analysis of clinical data from RCTs. They all looked at maintenance costs and the costs for COPD exacerbations,

including respiratory medications and hospitalizations. The setting for the evaluations was primary and secondary care in the UK, Greece, Netherlands, Spain and US> All the studies estimated tiotropium to be superior to salmeterol based on better clinical outcomes (exacerbations or quality of life_ and/or lower total costs. However, the authors of all evaluations reported there was substantial uncertainty around the results.

AUTHORS' CONCLUSIONS: In people with COPD, the evidence is equivocal as to whether or not tiotropium offers greater benefit than LABAs in improving quality of life; however, this is complicated by differences in effect among the LABA types. Tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalizations, although there were no statistical differences between groups in overall hospitalization rates or mortality during the study periods. There were fewer serious adverse events and study withdrawals recorded with tiotropium compared with LABAs. Symptom improvement and changes in lung function were similar between the treatment groups. Given the small number of studies to date, with high levels of heterogeneity among them, one approach may be to give a COPD patient a substantial trial of tiotropium, followed by a LABA (or vice-versa), then to continue prescribing the long-acting bronchodilator that the patient prefers. Further studies are needed to compare tiotropium with different LABAs, which are currently ongoing. The available economic evidence indicates that tiotropium may be cost-effective compared with salmeterol in several specific setting, but there is considerable uncertainty around this finding.

Cope, S., M. Kraemer, et al. (2012). "Efficacy of indacaterol 75 ug versusfixed-dose combinations of formoterol-budesonide or salmeterol-fluticasone for COPD: a network meta-analysis." Ïnternational Journal of Copd 7: 415-420.

BACKGROUND: The purpose of this study was to update our network meta-analysis in order to compare the efficacy of indacaterol 75 µg with that of a fixed-dose combination of formoterol and budesonide (FOR/BUD) and a fixed-dose combination salmeterol and fluticasone (SAL/FP) for the treatment of chronic obstructive pulmonary disease (COPD) based on evidence identified previously in addition to two new randomized clinical trials.

METHODS: Fifteen randomized, placebo-controlled clinical trials including COPD patients were evaluated: indacaterol 75 µg once daily (n = 2 studies), indacaterol 150 µg once daily (n = 5), indacaterol 300 µg once daily (n = 4), FOR/BUD 9/160 µg twice daily (n = 2), FOR/BUD 9/320 µg twice daily (n = 2), SAL/FP 50/500 µg twice daily (n = 4), and SAL/FP 50/250 µg twice daily (n = 1). All trials were analyzed simultaneously using a Bayesian network meta-analysis and relative treatment effects between all regimens were obtained. Treatment-by-covariate interactions were included where possible to improve the similarity of the trials. Outcomes of interest were trough forced expiratory volume in 1 second (FEV(1)) and transitional dyspnea index at 12 weeks.

RESULTS: Based on the results without adjustment for covariates, indacaterol 75 µg resulted in a greater improvement in FEV(1) at 12 weeks compared with FOR/BUD 9/160 µg (difference in change from baseline 0.09 L [95% credible interval 0.04-0.13]) and FOR/BUD 9/320 µg (0.07 L [0.03-0.11]) and was comparable with SAL/FP 50/250 µg (0.00 L [-0.07-0.07]) and SAL/FP 50/500 µg (0.01 L [-0.04-0.05]). For transitional dyspnea index, data was available only for indacaterol 75 µg versus SAL/FP 50/500 µg (-0.49 points [-1.87-0.89]).

CONCLUSION: Based on results of a network meta-analysis with and without covariates, indacaterol 75 µg is expected to be at least as efficacious as FOR/BUD (9/320 µg and 9/160 µg) and comparable with SAL/FP (50/250 µg and 50/500 µg) in terms of lung function. In terms of breathlessness (transitional dyspnea index) at 12 weeks, the results are inconclusive given the limited data.

Dong, Y.. –H., H.-H. Lin, et al. (2013). "Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomized controlled trials." ¨Thorax 65(1): 48-56.

BACKGROUND: The active-treatment comparative safety information for all inhaled medications in patients with chronic obstructive pulmonary disease (COPD) is limited. We aimed to compare the risk of overall and cardiovascular death for inhaled medications in patients with COPD.

METHODS: Through systematic database searching, we identified randomised controlled trials of tiotropium Soft Mist Inhaler, tiotropium HandiHaler, long-acting β2 agonists (LABAs), inhaled corticosteroids (ICS), and LABA-ICS combination with at least a 6-month treatment duration. Direct comparison and mixed treatment comparison (MTC) meta-analyses were conducted to estimate the pooled ORs of death for each comparison.

RESULTS: 42 trials with 52 516 subjects were included. The MTC meta-analysis with the fixed effect model indicated tiotropium Soft Mist Inhaler was associated with an universally increased risk of overall death compared with placebo (OR 1.51; 95% CI 1.06 to 2.19), tiotropium HandiHaler (OR 1.65; 95% CI 1.13 to 2.43), LABA (OR 1.63; 95% CI 1.10 to 2.44) and LABA-ICS (OR 1.90; 95% CI 1.28 to 2.86). The risk was more evident for cardiovascular death, in patients with severe COPD, and at a higher daily dose. LABA-ICS was associated with the lowest risk of death among all treatments. No excess risk was noted for tiotropium

HandiHaler or LABA. The results were similar for MTC and direct comparison meta-analyses, with less precision in the random effects model.

CONCLUSION: Our study provided a comparative safety spectrum for each category of inhaled medications. Tiotropium Soft Mist Inhaler had a higher risk of mortality and should be used with caution.

Karner, C. & Cates, C. J. "LABAin addition to tiotropium versus either tiotropium or LABAalone for chronic obstructive pulmonary disease." Cochrane Database Syst Rev 4, CD008989 (2012).

BACKGROUND: Long-acting bronchodilators comprising long-acting beta(2)-agonists and the anticholinergic agent tiotropium are commonly used for managing persistent symptoms of chronic obstructive pulmonary disease. Combining these treatments, which have different mechanisms of action, may be more effective than the individual components. However, the benefits and risks of combining tiotropium and long-acting beta(2)-agonists for the treatment of chronic obstructive pulmonary (COPD) disease are unclear.

OBJECTIVES: To assess the relative effects of treatment with tiotropium in addition to LABA compared to tiotropium or LABA alone in patients with chronic obstructive pulmonary disease.

SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register of trials and clinicaltrials.gov up to January 2012.

SELECTION CRITERIA: We included parallel group, randomised controlled trials of three months or longer comparing treatment with tiotropium in addition to LABA against tiotropium or LABA alone for patients with chronic obstructive pulmonary disease.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed trials for inclusion and then extracted data on trial quality and the outcome results. We contacted study authors for additional information. We collected information on adverse effects from the trials.

