

**Oregon Drug Use Review / Pharmacy & Therapeutics Committee**

Tuesday, September 23, 2014 1:00-5:00 PM  
Clackamas Community Training Center  
29353 SW Town Center Loop East  
Wilsonville, OR 97070

**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                | D. Weston (OHA)   |

**II. DUR OLD BUSINESS**

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|--|------------------|
| a. Hepatitis C Class Update                      | M. Herink (OSU)  |
| 1. Class Update                                  |                  |
| 2. PA Criteria                                   |                  |
| 3. Public Comment                                |                  |
| 4. Discussion of Clinical recommendations to OHA |                  |
| b. Botulinum Toxins PA Criteria                  | K. Ketchum (OSU) |
| 1. PA Criteria                                   |                  |
| 2. Public Comment                                |                  |
| 3. Discussion of Clinical recommendations to OHA |                  |

**III. DUR NEW BUSINESS**

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|--|------------------|
| a. Synagis® Policy Update                        | K. Sentena (OSU) |
| 1. 2014 AAP Guidelines                           |                  |
| 2. Public Comment                                |                  |
| 3. Discussion of Clinical Recommendations to OHA |                  |

**IV. PREFERRED DRUG LIST NEW BUSINESS**

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|--|------------------|
| a. Drug Class Scans                              | M. Herink (OSU)  |
| 1. Parkinson's Medications                       |                  |
| 2. Growth Hormones                               |                  |
| 3. Insulins                                      |                  |
| Afrezza® NDE                                     |                  |
| 4. Alzheimer Drugs                               |                  |
| 5. Other Lipotropics                             |                  |
| 6. Public Comment                                |                  |
| 7. Discussion of Clinical Recommendations to OHA |                  |
| b. Diabetes Class Update                         | K. Sentena (OSU) |

1. Class Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

c. Multiple Sclerosis Class Update

K. Sentena (OSU)

1. Class Update
2. Plegridy™ NDE
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

d. First Generation Antidepressants

B. Fouts (OSU)

1. Class Review
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

e. TAMS Class Update

M. Herink (OSU)

1. Class Update
2. Apremilast NDE
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

f. Topical Antifungals Class Update

K. Ketchum (OSU)

1. Class Update
2. Jublia® NDE
3. Kerydin™ NDE
4. Public Comment
5. Discussion of Clinical Recommendations to OHA

g. Vitamins & Electrolytes Abbreviated Class Review

M. Herink (OSU)

1. Class Review
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

V. EXECUTIVE SESSION

VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Medical director	Corvallis	December 2014
Joshua Bishop, Pharm.D.	Pharmacist	Pharmacy director	Bend	December 2014
Dave Pass, M.D.	Physician	Medical director	West Linn	December 2016
Tracy Klein, Ph.D., F.N.P.	Public	Nurse	Portland	December 2014
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2015
William Nunley, M.D.	Physician	Psychiatrist	Portland	December 2015
Stacy Ramirez, Pharm.D.	Pharmacist	Community pharmacist	Albany	December 2016
James Slater, Pharm.D.	Pharmacist	Associate pharmacy director	Beaverton	December 2014
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy manager	Silverton	December 2015
Kathryn Lueken, M.D., M.M.M.	Physician	Medical Director	Salem	December 2016
Arturo Salazar, M.D.	Physician	Pediatric Internist	Eugene	December 2017

**Oregon Drug Use Review / Pharmacy & Therapeutics Committee**

Thursday, July 31, 2014 1:00-5:00 PM

Wilsonville Training Center  
29353 SW Town Center  
Wilsonville, OR 97070

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**MEETING MINUTES**

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**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).