MAIN RESULTS: Five trials were included in this review, mostly recruiting participants with moderate or severe chronic obstructive pulmonary disease. All of them compared tiotropium in addition to LABA to tiotropium alone, but only one trial additionally compared a combination of the two types of bronchodilator with LABA (formoterol) alone. Two studies used the LABA indacaterol, two used formoterol and one used salmeterol. Compared to tiotropium alone (3263 patients), treatment with tiotropium plus LABA resulted in a slightly larger improvement in the mean health-related quality of life (St George's Respiratory Questionnaire (SGRQ) MD -1.61; 95% CI -2.93 to -0.29). In the control arm, tiotropium alone, the SGRQ improved by falling 4.5 units from baseline and with both treatments the improvement was a fall of 6.1 units from baseline (on average). High withdrawal rates in the trials increased the uncertainty in this result, and the GRADE assessment for this outcome was therefore moderate. There were no significant differences in the other primary outcomes (hospital admission or mortality).The secondary outcome of pre-bronchodilator FEV(1) showed a small mean increase with the addition of LABA (MD 0.07 L; 95% CI 0.05 to 0.09) over the control arm, which showed a change from baseline ranging from 0.03 L to 0.13 L on tiotropium alone. None of the other secondary outcomes (exacerbations, symptom scores, serious adverse events, and withdrawals) showed any statistically significant differences between the groups. There were wide confidence intervals around these outcomes and moderate heterogeneity for both exacerbations and withdrawals. The results from the one trial comparing the combination of tiotropium and LABA to LABA alone (417 participants) were insufficient to draw firm conclusions for this comparison.

AUTHORS' CONCLUSIONS: The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and LABA compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. Hospital admission and mortality have not been shown to be altered by adding long-acting beta(2)-agonists to tiotropium. There were not enough data to determine the relative efficacy and safety of tiotropium plus LABA compared to LABA alone. There were insufficient data to make comparisons between the different long-acting beta(2)-agonists when used in addition to tiotropium.

Nannin, L. J., T. J. Lasserson, et al. (2012). "Combined corticosteroid and LABA in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease." Cochrane Database of Systematic Reviews **9: CD006829.**

BACKGROUND: Both inhaled steroids (ICS) and long-acting beta(2)-agonists (LABA) are used in the management of chronic obstructive pulmonary disease (COPD). This updated review compared compound LABA plus ICS therapy (LABA/ICS) with the LABA component drug given alone.

OBJECTIVES: To assess the efficacy of ICS and LABA in a single inhaler with mono-component LABA alone in adults with COPD.

SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register of trials. The date of the most recent search was November 2011.

SELECTION CRITERIA: We included randomised, double-blind controlled trials. We included trials comparing compound ICS and LABA preparations with their component LABA preparations in people with COPD.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed study risk of bias and extracted data. The primary outcomes were exacerbations, mortality and pneumonia, while secondary outcomes were health-related quality of life (measured by

validated scales), lung function, withdrawals due to lack of efficacy, withdrawals due to adverse events and side-effects. Dichotomous data were analysed as random-effects model odds ratios or rate ratios with 95% confidence intervals (CIs), and continuous data as mean differences and 95% CIs. We rated the quality of evidence for exacerbations, mortality and pneumonia according to recommendations made by the GRADE working group.

MAIN RESULTS: Fourteen studies met the inclusion criteria, randomising 11,794 people with severe COPD. We looked at any LABA plus ICS inhaler (LABA/ICS) versus the same LABA component alone, and then we looked at the 10 studies which assessed fluticasone plus salmeterol (FPS) and the four studies assessing budesonide plus formoterol (BDF) separately. The studies were well-designed with low risk of bias for randomisation and blinding but they had high rates of attrition, which reduced our confidence in the results for outcomes other than mortality. Primary outcomes There was low quality evidence that exacerbation rates in people using LABA/ICS inhalers were lower in comparison to those with LABA alone, from nine studies which randomised 9921 participants (rate ratio 0.76; 95% CI 0.68 to 0.84). This corresponds to one exacerbation per person per year on LABA and 0.76 exacerbations per person per year on ICS/LABA. Our confidence in this effect was limited by statistical heterogeneity between the results of the studies (I(2) = 68%) and a risk of bias from the high withdrawal rates across the studies. When analysed as the number of people experiencing one or more exacerbations over the course of the study, FPS lowered the odds of an exacerbation with an odds ratio (OR) of 0.83 (95% CI 0.70 to 0.98, 6 studies, 3357 participants). With a risk of an exacerbation of 47% in the LABA group over one year, 42% of people treated with LABA/ICS would be expected to experience an exacerbation. Concerns over the effect of reporting biases led us to downgrade the quality of evidence for this effect from high to moderate. There was no significant difference in the rate of hospitalisations (rate ratio 0.79; 95% CI 0.55 to 1.13, very low quality evidence due to risk of bias, statistical imprecision and inconsistency). There was no significant difference in mortality between people on combined inhalers and those on LABA, from 10 studies on 10,680 participants (OR 0.92; 95% CI 0.76 to 1.11, downgraded to moderate quality evidence due to statistical imprecision). Pneumonia occurred more commonly in people randomised to combined inhalers, from 12 studies with 11,076 participants (OR 1.55; 95% CI 1.20 to 2.01, moderate quality evidence due to risk of bias in relation to attrition) with an annual risk of around 3% on LABA alone compared to 4% on combination treatment. There were no significant differences between the results for either exacerbations or pneumonia from trials adding different doses or types of inhaled corticosteroid. Secondary outcomes ICS/LABA was more effective than LABA alone in improving health-related quality of life measured by the St George's Respiratory Questionnaire (1.58 units lower with FPS; 2.69 units lower with BDF), dyspnoea (0.09 units lower with FPS), symptoms (0.07 units lower with BDF), rescue medication (0.38 puffs per day fewer with FPS, 0.33 puffs per day fewer with BDF), and forced expiratory volume in one second (FEV(1)) (70 mL higher with FPS, 50 mL higher with BDF). Candidiasis (OR 3.75) and upper respiratory infection (OR 1.32) occurred more frequently with FPS than SAL. We did not combine adverse event data relating to candidiasis for BDF studies as the results were very inconsistent.

AUTHORS' CONCLUSIONS: Concerns over the analysis and availability of data from the studies bring into question the superiority of ICS/LABA over LABA alone in preventing exacerbations. The effects on hospitalisations were inconsistent and require further exploration. There was moderate quality evidence of an increased risk of pneumonia with ICS/LABA. There was moderate quality evidence that treatments had similar effects on mortality. Quality of life, symptoms score, rescue medication use and FEV(1) improved more on ICS/LABA than on LABA, but the average differences were probably not clinically significant for these outcomes. To an individual patient the increased risk of pneumonia needs to be balanced against the possible reduction in exacerbations. More information would be useful on the relative benefits and adverse event rates with combination inhalers using different doses of inhaled corticosteroids. Evidence from head-to-head comparisons is needed to assess the comparative risks and benefits of the different combination inhalers

Rodrigo, G.J. and H. Neffen (2012). “Comparison of indacaterol with tiotropium or twice-daily long-acting agonists for stale COPD: a systematic review.” Chest 142(5) 1104-1110.

BACKGROUND: Bronchodilators are central to the symptomatic management of patients with COPD. Previous data have shown that inhaled indacaterol improved numerous clinical outcomes over placebo.

METHODS: This systematic review explored the efficacy and safety of indacaterol in comparison with tiotropium or bid long-acting β 2 -agonists (TD-LABAs) for treatment of moderate to severe COPD. Randomized controlled trials were identified after a search of different databases of published and unpublished trials.

RESULTS: Five trials (5,920 participants) were included. Compared with tiotropium, indacaterol showed statistically and clinically significant reductions in the use of rescue medication and dyspnea(43% greater likelihood of achieving a minimal clinically important difference [MCID] in the transitional dyspnea index [TDI]; number needed to treat for benefit [NNTB] 5 10). Additionally, the MCID in health status was more likely to be achieved with indacaterol than with tiotropium (OR = 1.43; 95% CI, 1.22–1.68; P = .00001; [NNTB]= 10). Trough FEV 1 was significantly higher at the end of treatment with indacaterol than with TD-LABAs (80 mL, P = .00001). Similarly, indacaterol significantly improved dyspnea (61% greater likelihood of

achieving an MCID in TDI, P = .008) and health status (21% greater likelihood of achieving an MCID in St. George's Respiratory Questionnaire, P 5 .04) than TD-LABA. Indacaterol showed similar levels of safety and tolerability to both comparators.

CONCLUSIONS: Available evidence suggests that indacaterol may prove useful as an alternative to tiotropium or TD-LABA due to its effects on health status, dyspnea, and pulmonary function.

Rodrigo, G. J., Plaza, V. & Castro-Rodríguez, J. A. "Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review." Pulm Pharmacol Ther **25,** 40–47 (2012).

BACKGROUND: Guidelines recommend the use of inhaled long-acting bronchodilators, inhaled corticosteroids (ICS) and their combinations for maintenance treatment of moderate to severe COPD. However, there are limited data supporting combination therapy.

METHODS: This systematic review assessed the efficacy of three therapeutic approaches: tiotropium plus long-acting beta2-agonist (LABA) ("dual" therapy), LABA/ICS ("combined" therapy), and tiotropium plus LABA/ICS ("triple" therapy), all compared with tiotropium monotherapy. Randomized controlled trials were identified after a search of different databases of published and unpublished trials.

RESULTS: Twenty trials (6803 participants) were included. "Dual" therapy showed significant improvements in forced volume in the first second (FEV(1)), health-related quality of life (HRQoL), and dyspnea. However, it failed to reduce the risk of COPD exacerbations. Compared with tiotropium, "combined" therapy presented modest but significant effects on FEV(1), HRQoL, and dyspnea. Again, there was no significant difference in exacerbations, but it was associated with a significant increase of serious adverse effects (SAE) (number need to treat for harm [NNTH] = 20; 95% CI: 11-119). Finally, "triple therapy" increased FEV(1), improved HRQoL (both benefits exceeded minimal important differences) and decrease COPD exacerbations in anon-significant way. (Odds ratio [OR] = 0.57; 95% CI: 0.24 to 1.37, p = 0.21).

CONCLUSIONS: "Dual" and "triple" therapy seem like the most promising for patients with moderate to very severe COPD. However, data are still scarce and studies too short to generate a strong recommendation. Future studies should examine long-term efficacy and safety**.**

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: September 2013
PDL Classes: Growth Hormones

Date of Last Review: September 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: SOMATROPIN (OMNITROPE®) CARTRIDGE, SOMATROPIN (SAIZEN®) CARTRIDGE & VIAL
- Non-Preferred Agents: SOMATROPIN (GENOTROPIN MINIQUICK) VIAL, SOMATROPIN (GENOTROPIN) VIAL, SOMATROPIN (HUMATROPE), SOMATROPIN (NORDITROPIN FLEXPRO), SOMATROPIN (NUTROPIN AQ NUSPIN), SOMATROPIN (OMNITROPE) VIAL, SOMATROPIN (TEV-TROPIN)

Previous Conclusions and Recommendation:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Evidence is insufficient to identify a clinically meaningful benefit in adults
- Recommend inclusion of at least one product with pediatric indications

PA Criteria: Prior authorization criteria are currently in place for growth hormone to cover only for covered diagnosis and for medically appropriate conditions (Appendix 1). Use for adults is not covered.

Conclusions and Recommendations:

- There is no comparative evidence that there is a difference in efficacy or safety between somatropin products.
- No further review or research needed at this time
- Evaluate comparative costs in executive session.

Methods:

A Medline OVID search was conducted with the following search terms: cachexia, deficiency, disorder, dwarfism, pituitary, growth disorders, human growth hormone, Noonan syndrome, Prader-Willi syndrome, short bowel syndrome, short stature disorder, shox, somatropin, stature, Turner syndrome. The search was limited to English language articles of controlled trials conducted on humans published from September 2012 to August week one 2013. The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

Wu et al evaluated the efficacy and safety in treating pediatric renal transplant patients with growth hormone (somatropin) to counter potential growth retardation.[1] Five randomized control trials were included in their meta-analysis with a total of 401 children aged 18 years or younger. The primary outcome measured was increase in the baseline height standard deviations score (HSDS); secondary safety outcomes examined allograft rejection rates and change in glomerular filtration rate (GFR). After one year, patients given growth hormone were significantly more likely to have an increase in baseline height standard deviation score (HSDS) than the control group, with a mean HSDS difference of 0.68 (95% CI 0.25 to 1.11) between the two groups. Growth hormone patients were more likely to experience an allograft rejection than placebo patients, although this difference was not significant (risk ratio 1.56; 95 % CI 0.97 to 2.53). Placebo patients however were more likely to have a negative change in GFR: 3.27ml/min per 1.73m2 (95% CI −3.54 to 10.09) which was also not statistically significant. No quality assessment was reported for the trials included in this analysis.[1]

Sanchez et al performed a meta-analysis examining the effects of growth hormone therapy on adults with Prader-Willi syndrome (PWS).[1] Eight randomized control trials were included with 134 PWS adult subjects. Outcomes studied were the mean difference in body composition metrics (percent body fat, body mass index, and lean body mass) and metabolic changes (fasting glucose and insulin, insulin resistance, and lipids) after twelve months of growth hormone treatment and compared with placebo. Subjects on growth hormone therapy showed decreased body fat compared with placebo subjects: mean difference -2.9% (95% CI -3.9 to -1.91). They also had statistically significant increased lean body mass: mean difference from placebo 2.82 kg (95% 1.31 to 4.33). No difference was found between groups in body mass index (-0.48kg/m^3; 95% -1.32 to 0.35). Growth hormone patients also had increased fasting glucose (0.27mmol/L; 95% CI 0.05 to 0.49mmol/L), and a nonsignificant increase in fasting insulin (20.24 pmol/L; 95% CI -0.55 to 41.02) and insulin resistance (0.60; 95% CI -0.04 to 1.24). No difference was found in mean difference in fasting lipids: total cholesterol -0.12mmol/L (-0.29 to 0.05) and LDL -0.11 mmol/L (-0.3 to 0.07). Individual trial quality assessment was not performed.[2]