**Members Present:** Tracy Klein, PhD, FNP; Cathy Zehrung, RPh; Phillip Levine, PhD; James Slater, PharmD;

**Members Present by Phone:** Dave Pass, MD; Joshua Bishop, PharmD

**Staff Present:** Kathy Ketchum, RPh, MPA:HA; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Trevor Douglass, DC, MPH; Shannon Jasper; Amanda Meeker, PharmD; Dee Weston; Karina Porter;

**Staff Present by Phone:** Kathy Sentena, PharmD; Bing-Bing Liang, PharmD; Walter Shaffer, MD; Chris Barber, RN

**Audience:** Alison Martens, RN (Meda)\*; Shall Hall (Purdue); Troy Larsen (Takeda); Seth M. Adams (WVP Health Authority); Ken Fritsche; Deirdre Monroe (Allergan)\*; Camille Kerr (Allergan); Ralph Magresh (Merck); David Barba (Forest); Tara Bannow (The Bulletin, Bend OR); Stuart O' Brochta (Gilead)\*; Lisa Roessel (Actelion)\*; Lori Howarth (Bayer); Elizabeth Skovrow (Bayer)\*; Laura Hill (Abbvie); Desiree Allen (Abbvie); Mila Whitem (Lilly); Steve Nemirow\*; Bart Benson; Isaac Lloyd; David Barnhoum (Genentech); Amy Jay (Pacific University); Arlette Munoz (OSU/ OHSU COP); Richard McLeod (Pfizer); John McDonald (Meda); Mark Pledger (Novartis); Mike Willett (Pfizer); Trish McDaid-O'Neill (Astra Zeneca); Kristen Harrington (Astra Zeneca); Larry Hinson (Astra Zeneca); Jacki Gethner (Women of a Certain Age)\*; Anne Murray (BMS); Shelly Bailey (Central Drugs); Kristi Bronson (Astra Zeneca)\*; Jim Graves (BMS); Brad Peacock (Gilead); Lorren Sandt (Caring Ambassadors)\*; BJ Cavnor (1 in 4 Org)\*; Robert Snediker (J&J)\*; Jennifer Morrison (Boehringer Ingelheim); Lauren Kael\*; Ruby Grzelecki; Dr. Atif Zaman\*; Scott Larson (BMS); John McIlveen, PhD (AMH/ OHA); Judith Leahy (OHA); Caryn Mickelson (WOAH); Diana Dills (Pfizer)\*

(\*) Provided verbal testimony

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**I. CALL TO ORDER**

- a. The meeting was called to order at approximately 1:00 pm. Introductions of Committee members and staff.



- b. Mr. Citron reported there are no new conflicts of interest to declare.  
Requested any nominations for P&T members to send information to Roger Citron.
- c. Approval of agenda and minutes presented by Tracy Klein, (pages 1 - 9)

**ACTION:** Approved as is.

- d. Department updates presented by Dee Weston.  
Requested all Pharmaceutical manufacturer meetings be scheduled thru Dee Weston or Linnea Saris.

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## **II. DUR ACTIVITIES**

- a. Quarterly Utilization Reports presented by Kathy Ketchum, RPh (pages 10 – 14)
- b. ProDUR Report presented by Rich Holsapple, RPh (pages 15 – 17)
- c. RetroDUR Report presented by Dr. Williams (pages 18 - 23)
- d. Oregon State Drug Reviews presented by Dr. Sentena
  - 1. 2<sup>nd</sup> Generation Antipsychotics: Are these Drugs effective in treating PTSD?  
(pages 24 – 25)
  - 2. New Cholesterol Guidelines: A Significant Shift in Cholesterol Management  
(pages 26 – 27)
- e. FDB Drug File Update presented by Dr. Williams (page 28)

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## **III. DUR BUSINESS**

- a. Hepatitis C Class Update (pages 29 – 54)  
Dr. Zaman presented information from the Hepatitis C Advisory Committee.  
Dr. Herink presented the following information:
  - 1. Recommend including additional changes to PA criteria based on Hepatitis C Advisory Committee Recommendations, including limiting approval to the following patient populations:
    - a. Patients with extra hepatic manifestations of HCV who have formal documentation from a relevant specialist that their condition is HDV related.
    - b. HCV / HIV co-infected patients with cirrhosis.
    - c. HCV infection in the transplant setting (approval needs to be cleared by the DMAP Medical Director).
    - d. Cirrhotic (stage 4) patients without ongoing progressive decompensation.
    - e. Strike question #5 from original criteria.
    - f. Add “and marijuana” to question #11.

- g. Revisit at September P&T meeting.

**Public Comment:**

Stuart O'Brochta from Gilead.  
Jacki Gethner from Women of a Certain Age.  
Steve Nemirow.  
Lorren Sandt from Caring Ambassadors.  
BJ Cavnor from 1 in 4 Org.