The Cochrane Collaboration also looked at the effects of growth hormone treatment in children and young adults with cystic fibrosis. Thaker et al performed a systematic review to look for potential differences in height, weight, pulmonary function, blood glucose, and exacerbations.[3] Four controlled trials were included with 161 subjects aged 25 years and younger, but only one study (n=67) was used for outcome analysis. After 24 weeks, subjects treated with growth hormone had a nonsignificant change in pulmonary function compared with placebo patients: percent change in baseline mean difference for FVC 3.8% (95% CI -4.72 to 12.32) and FEV1 2.5% (95% CI -8.6 to 13.60). Changes in weight (mean difference 1.00 kg; 95% CI -0.08 to 2.08) and height (2.5 cm; 95% CI -0.77 to 5.77) were also not significant. Growth hormone subjects did see a significant increase in fasting blood glucose levels (12.4 mg/dL; 95% CI 3.76 to 21.04). No difference was seen in exacerbation rate. Trial quality was evaluated as fair to poor. The authors felt the risk of bias in the four studies was high with most studies' allocation concealment, blinding and randomization not present or poorly explained.[3]

Finally, Breederveld et al examined the effect of growth hormone treatment on burn healing in adults and children. Thirteen randomized controlled trials (n=701) were included in the systematic review; the average total burn surface area was greater than 49%.[4] Endpoints included time to heal and hyperglycemia. In two trials with adult subjects, growth hormone subjects healed significantly more quickly (9.07 days; 95% CI4.39 to 13.76) than placebo subjects. Adult donor sites also had a significantly shorter healing time (3.15 days; 95% CI 1.54 to 4.75). Hyperglycemia was more likely to occur in growth hormone treated adults than placebo subjects (risk ratio 2.43; 95% CI 1.54 to 3.85). In two trials with children subjects, donor site healing time was also increased in growth hormone subjects than placebo patients (1.7days; 95% CI 1.54 to 3.85). No difference was seen in children for hyperglycemia. Trial quality was assessed as fair to poor. Allocation concealment was not performed in any study and randomization methods were not described for most.[4]

Guidelines:

The Growth Hormone Research Society Workshop created consensus guidelines for Recombinant Human Growth Hormone (rhGH) Therapy in Prader-Willi Syndrome.[5] Forty-three experts participated in a workshop to review the available data from a literauture search and review. The level of evidence was evaluated using the scoring procedure based on the Oxford Centre for Evidence-Based Medicine Level of Evidence scale. Most of the trials were performed in small populations, and durations were short compared to the length of rhGH treatment in the real-life setting. Most of the trials were graded of low quality. No specific preference to individual products was given. The workshop participants established the following recommendations:

- After genetic confirmation of the diagnosis of Prader-Willi, rhGH treatment should be considered and, if initiated, should be continued for as long as demonstrated benefits outweigh the risks (Recommendation level A; level of evidence 1).

- Before initiation of therapy, patients should have a genetically confirmed diagnosis and expert multidisciplinary evaluation (Recommendation level A; level of evidence 5).
- Exclusion criteria for starting patients on treatment include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis (Recommendation level A; level of evidence 4).
- Treatment with rhGH must be in the context of appropriate dietary, environmental, and lifestyle interventions necessary for care of all patients.

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
None

New Trials (Appendix 2):
A total of 214 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, one relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Decker et al conducted a follow up study on children receiving growth hormone treatment to determine if dose changes would affect metabolic outcomes.[6] Children with growth hormone deficiency or idiopathic short stature disorder were originally randomized to either individual growth hormone doses (17-1000 mg/kg/day) or a standard dose (43mg/kg/day) for a two year study. For this follow up, children in the individual treatment group were randomized to either an unchanged dose (n=28) or a 50% decrease in dose (n=37). Patients originally on a fixed dose regimen remained on that dose (n=33). The primary endpoint of the study was comparison in metabolic changes (fasting insulin, insulin sensitivity) and body composition changes (lean soft tissue, bone mineral content). After two years, subjects in the reduced dose group compared with the unchanged group had a significantly reduced level of fasting insulin (50%; $p < 0.05$) and insulin sensitivity (55.1%; $p < 0.05$), although no difference was seen when compared with the fixed dose group. No difference was seen in bone mineral composition and lean soft tissue between the three groups after two years. This was a poor quality study; randomization was not performed, and the study was essentially unblinded after its original trial.[6]

References:

1. Wu Y, Cheng W, Yang X, Xiang B. Growth hormone improves growth in pediatric renal transplant recipients—a systemic review and meta-analysis of randomized controlled trials. *Pediatric Nephrology*. 2012;28(1):129–133. doi:10.1007/s00467-012-2208-7.

2. Sanchez-Ortiga R, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy in adults with Prader-Willi syndrome: a meta-analysis: Growth hormone therapy in Prader-Willi syndrome. *Clinical Endocrinology*. 2012;77(1):86–93. doi:10.1111/j.1365-2265.2011.04303.x.

3. Thaker V, Haagensen AL, Carter B, Fedorowicz Z, Houston BW. Recombinant growth hormone therapy for cystic fibrosis in children and young adults. In: The Cochrane Collaboration, Thaker V, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2013. Available at: http://doi.wiley.com/10.1002/14651858.CD008901.pub2. Accessed August 20, 2013.

4. Breederveld RS, Tuinebreijer WE. Recombinant human growth hormone for treating burns and donor sites. In: The Cochrane Collaboration, Tuinebreijer WE, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD008990.pub2. Accessed August 20, 2013.

5. Deal CL, Tony M, Hoybye C, et al. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. 2013 Jun;98(6):E1072-87. Epub 2013 Mar 29.

6. Decker R, Albertsson-Wikland K, Kriström B, Halldin M, Dahlgren J. Decreased GH dose after the catch-up growth period maintains metabolic outcome in short prepubertal children with and without classic GH deficiency. *Clinical Endocrinology*. 2012;77(3):407–415. doi:10.1111/j.1365-2265.2012.04386.x.

Hormones – Growth Hormone

(Somatropin)

Goal(s): Cover drugs only for covered diagnoses and those where there is medical evidence of effectiveness and safety.

NOTE: Growth Hormone treatment is no longer covered by OHP for adult diagnoses, including isolated deficiency of human growth hormone, AIDS wasting in adults or other conditions in adults.

Length of Authorization: 1 year

Preferred Alternatives: All medications require a PA for OHP Coverage. GH for adults is not covered by OHP. For preferred products for children see: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Note: Criteria is divided by: **Pediatric (<18 years old)**
- New therapy
- Renewal therapy

Requires PA: All drugs in HIC3 = P1A

Pediatric Approval Criteria (<18 years old) - New Therapy		
1. Is the patient an adult (> 18 years old)?	**Yes:** Pass to RPH; Deny, (Not Covered by the OHP).	**No:** Go to #2.
2. Is this a request for initiation of growth hormone?	**Yes:** Go to question #3	**No:** Go to renewal therapy
3. Is the prescriber a pediatric endocrinologist or pediatric nephrologist?	**Yes:** Go to #4	**No:** Pass to RPH; Deny, (Medical Appropriateness)
4. Is the diagnosis promotion of growth delay in a child with 3rd degree burns (ICD-9 codes 941.3-949.3)?	Yes: Document and send to DHS Medical Director for review and pending approval	**No:** Go to #5.
5. Is the diagnosis one of the following? • Turner's Syndrome (758.6)	**Yes:** Document and go to #6	**No:** Pass to RPH; Deny, (Not

• Noonan Syndrome (759.89) • Pre-transplant chronic renal insufficiency (CRI) (593.9) • Prader - Willi Syndrome(PWS) (759.81) • Neonatal Hypoglycemia associated with Growth Hormone Deficiency (775.6) • X-linked Hypophosphotemia • Pituitary Dwarfism (253.3) • SHOX (Short stature homeobox gene)(783.43)		Covered by the OHP).
6. If male, is bone age <16 years? If female, is bone age <14 years?	**Yes:** Go to #7.	**No:** Pass to RPH; Deny, (Medical Appropriateness)
7. Is there evidence of non-closure of epiphyseal plate?	**Yes:**.Go to #8.	**No:** Pass to RPH; Deny, (Medical Appropriateness)
8. Is the product requested preferred?	**Yes**: Approve for 1 year.	**No:** Go to #9.
9. Will the prescriber consider a change to a preferred product? **Message:** • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes**: Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml. Approve for 1 year.	**No**: Approve for 1 year.

Pediatric Approval Criteria (<18 years old) – Renewal Therapy		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Is growth velocity greater than 2.5 cm per year?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny, (Medical Appropriateness)

3. Is male bone age <16 years and Is female bone age <14 years?	**Yes:** Approve for 1 year.	**No:** Pass to RPH; Deny, (Medical Appropriateness)

DUR Board Action: *9/16/10(KS), 5-27-10(KS), 9-18-08ca, 2-23-06, 11-18-03, 9-9-03,*
Revision(s) *1/1/11, 7-1-10, 4-15-09, 10-1-03, 9/1/06*
Initiated: *10-1-03*

Appendix 2: Abstracts of Randomized Control Trials

Decker R, Albertsson-Wikland K, Kriström B, Halldin M, Dahlgren J. Decreased GH dose after the catch-up growth period maintains metabolic outcome in short prepubertal children with and without classic GH deficiency. *Clinical Endocrinology*. 2012;77(3):407–415. doi:10.1111/j.1365-2265.2012.04386.x.

Objective Few studies have evaluated metabolic outcomes following growth hormone (GH) treatment in short prepubertal children during different periods of growth. Previously, we found that individualized GH dosing in the catch-up period reduced the variation in fasting insulin levels by 34% compared with those receiving a standard GH dose. We hypothesized that the GH dose required to maintain beneficial metabolic effects is lower during the prepubertal growth phase after an earlier catch-up growth period.

Design Short prepubertal children with isolated GH deficiency or idiopathic short stature were randomized to individualized GH treatment (range, 17–100 lg/kg/day) or a standard dose in a preceding 2-year study. After achieving near mid-parental height SDS, children receiving an individualized dose were randomized to either a 50% reduced individualized dose (RID, n = 28) or an unchanged individualized dose (UID, n = 37) for 2 years. The dose remained unchanged in 33 children initially randomized to receive a standard dose (FIX, 43 lg/kg/day).We evaluated whether the variations in metabolic parameters measured during maintenance growth diminished in RID compared with UID or FIX.

Results We observed less variation in fasting insulin levels (_50%), insulin sensitivity as assessed by homoeostasis model assessment (_55·1%), lean soft tissue (_27·8%) and bone mineral content (_31·3%) in RID compared with UID (all P < 0·05), but no differences compared with FIX.

Conclusions Continued reduced individualized GH treatment after the catch-up growth period is safe and reduces hyperinsulinism. Individualized GH dose can be reduced once the desired height SDS is achieved to avoid overtreatment in terms of metabolic outcome.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: September 2013
PDL Classes: Alzheimer's Agents

Date of Last Review: February 2012
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: DONEPEZIL TABLET, GALANTAMINE TABLET, MEMANTINE (NAMENDA®)
- Non-Preferred Agents: RIVASTIGMINE (EXELON PATCH®), DONEPEZIL ODT (ARICEPT ODT®), MEMANTINE XR (NAMENDA XR®)

Previous Conclusions and Recommendation:

- There is insufficient evidence that any one of the Alzheimer's disease (AD) drugs is superior to the others in terms of efficacy or effectiveness and there is no evidence that any drug prevents the progression of disability or delays institutionalization.
- Make Aricept 23 mg non-preferred due to increased adverse drug events.
- Add ProDUR edits to prevent duplicate therapy.

PA Criteria: Prior authorization criteria ensure that patients have an OHP covered diagnosis.

Conclusions and Recommendations:

- There remains insufficient evidence for the treatment of AD beyond 6 months and on important clinical outcomes such as mortality and institutionalization.
- There is moderate quality evidence that cholinesterase inhibitors can alleviate AD symptoms and there is no strong evidence that one agent is more efficacious or safer than others.
- There is low quality and conflicting evidence that the combination of memantine with cholinesterase inhibitors may provide a small improvement in cognition and behavior, however the magnitude of effect is low and the clinical significance is unknown. There is no evidence of an improvement in function with the combination compared to monotherapy.
- No further review or research needed at this time. Evaluate comparative costs in executive session.

Methods:

A Medline OVID search was conducted with the following search terms: Alzheimer disease, dementia, donepezil, galantamine, memantine, rivastigmine, Namenda, Aricept, and Exelon. The search was limited to English language articles of controlled trials conducted on humans published from February 2012 to August week one 2013. The Cochrane Collection, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ), Dynamed, and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

1. National Institute for Clinical Excellence (NICE) guidance does not recommend the use of memantine in combination with cholinesterase inhibitors due to a lack of evidence of additional clinical efficacy compared with monotherapy. A recent systematic review by Farrimond et al., compared the efficacy of cholinesterase inhibitor monotherapy with combination memantine and cholinesterase inhibitor in patients with moderate-to-severe AD and examined the impact of including unpublished data in the results.[1] A literature search through May 2011 was conducted and randomized, double blind, placebo controlled trials were included. The outcomes of interest

were clinical global impression, cognitive function, functional performance in activities of daily living (ADL) and mood and behavioral disturbance.

Five trials were identified and three were included in the meta-analysis. The risk of bias was judged to be low based on the Cochrane Collaboration assessment. The meta-analysis demonstrated a small improvement in clinical global impression (standardized mean difference [SMD] -0.20 95% CI -0.32 to -0.09; I^2=9%), cognition (SMD -0.25 95% CI -0.36 to -0.14; I^2=0%), but no significant difference in functioning (SMD -0.04 95% CI -0.21 to 0.13; I^2=58%) with the combination of memantine and a cholinesterase inhibitor compared to monotherapy, respectively. The authors concluded that there may be a small benefit of adding memantine to cholinersterase inhibitors; however the clinical relevance remains unknown. [1]

2. A systematic review and economic model from the Health Technology Assessment program reviewed the clinical effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of AD.[2] The literature review found trials of a maximum of 6 months and a lack of evidence from trials on key outcomes, such as mortality and institutionalization. Overall, the quality of the trials was moderate to poor. The authors concluded that the evidence continues to suggest clinical benefit from cholinesterase inhibitors in alleviating symptoms, although the magnitude of effect remains controversial. The evidence for the effectiveness of memantine remains weaker. In addition, for the treatment of mild to moderate AD, a sensitivity analysis suggested that donepezil is the most cost effective cholinesterase inhibitor.