**ACTION:** Motion, 2<sup>nd</sup>, All in Favor. Approved.

- b. Hepatitis C Readiness to Treat (pages 55 – 64)  
Dr. Herink presented the following information:  
Jude Leahy presented information about the document with revisions to treat information for public health and criteria for physicians.
  - 1. Approve readiness to refer assessment with goal to support patient readiness through actions initiated by primary care providers to prepare patients interested in hepatitis C treatment to engage successfully with specialists.
  - 2. Post resource to the College of Pharmacy website, bring to the CCO Medical Directors meeting and work with public health to facilitate dissemination and education regarding new assessment.
  - 3. Mirror PA Criteria language and consistently call out PCP.
  - 4. Get feedback from hepatologists and primary care physicians on utility of assessment.

**ACTION:** Motion, 2<sup>nd</sup>, All in Favor. Approved.

- c. Botulinum Toxins Drug Use Evaluation (pages 65 – 77)  
Ms. Ketchum presented the following evaluation:
  - 1. Implement proposed PA criteria in FFS patients to limit use to evidence supported diagnosis.
  - 2. Revisit #4 for clarification at September P&T meeting.

**Public Comment:**

Deidre Monroe from Allergan.

**ACTION:** Motion, 2<sup>nd</sup>, All in Favor. Approved.

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#### IV. PREFERRED DRUG LIST NEW BUSINESS

- a. Alcohol Dependence Class Review (pages 78 – 97)  
Dr. Liang presented the following review:
  - 1. Combine the alcohol dependence agents and opioid dependence into one PDL class. Oral naltrexone and acamprosate should be preferred on the PDL based on moderate level evidence to support the similar efficacy and safety for the treatment of alcohol use disorder.

2. Maintain injectable naltrexone non-preferred and reserve as a treatment option for those patients unable or unwilling to take oral therapy or are not likely to adhere with oral naltrexone therapy.
3. Maintain naltrexone depot injection prior authorization criteria.
4. Designate disulfiram non-preferred and grandfather current clients for 12 months.

**Public Comment:**

Dr. John McIlveen from OHA – Addictions and Mental Health

**ACTION:** Motion, 2<sup>nd</sup>, All in Favor. Approved.

- b. Androgens Class Update (pages 98 – 106)  
Dr. Liang presented the following update:

1. Re-evaluate safety of testosterone therapy once FDA concludes its review.
2. Remove ovarian failure from list of covered diagnosis in PA criteria.

**ACTION:** Motion, 2<sup>nd</sup>, All in Favor. Approved.

3. Evaluate comparative costs in executive session.
4. Designate Aveed non-preferred and no grandfathering.

**\*ACTION:** After Executive Session, all in favor.

- c. Pulmonary Arterial Hypertension (pages 107 – 128)  
Dr. Sentena presented the following update:

1. Prior authorize riociguat to ensure appropriate use by qualified providers.
2. Prior authorize macitentan to ensure appropriate use by qualified providers.
3. Limited evidence is insufficient to prefer macitentan over bosentan for placement on PDL.
4. Prior authorize oral treprostinil to ensure appropriate use by qualified providers.

**ACTION:** Motion, 2<sup>nd</sup>, All in Favor. Approved.

5. Continue to include an agent from each class on the PDL and evaluate comparative costs in executive session.
6. \*After executive session. No changes to the PMPDP.

**Public Comment:**

Stuart O'Brochta from Gilead.

Lisa Roessel NP from Actelion.

Elizabeth Skovrow from Bayer.

**\*ACTION:** After Executive Session, all in favor.

- d. Anticoagulant Class Update (pages 129 – 158)  
Dr. Sentena presented the following update:

1. Atrial Fibrillation: Recommend warfarin as first-line therapy and offer dabigatran and apixaban as non-preferred agents subject to PA approval. No changes to the PDL are recommended.
2. VTE treatment: Recommend warfarin or enoxaparin first line with dabigatran, rivaroxaban and apixaban as non-preferred options if clinical criteria are met. Recommend adding apixaban to current PA criteria as a second line option.
3. Orthopedic Prophylaxis: Recommend LMWH as an appropriate first-line treatment option. Recommend rivaroxaban and apixaban as non-preferred options if clinical criteria are met. Recommend adding apixaban to current PA criteria as a second line option.
4. Medically Ill: If continued anticoagulation is warranted in medically ill patients recommend warfarin as first-line option. Fourteen day supply of rivaroxaban allows transition to preferred therapy in current PA criteria. No changes to the PDL are recommended.
5. Add “difficulty obtaining INR monitoring” to questions #5 and #9 in Oral Direct Factor Xa Inhibitors criteria, and questions #3 and #8 in Oral Direct Thrombin Inhibitors.
6. \*After executive session. No changes to the PMPDP.

**Public Comment:**

Diane Dills from Pfizer.

Robert Snediker from J&J.

**ACTION:** Motion, 2<sup>nd</sup>, All in Favor. Approved.

e. Antiplatelet Class Update (pages 159 – 179)

Ms. Ketchum presented the following update:

1. Continue to list aspirin and clopidogrel as preferred drugs due to high level evidence of benefit for multiple indications (Coronary Artery Disease [CAD], ACS, stroke and PAD).

**ACTION:** Motion, 2<sup>nd</sup>, All in Favor. Approved.

2. Evaluate other antiplatelet drugs in executive session for potential inclusion.
3. Add Vorapoxar to antiplatelet criteria.
4. \*After executive session, no changes to PMPDP.

**\*ACTION:** After Executive Session, all in favor.

f. Asthma / COPD Class Update (pages 180 – 202)

Dr. Meeker presented the following update:

1. Due to no evidence demonstrating clinical superiority of umeclidinium / vilanterol over current agents, recommend making it non-preferred.

2. Recommend including umeclidinium / vilanterol in the prior authorization criteria to ensure it is being used appropriately and limiting to patients who have COPD.
3. Due to no evidence demonstrating clinical superiority of safety of umeclidinium over current agents, recommend making it non-preferred.
4. Due to no evidence demonstrating clinical superiority of safety of mometasone HFA over current agents, recommend making it non-preferred.
5. Due to no strong comparative effectiveness of superiority between other agents, recommend comparing costs in executive session.
6. Reorganize PDL classes bases on drug class as followed:
  - a. Long-acting Bronchodilators
  - b. Short-acting Beta Agonists
  - c. Anticholinergic Inhalers
  - d. Combination Inhalers
  - e. Inhaled Corticosteroids
  - f. Miscellaneous Pulmonary Drugs
7. Due to no evidence demonstrating clinical superiority, designate flunisolide HFA as non-preferred on the PMPDP.
8. No changes to any of the listed PMPDP classes.

**ACTION:** Motion, 2<sup>nd</sup>, All in Favor. Approved.

**Public Comment:**

Alison Martens RN from Meda Pharmaceuticals.  
Kristi Bronson from Astra Zeneca.

**\*ACTION:** After Executive Session, all in favor.

- g. First Generation Antidepressants (pages 203 – 220)

Deferred

- h. Insomnia Class Update (pages 221 -231)

Deferred

- i. Drug Class Scans

1. Insulins (pages 232 – 253)

Deferred

2. Skeletal Muscle Relaxants (pages 254 – 266)

Deferred

3. NSAIDs (pages 267 – 286)

Deferred

4. Oral Hypoglycemics (pages 287 – 306)

Deferred

5. New Antiemetics (pages 307 – 348)

Deferred

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## **V. EXECUTIVE SESSION**

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## **VI. RECONVENE for PUBLIC RECOMMENDATIONS**

Mr. Citron announced the next P & T meeting will be held Tuesday Sept. 23<sup>rd</sup>.