Guidelines:

The Canadian Neurological Society:

A 2012 update on the guidelines for AD were completed using the AGREE methodology.[3] Specific recommendations on the treatment of AD are as followed:

- Cholinesterase inhibitors are recommended as a treatment option for AD with cerebrovascular disease (Grade 1B).
- All cholinesterase inhibitors have demonstrated efficacy for mild to severe AD (Grade 1A).
- Direct comparisons do not suggest differences between cholinesterase inhibitors (Grade 2B). Selection should be based on adverse effect profile, ease of use, and differences in pharmacokinetics and mechanism of action.
- Combination therapy of a cholinesterase inhibitor and memantine is rational and appears to be safe, but there is insufficient evidence to recommend for or against this combination (Grade 2B).
- When a decision has been made to discontinue therapy because of a perceived lack of effectiveness, it is suggested that the dose be tapered before stopping the agent and the patient be monitored over the next 1-3 months for evidence of an observable decline. If this occurs, it is suggested that consideration be given to reinstating therapy (Grade 2C).

New drugs:

None

New Formulations/Indications:

None

New FDA safety alerts:

None

New Trials (Appendix 2):

A total of 121 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, five

relevant clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Study	Comparison	Population	Primary Outcome	Results
Howard et al.[4] 2012	Continue donepezil monotherapy vs. Donepezil + memantine (n=295)	Patients who had been treated with donepezil for at least 3 months with moderate-severe AD.	Cognitive function (SMMSE scores) and activities of daily living (BADLS scores)	There was no significant benefit of adding memantine to donepezil, with respect to scores on the SMMSE (0.8 points higher with memantine than with placebo; 95% CI, −0.1 to 1.6; P = 0.07) or with respect to scores on the BADLS (0.5 points lower with memantine than with placebo; 95% CI, −2.2 to 1.2; P = 0.57). Patients assigned to continue donepezil, as compared to discontinuing donepezil, had improved cognition scores
Fox et al.[5] 2012	Memantine 10 mg vs. placebo (n=149)	AD with clinically significant agitation	Cohen-Mansfield Agitation Inventory (CMAI) at 6 weeks	No significant difference between memantine and placebo of CMAI scores at 6 weeks (mean difference -3.0, 95% CI -8.3 to 2.2; p=0.26).
Farlow et al.[6] 2013	Rivastigmine patch 13.3 mg/24 hr vs. rivastigmine patch 4.6 mg/24 hr	Patients with severe AD (n=716)	Cognition, as measured by the severe impairment battery (SIB) score and function (activities of daily living scale) at week 24	The 13.3 mg/ 24 h patch was significantly superior to 4.6 mg/24 h patch on cognition (SIB) and function (ADCS-ADL-SIV) at Week 24 (P < 0.0001 and P = 0.025).
Doody et al.[7] 2013	Semagacestat 100mg vs. semagacestat 140 mg vs. placebo	Patients with mild to moderate AD (n=1537)	Changes in cognition from baseline to week 76 (ADAS-cog scale) and changes in functioning (ADCS-ADL scale)	The trial was terminated early. Cognition worsened in all three groups (mean change, 6.4 points placebo, 7.5 points 100mg, 7.8 points 140mg; p=0.15 and p=0.07 vs. placebo). Functioning also worsened. Patients on semagacestat lost more weight and had more infections, treatment discontinuations due to adverse events, and serious adverse events (P<0.001 for all comparisons).
Tariot et al.[8] 2012	1 year Open-label safety and	Adults with moderate to severe	Adverse events	74.7% of patients reported at least one AE, of which 47.5%

	tolerability extension trial of donepezil 23mg/day	AD previously on donepezil 10mg who were then started on 23 mg/day		were considered related to the study drug. Most common were weight decrease (11.2%), fall, agitation, UTI, and aggression. Patients had higher rates of AE's during the first 4 weeks of the study, then in the extension phase. Serious AE occurred in 15.1% of patients.

References:

1. Farrimond LE, Roberts E, McShane R. Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. *BMJ Open*. 2012;2(3). doi:10.1136/bmjopen-2012-000917.

2. Bond M, Rogers G, Peters J, et al. The Effectiveness and Cost-Effectiveness of Donepezil, Galantamine, Rivastigmine and Memantine for the Treatment of Alzheimer's Disease (Review of Technology Appraisal No. 111): A Systematic Review and Economic Model. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0047569/. Accessed August 28, 2013.

3. Gauthier S, Patterson C, Chertkow H, et al. 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia. *Can J Neurol Sci*. 2012;39(6 Suppl 5):S1–8.

4. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366(10):893–903. doi:10.1056/NEJMoa1106668.

5. Fox C, Crugel M, Maidment I, et al. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. *PLoS ONE*. 2012;7(5):e35185. doi:10.1371/journal.pone.0035185.

6. Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M. A 24-Week, Randomized, Controlled Trial of Rivastigmine Patch 13.3 mg/24 h Versus 4.6 mg/24 h in Severe Alzheimer's Dementia. *CNS Neurosci Ther*. 2013. doi:10.1111/cns.12158.

7. Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*. 2013;369(4):341–350. doi:10.1056/NEJMoa1210951.

8. Tariot P, Salloway S, Yardley J, Mackell J, Moline M. Long-term safety and tolerability of donepezil 23 mg in patients with moderate to severe Alzheimer's disease. *BMC Res Notes*. 2012;5:283. doi:10.1186/1756-0500-5-283.

Abstract 1: Abstracts of Randomized Controlled Trials

Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366(10):893–903

BACKGROUND: Clinical trials have shown the benefits of cholinesterase inhibitors for the treatment of mild-to-moderate Alzheimer's disease. It is not known whether treatment benefits continue after the progression to moderate-to-severe disease.

METHODS: We assigned 295 community-dwelling patients who had been treated with donepezil for at least 3 months and who had moderate or severe Alzheimer's disease (a score of 5 to 13 on the Standardized Mini-Mental State Examination [SMMSE, on which scores range from 0 to 30, with higher scores indicating better cognitive function]) to continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine. Patients received the study treatment for 52 weeks. The coprimary outcomes were scores on the SMMSE and on the Bristol Activities of Daily Living Scale (BADLS, on which scores range from 0 to 60, with higher scores indicating greater impairment). The minimum clinically important differences were 1.4 points on the SMMSE and 3.5 points on the BADLS.

RESULTS: Patients assigned to continue donepezil, as compared with those assigned to discontinue donepezil, had a score on the SMMSE that was higher by an average of 1.9 points (95% confidence interval [CI], 1.3 to 2.5) and a score on the BADLS that was lower (indicating less impairment) by 3.0 points (95% CI, 1.8 to 4.3) (P<0.001 for both comparisons). Patients assigned to receive memantine, as compared with those assigned to receive memantine placebo, had a score on the SMMSE that was an average of 1.2 points higher (95% CI, 0.6 to 1.8; P<0.001) and a score on the BADLS that was 1.5 points lower (95% CI, 0.3 to 2.8; P=0.02). The efficacy of donepezil and of memantine did not differ significantly in the presence or absence of the other. There were no significant benefits of the combination of donepezil and memantine over donepezil alone.