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## **VII. ADJOURN**

## Abbreviated Class Update: Hepatitis C

**Month/Year of Review:** September 2014

**Last Review:** July 2014

**Current PDL Class:** Hepatitis C Agents

**Source Document:** OSU College of Pharmacy

- **Preferred Agents:** BOCEPREVIR (VICTRELIS®), TELAPREVIR (INCIVEK®), SOFOSBUVIR (SOLVALDI®), SIMEPREVIR (OLYSIO®), PEGINTERFERON ALPHA-2A (PEGASYS®), PEGINTERFERON ALPHA-2A SUBQ (PEGASYS®, PEGASYS PROCLICK®), PEGINTERFERON ALFA-2B, PEGINTERFERON ALFA-2B, RIBAVIRIN
- **Non-Preferred Agents:** INTERFERON ALFA-1 (INGERGEN®), RIBAVIRIN DOSE-PACK (RIBAPAK®)

**Current PA:** Prior authorizations are currently in place or have been recommended for pegylated interferon and ribavirin (PR), for the oral protease inhibitors, and for sofosbuvir (Appendix 1) to ensure treatments are supported by the medical literature.

### 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:

- A new section from the poor quality AASLD/IDSA guidelines on when and in whom to initiate HCV therapy recommends treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C.<sup>1</sup>
- There remains insufficient evidence on the long-term efficacy and safety of sofosbuvir based treatment in interferon ineligible genotype 1 (GT1) patients. New guidance from NICE does not recommend sofosbuvir in this patient population.<sup>2</sup>
- There is low quality evidence that the vast majority of subjects treated with sofosbuvir reach an HCV RNA level below the limit of quantification (<25 IU/ml) at or before week 4 of therapy. Monitoring for response at week 4 of therapy is recommended to evaluate for adherence and efficacy.

### Recommendations

- Recommend including additional changes to PA criteria (Appendix 1):
  - Excluding patients who have had previous treatment with an oral direct acting antiviral
  - Requiring a HCV RNA level at week 4 to determine response. If the HCV RNA is detectable at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the HCV RNA increases or if the 8 week HCV RNA is detectable, discontinue treatment.

- Consider excluding GT1 interferon ineligible patients due to insufficient evidence in this population.
- Continue to prioritize patients for treatment based on disease severity and stage of fibrosis.
- With evolving pipeline of medications for the treatment of hepatitis C, create general Hepatitis C prior authorization criteria (Appendix 2) to ensure new treatments are being used appropriately until they can be reviewed in full by the Pharmacy & Therapeutics Committee.
- The sale and distribution of telaprevir has been discontinued; remove from PDL.

#### **Previous Conclusions and Recommendations:**

- New guidelines recommend prioritization of HCV patients for treatment based on disease severity, including those patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extra-hepatic manifestations.<sup>3,4</sup>
- There remains insufficient evidence evaluating treatment with sofosbuvir or simeprevir in patients with decompensated cirrhosis. New guidelines recommend that those with decompensated cirrhosis not on a transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy and safety outcomes have not yet been established for this group.<sup>5</sup>
- There is new low quality evidence that simeprevir in combination with peginterferon alfa and ribavirin results in a higher SVR rate compared to peginterferon plus ribavirin dual therapy in GT1 chronic HCV patients, both treatment naïve and previous relapsers.<sup>6,7</sup>
- There remains insufficient evidence evaluating sofosbuvir in subpopulations and comorbidities including those with decompensated cirrhosis, HBV or HIV co-infection, treatment experienced patients, patients with alcohol or drug use within the past year, significant cardiac or pulmonary disease, uncontrolled hypertension or diabetes, seizure disorder, and renal disease.<sup>8</sup>
- There is a lack of comparative evidence and evidence from randomized controlled trials evaluating the efficacy and long term safety of sofosbuvir in patients with genotype 1 HCV. New guidance from the National Institute for Health and Care Excellence and the German Institute for Quality and Efficiency in Healthcare have concluded they cannot decide if sofosbuvir is a cost-effective use of resources, particularly in genotype 1 patients, until more comparative evidence is available.<sup>9,10</sup>
- There is insufficient evidence to evaluate the use of simeprevir or sofosbuvir in treatment-naïve genotype 1 patients who are interferon-ineligible.
- There is insufficient data to evaluate sofosbuvir plus ribavirin for genotype 1 treatment experienced patients or simeprevir plus PR.
- There is low quality evidence that in genotypes 2 CHC, sofosbuvir-based therapy improves SVR rates compared to dual therapy with pegylated interferon and ribavirin.
- There is low quality evidence, based on one unpublished open-label trial, that the combination of sofosbuvir plus simeprevir with or without ribavirin for 12 to 24 weeks results in high SVR12 rates (79-96%) in HCV genotype 1 null responders with METAVIR F0-F2 fibrosis.<sup>11</sup>
- There is insufficient evidence that the combination of sofosbuvir plus simeprevir with or without ribavirin for 12 to 24 weeks is efficacious in HCV genotype 2 treatment naïve and null responder patients with METAVIR F3-F4 fibrosis. Only preliminary data is available demonstrating SVR4 rates of 96-100%; SVR12 rates have not yet been released.<sup>11</sup>
- There is insufficient evidence evaluating the safety and efficacy of simeprevir in HCV patients with moderate or severe hepatic impairment. Clinical trials with simeprevir have been limited to patients with compensated disease who have CTP class A, total bilirubin level of 1.5 ULN or lower, and transaminase level of 10 x ULN or lower. It should be limited to patients with compensated liver disease.
- There is insufficient data evaluating sofosbuvir in patients with severe renal impairment (CrCl <30 ml/min) or those who require hemodialysis. There is no dosing data currently available for this patient population.



**Reason for Review:** The evidence and clinical practice guidelines for the treatment of chronic Hepatitis C continues to evolve. New evidence, including systematic reviews and clinical guidelines, will be reviewed for further decision-making.

**Background:**

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma.<sup>12</sup> The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long term clinical trials that are large enough to provide direct evidence for these outcomes. The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer.<sup>12</sup> The two major predictors of SVR are viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. The studies evaluating sofosbuvir use SVR at week 12 of follow-up (SVR12) as the primary endpoint, based on evidence that the majority of patients who have an SVR at week 12 maintain it until week 24.<sup>13</sup> Relapse is defined as a patient achieving HCV RNA less than the lower limit of quantitation or the lower limit of detection at the last measurement on treatment but subsequently having a HCV RNA greater than or equal to the lower limit of quantitation or detection post treatment.<sup>8</sup>

In the United States, genotype 1 infection is found in around three-quarters of patients and is associated with a lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of patients.<sup>12</sup> Previous standard of care for Genotype 1 CHC is a protease inhibitor (boceprevir or telaprevir) plus pegylated interferon and ribavirin.<sup>14</sup> This is based on several RCTs showing improved rates of SVR (63-79%) with triple therapy compared to pegylated interferon and ribavirin dual therapy (55-60%). There is no direct comparative evidence on the effectiveness of the currently available protease inhibitors. However, these agents come with several safety concerns and still depend on combination therapy with interferon and ribavirin which can result in serious adverse reactions. There are also important drug interactions seen with these protease inhibitors. For genotypes 2 and 3, the previous standard of care is still dual therapy with pegylated interferon and ribavirin for 24 weeks, which has shown SVR rates of 71-75% in genotype 2 and 61-66% in genotype 3.<sup>15</sup>

Patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (Metavir fibrosis stage 2 or greater). Patients with compensated cirrhosis are at risk of progressing to decompensation hepatocellular carcinoma, or death. The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver-related disease, and prolonging graft survival in liver transplant recipients. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent long term outcomes is dependent on the baseline risk for events. The newer costly treatments with high SVR rates will have the most benefit among patients at highest risk of cirrhosis-related events.<sup>16</sup>

Simeprevir is a recently approved protease inhibitor used in combination with pegylated interferon and ribavirin for the treatment of adult patients with genotype 1 CHC. This includes patients with compensated liver disease, including patients with cirrhosis, who are treatment-naïve or who failed prior interferon therapy with or without ribavirin. There are trials underway evaluating its use in genotype 4 infection and HCV/HIV co-infection. Studies investigating the use of simeprevir as part of interferon-free regimens have also been initiated.<sup>17</sup> Simeprevir structurally binds to a target enzyme which is different than telaprevir and

boceprevir (14-membered macrocycle). It is given orally once a day with any type of food for 12-48 weeks depending on whether the patient is treatment-naïve, a prior relapse, or a nonresponder.