CONCLUSIONS: In patients with moderate or severe Alzheimer's disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months. (Funded by the U.K. Medical Research Council and the U.K. Alzheimer's Society; Current Controlled Trials number, ISRCTN49545035.).

Fox C, Crugel M, Maidment I, et al. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. *PLoS ONE*. 2012;7(5):e35185

BACKGROUND: Agitation in Alzheimer's disease (AD) is common and associated with poor patient life-quality and carer distress. The best evidence-based pharmacological treatments are antipsychotics which have limited benefits with increased morbidity and mortality. There are no memantine trials in clinically significant agitation but post-hoc analyses in other populations found reduced agitation. We tested the primary hypothesis, memantine is superior to placebo for clinically significant agitation, in patients with moderate-to-severe AD.
METHODS AND FINDINGS: We recruited 153 participants with AD and clinically significant agitation from care-homes or hospitals for a double-blind randomised-controlled trial and 149 people started the trial of memantine versus placebo. The primary outcome was 6 weeks mixed model autoregressive analysis of Cohen-Mansfield Agitation Inventory (CMAI). Secondary outcomes were: 12 weeks CMAI; 6 and 12 weeks Neuropsychiatric symptoms (NPI), Clinical Global Impression Change (CGI-C), Standardised Mini Mental State Examination, Severe Impairment Battery. Using a mixed effects model we found no significant differences in the primary outcome, 6 weeks CMAI, between memantine and placebo (memantine lower -3.0; -8.3 to 2.2, p = 0.26); or 12 weeks CMAI; or CGI-C or adverse events at 6 or 12 weeks. NPI mean difference favoured memantine at weeks 6 (-6.9; -12.2 to -1.6; p = 0.012) and 12 (-9.6; -15.0 to -4.3 p = 0.0005). Memantine was significantly better than placebo for cognition. The main study limitation is that it still remains to be determined whether memantine has a role in milder agitation in AD.
CONCLUSIONS: Memantine did not improve significant agitation in people with in moderate-to-severe AD. Future studies are urgently needed to test other pharmacological candidates in this group and memantine for neuropsychiatric symptoms.

Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M. A 24-Week, Randomized, Controlled Trial of Rivastigmine Patch 13.3 mg/24 h Versus 4.6 mg/24 h in Severe Alzheimer's Dementia. *CNS Neurosci Ther*. 2013.

AIMS: The 24-week, prospective, randomized, double-blind ACTION study investigated the efficacy, safety, and tolerability of 13.3 versus 4.6 mg/24 h rivastigmine patch in patients with severe Alzheimer's disease (AD).

METHODS: Patients had probable AD and Mini-Mental State Examination scores ≥3-≤12. Primary outcome measures were as follows: Severe Impairment Battery (SIB) and AD Cooperative Study-Activities of Daily Living scale-Severe Impairment Version (ADCS-ADL-SIV). Secondary outcomes were as follows: ADCS-Clinical Global Impression of Change (ADCS-CGIC), 12-item Neuropsychiatric Inventory (NPI-12), and safety/tolerability.

RESULTS: Of 1014 patients screened, 716 were randomized to 13.3 mg/24 h (N = 356) or 4.6 mg/24 h (N = 360) patch. Baseline characteristics/demographics were comparable. Completion rates were as follows: 64.3% (N = 229) with 13.3 mg/24 h and 65.0% (N = 234) with 4.6 mg/24 h patch. The 13.3 mg/24 h patch was significantly superior to 4.6 mg/24 h patch on cognition (SIB) and function (ADCS-ADL-SIV) at Week 16 ($P < 0.0001$ and $P = 0.049$, respectively) and 24 (primary endpoint; $P < 0.0001$ and $P = 0.025$). Significant between-group differences (Week 24) were observed on the ADCS-CGIC ($P = 0.0023$), not NPI-12 ($P = 0.1437$). A similar proportion of the 13.3 mg/24 h and 4.6 mg/24 h patch groups reported adverse events (AEs; 74.6% and 73.3%, respectively) and serious AEs (14.9% and 13.6%).

CONCLUSIONS: The 13.3 mg/24 h patch demonstrated superior efficacy to 4.6 mg/24 h patch on SIB and ADCS-ADL-SIV, without marked increase in AEs, suggesting higher-dose patch has a favorable benefit-to-risk profile in severe AD.

Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*. 2013;369(4):341–350.

BACKGROUND: Alzheimer's disease is characterized by the presence of cortical amyloid-beta (Aβ) protein plaques, which result from the sequential action of β-secretase and γ-secretase on amyloid precursor protein. Semagacestat is a small-molecule γ-secretase inhibitor that was developed as a potential treatment for Alzheimer's disease.

METHODS: We conducted a double-blind, placebo-controlled trial in which 1537 patients with probable Alzheimer's disease underwent randomization to receive 100 mg of semagacestat, 140 mg of semagacestat, or placebo daily. Changes in cognition from baseline to week 76 were assessed with the use of the cognitive subscale of the Alzheimer's Disease Assessment Scale for cognition (ADAS-cog), on which scores range from 0 to 70 and higher scores indicate greater cognitive impairment, and changes in functioning were assessed with the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale, on which scores range from 0 to 78 and higher scores indicate better functioning. A mixed-model repeated-measures analysis was used.

RESULTS: The trial was terminated before completion on the basis of a recommendation by the data and safety monitoring board. At termination, there were 189 patients in the group receiving placebo, 153 patients in the group receiving 100 mg of semagacestat, and 121 patients in the group receiving 140 mg of semagacestat. The ADAS-cog scores worsened in all three groups (mean change, 6.4 points in the placebo group, 7.5 points in the group receiving 100 mg of the study drug, and 7.8 points in the group receiving 140 mg; $P=0.15$ and $P=0.07$, respectively, for the comparison with placebo). The ADCS-ADL scores also worsened in all groups (mean change at week 76, -9.0 points in the placebo group, -10.5 points in the 100-mg group, and -12.6 points in the 140-mg group; $P=0.14$ and $P<0.001$, respectively, for the comparison with placebo). Patients treated with semagacestat lost more weight and had more skin cancers and infections, treatment discontinuations due to adverse events, and serious adverse events ($P<0.001$ for all comparisons with placebo). Laboratory abnormalities included reduced levels of lymphocytes, T cells, immunoglobulins, albumin, total protein, and uric acid and elevated levels of eosinophils, monocytes, and cholesterol; the urine pH was also elevated.

CONCLUSIONS: As compared with placebo, semagacestat did not improve cognitive status, and patients receiving the higher dose had significant worsening of functional ability. Semagacestat was associated with more adverse events, including skin cancers and infections. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT00594568.)