Sofosbuvir is a nucleotide inhibitor of HSV NS5B RNA-dependent RNA polymerase with broad genotypic activity. Sofosbuvir was given breakthrough therapy designation as the first potential interferon-free CHC therapy from the FDA that allowed an expedited approval program.<sup>13</sup> The criteria for a breakthrough therapy designation from the FDA is that a) it is used for a serious condition, and b) preliminary clinical evidence demonstrates substantial improvement over available therapy on one more clinically significant endpoints. Unlike the other available protease inhibitors, there is no response guided therapy criteria for its use. Since approval and uptake of these newer agents, Vertex has discontinued the sale and distribution telaprevir (Incivek®).<sup>18</sup>

#### **Methods:**

A Medline literature search beginning July 2014 (since the most recent Hepatitis C Class Update) and ending August 2014 for new systematic reviews and randomized controlled trials (RCTs) that compared antiviral regimens and oral protease inhibitors, including boceprevir (BOC), telaprevir (TVR), simeprevir (SIM), and sofosbuvir (SOF) 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:**

None

#### **Clinical Guidelines:**

##### American Association for the Study of Liver Diseases (AASLD)/ Infectious Diseases Society of America (IDSA)

Guidelines on when and in whom to initiate HCV therapy were released by the AASLD and IDSA.<sup>1</sup> This is one section of the entire guideline, which was previously discussed.<sup>19</sup> However, the guidelines have many limitations and the overall methodological quality of the guidance was poor.<sup>8</sup> The panel lacked non-specialist members and there was no assessment of risk of bias for individual studies. The authors and sponsors of the guidance had multiple conflicts of interest. The following additional recommendations were provided in this section:

- The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of SVR (Class 1 level of evidence, Level A recommendation).
- Treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir F4) (Class 1, Level A), liver transplant recipients (Class 1, Level B), and patients with severe extrahepatic hepatitis C (Class 1, Level B).
- Based on available resources, treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority. This includes patients with:
  - Fibrosis (Metavir F2) (Class 1, Level B).
  - HIV-1 coinfection (Class 1, Level B)

- HBV coinfection (Class IIa, level C)
- Other coexistent liver disease (Class IIa, Level C)
- Debilitating fatigue (Class 11a, Level B)
- Type 2 Diabetes mellitus (insulin resistant) (Class IIa, Level B)
- Porphyria cutanea tarda (Class IIb, Level C)
- Persons whose risk of transmission is high should be prioritized for treatment (Class IIa, Level C):
  - Men who have sex with men (MSM) with high-risk sexual practices
  - Active injection drug users
  - Incarcerated persons
  - Persons on long-term hemodialysis
- An assessment of the degree of hepatic fibrosis, using noninvasive testing of liver biopsy, is recommended (Class 1, level A)
- Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred (Class 1, Level C)

#### Canadian Agency for Drugs and Technologies in Health (CADTH):

In August 2014, CADTH released draft recommendations for direct acting antiviral agents for chronic Hepatitis C Genotype 1.<sup>20</sup> Evidence informed recommendations were developed by the Canadian Drug Expert Committee. The summary of recommendations are as followed:

- Recommends simeprevir daily for 12 weeks, in combination with peginterferon and ribavirin for 24 to 48 weeks as the protease inhibitor of choice for treatment-naïve patients or for treatment-experienced patients with prior relapse.
  - This is based on evidence showing that simeprevir was more effective in achieving SVR compared with dual therapy and showed no statistically significant difference compared with other protease inhibitors based on indirect evidence.
  - For partial and null responders to dual therapy with peginterferon and ribavirin, there is insufficient evidence to identify an optimal therapy and the committee was unable to make a recommendation at this time.
- No definitive recommendation regarding the place in therapy for sofosbuvir, relative to available protease inhibitors, can be made at this time.
- Recommends that treatment should be offered only to persons living with chronic hepatitis C who have fibrosis stages F2, F3, or F4.
  - In all analyses, treatment of patients with higher grades of fibrosis was more cost-effective.
- Persons in whom a direct acting antiviral plus peginterferon and ribavirin regimen has failed should not be retreated with another direct acting antiviral plus peginterferon ribavirin regimen.
  - There is insufficient evidence to evaluate efficacy of retreatment.