Tariot P, Salloway S, Yardley J, Mackell J, Moline M. Long-term safety and tolerability of donepezil 23 mg in patients with moderate to severe Alzheimer's disease. *BMC Res Notes*. 2012;5:283. doi:10.1186/1756-0500-5-283

BACKGROUND: Donepezil (23 mg/day) is approved by the US Food and Drug Administration for the treatment of patients with moderate to severe Alzheimer's disease (AD). Approval was based on results from a 24-week, randomized, double-blind study of patients who were stable on donepezil 10 mg/day and randomized 2:1 to either increase their donepezil dose to 23 mg/day or continue taking 10 mg/day. The objective of this study was to assess the long-term safety and tolerability of donepezil 23 mg/day in patients with moderate to severe AD.

METHODS: Patients who completed the double-blind study and were eligible could enroll into a 12-month extension study of open-label donepezil 23 mg/day. Clinic visits took place at open-label baseline and at months 3, 6, 9, and 12. Safety analyses comprised examination of the incidence, severity, and timing of treatment-emergent adverse events (AEs); changes in weight, electrocardiogram, vital signs, and laboratory parameters; and discontinuation due to AEs.

RESULTS: 915 double-blind study completers were enrolled in the open-label extension study and 902 comprised the safety population. Mean treatment duration in this study was 10.3 ± 3.5 months. In total, 674 patients (74.7%) reported at least one AE; in 320 of these patients (47.5%) at least one AE was considered to be possibly or probably study drug related. The majority of patients reporting AEs (81.9%) had AEs of mild or moderate severity. There were 268 patients (29.7%) who discontinued early, of which 123 (13.6%) were due to AEs.Patients increasing donepezil dose from 10 mg/day in the double-blind study to 23 mg/day in the extension study had slightly higher rates of AEs and SAEs than patients who were already receiving 23 mg (78.0% and 16.9% vs 72.8% and 14.0%, respectively). The incidence of new AEs declined rapidly after the first 2 weeks and remained low throughout the duration of the study.

CONCLUSION: This study shows that long-term treatment with donepezil 23 mg/day is associated with no new safety signals. The elevated incidence of AEs in patients increasing the dose of donepezil from 10 mg/day to 23 mg/day was limited to the initial weeks of the study

TIMS

Current PDL Status	Generic Name	Brand Name
N	ABATACEPT	ORENCIA
Y	ADALIMUMAB	HUMIRA
N	ANAKINRA	KINERET
N	CERTOLIZUMAB PEGOL	CIMZIA
Y	ETANERCEPT	ENBREL
N	GOLIMUMAB	SIMPONI
N	INFLIXIMAB	REMICADE
N	RITUXIMAB	RITUXAN
N	TOCILIZUMAB	ACTEMRA
N	TOFACITINIB CITRATE	XELJANZ
N	USTEKINUMAB	STELARA

UC

Current PDL Status	Generic Name	Brand Name
Y	BALSALAZIDE DISODIUM	BALSALAZIDE DISODIUM
Y	BALSALAZIDE DISODIUM	COLAZAL
N	BALSALAZIDE DISODIUM	GIAZO
Y	MESALAMINE	APRISO
N	MESALAMINE	DELZICOL
N	MESALAMINE	LIALDA
Y	MESALAMINE	CANASA
N	MESALAMINE	ASACOL HD
N	MESALAMINE	PENTASA
N	MESALAMINE	MESALAMINE
N	MESALAMINE	SFROWASA
N	MESALAMINE W/CLEANSING WIPES	MESALAMINE
N	MESALAMINE W/CLEANSING WIPES	ROWASA
Y	OLSALAZINE SODIUM	DIPENTUM
Y	SULFASALAZINE	SULFASALAZINE
Y	SULFASALAZINE	SULFAZINE
Y	SULFASALAZINE	SULFASALAZINE DR
Y	SULFASALAZINE	SULFAZINE EC
Y	SULFASALAZINE	AZULFIDINE

AED

Current PDL Status	Generic Name	Brand Name
Y	CARBAMAZEPINE	TEGRETOL XR
Y	CARBAMAZEPINE	EPITOL
Y	CARBAMAZEPINE	CARBAMAZEPINE
Y	CARBAMAZEPINE	TEGRETOL
N	CARBAMAZEPINE	CARBATROL
Y	CARBAMAZEPINE	CARBAMAZEPINE XR
N	CLOBAZAM	ONFI
Y	CLONAZEPAM	CLONAZEPAM
Y	CLONAZEPAM	KLONOPIN
Y	DIAZEPAM	DIASTAT ACUDIAL
N	DIAZEPAM	DIAZEPAM
Y	DIVALPROEX SODIUM	DEPAKOTE SPRINKLE
Y	DIVALPROEX SODIUM	DEPAKOTE
Y	DIVALPROEX SODIUM	DEPAKOTE ER
Y	DIVALPROEX SODIUM	DIVALPROEX SODIUM
Y	DIVALPROEX SODIUM	DIVALPROEX SODIUM ER
Y	ETHOSUXIMIDE	ZARONTIN
Y	ETHOSUXIMIDE	ETHOSUXIMIDE
Y	ETHOSUXIMIDE	ZARONTIN
Y	ETHOTOIN	PEGANONE
N	EZOGABINE	POTIGA
N	FELBAMATE	FELBATOL
N	FELBAMATE	FELBAMATE
Y	GABAPENTIN	GABAPENTIN
N	GABAPENTIN	NEURONTIN
N	GABAPENTIN	FANATREX
Y	LACOSAMIDE	VIMPAT
Y	LAMOTRIGINE	LAMOTRIGINE
V	LAMOTRIGINE	LAMICTAL
V	LAMOTRIGINE	LAMICTAL XR
V	LAMOTRIGINE	LAMICTAL ODT
Y	LEVETIRACETAM	LEVETIRACETAM
Y	LEVETIRACETAM	KEPPRA
N	LEVETIRACETAM	KEPPRA XR
Y	METHSUXIMIDE	CELONTIN
Y	OXCARBAZEPINE	OXCARBAZEPINE
Y	OXCARBAZEPINE	TRILEPTAL
N	OXCARBAZEPINE	OXTELLAR XR

Y	PHENOBARBITAL	PHENOBARBITAL
Y	PHENYTOIN	PHENYTOIN
Y	PHENYTOIN	DILANTIN
Y	PHENYTOIN SODIUM EXTENDED	DILANTIN
Y	PHENYTOIN SODIUM EXTENDED	PHENYTOIN SODIUM EXTENDED
Y	PHENYTOIN SODIUM EXTENDED	PHENYTEK
N	PREGABALIN	LYRICA
Y	PRIMIDONE	PRIMIDONE
Y	PRIMIDONE	MYSOLINE
N	RUFINAMIDE	BANZEL
Y	TIAGABINE HCL	GABITRIL
Y	TIAGABINE HCL	TIAGABINE HCL
Y	TOPIRAMATE	TOPIRAGEN
Y	TOPIRAMATE	TOPIRAMATE
N	TOPIRAMATE	TOPAMAX
N	VALPROATE SODIUM	DEPAKENE
N	VALPROATE SODIUM	VALPROIC ACID
Y	VALPROIC ACID	VALPROIC ACID
Y	VALPROIC ACID	DEPAKENE
V	VALPROIC ACID	STAVZOR
N	VIGABATRIN	SABRIL
Y	ZONISAMIDE	ZONISAMIDE
Y	ZONISAMIDE	ZONEGRAN