#### The National Institute for Health and Care Excellence (NICE):

NICE recently released an appraisal document for sofosbuvir in the treatment of chronic hepatitis C.<sup>2</sup> This is still not the final appraisal and will go through further public comment processes. The following preliminary recommendations are given:

- Sofosbuvir, in combination with peginterferon alfa and ribavirin, is recommended as an option for treatment GT1 CHC in adults.
- Sofosbuvir, in combination with peginterferon and ribavirin, is recommended as an option for treatment genotype 3 CHC in adults with cirrhosis.
- Sofosbuvir, in combination with peginterferon alfa and ribavirin, is recommended as an option for treatment genotype 3 CHC in adults without cirrhosis, only if they had treatment for hepatitis C before.
- Sofosbuvir, in combination with peginterferon alfa and ribavirin, is not recommended for treatment genotype 4, 5, and 6 chronic hepatitis C in adults.

- Sofosbuvir, in combination with ribavirin alone is not recommended for treating adults with genotype 1, 4, 5 and 6 CHC.
- Sofosbuvir, in combination with ribavirin, is recommended as an option for treating genotype 2 CHC in adults only if they:
  - Have not had treatment for chronic hepatitis C before and are intolerant to or ineligible for interferon therapy or
  - Have had treatment for chronic hepatitis C before, regardless of interferon eligibility.
- Sofosbuvir, in combination with ribavirin, is recommended as an option for treating genotype 3 CHC only in adults with cirrhosis.

### **Monitoring:**

In April 2014, the European Association for the Study of the Liver (EASL) published guidelines for the treatment of HCV, including recommendations for monitoring.<sup>3</sup>

#### *Monitoring:*

- A real-time PCR-based assay with a lower limit of detection of <15 IU/ml should be used to monitor HCV RNA levels during and after therapy.
- For patients on the combination of pegylated interferon, ribavirin, and sofosbuvir, HCV RNA should be measured at baseline and at weeks 4, 12, and 12 or 24 weeks after the end of therapy (Recommendation A2).
- In patients treated with an interferon-free regimen, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24, and 12 or 24 weeks after the end of therapy.
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs, or men who have sex with men with on-going risk behavior

### **Department of Veterans Affairs (VA)**

The VA National Hepatitis C Resource Center Program released treatment considerations for Chronic HCV earlier in 2014.<sup>5</sup> The panel provided laboratory monitoring recommendations. They recommend that patients should have HCV RNA assessed at week 4 of treatment. If the HCV RNA is detectable at week 4 or any time point thereafter, reassess in 2 weeks. If HCV RNA increases at any time point (i.e., >1 log<sub>10</sub> IU/mL from nadir) or if the 8-week level remains detectable (HCV RNA is ≥25 IU/mL), discontinuation of all treatment should be strongly considered (Strong recommendation; expert opinion). In addition, the panel notes that to assess treatment response, commercial assays that have a lower limit of HCV RNA quantification (LLOQ) of ≤25 IU/mL is strongly recommended.

The following criteria were used in the NEUTRINO protocol to define on-treatment virologic failure<sup>21</sup> (note, HCV RNA levels were checked at least every 2 weeks using an assay with an LLOQ of <25 IU/mL), and provide more detailed information about specific situations where discontinuation of sofosbuvir-based therapy should be strongly considered<sup>4</sup>:

- HCV RNA is ≥LLOQ (confirmed on at least one repeat test) after having previously had HCV RNA <LLOQ while on treatment
- >1 log<sub>10</sub> IU/ml increase in HCV RNA (confirmed on at least one repeat test) from nadir while on treatment
- HCV RNA persistently ≥LLOQ through 8 weeks of treatment

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In the NEUTRINO study, by week 4, the proportion of patients with this reduced level of HCV RNA was 99%, a rate that was maintained throughout the treatment period. SVR12 rates were 90% (295/327).

#### UpToDate

According to UpToDate, the vast majority of subjects treated with sofosbuvir reach an HCV RNA level below the limit of quantification (<25 IU/ml) at or before week 4 of therapy (97% in one study of HIV/HCV coinfecting patients).<sup>22</sup> Any detectable HCV RNA should raise the possibility of nonadherence and patients being treated with a 24 course of sofosbuvir who have detectable HCV RNA at week 12 should have the HCV RNA repeated. A persistently detectable HCV RNA should trigger consideration of discontinuation.

#### Pipeline:

The pipeline is expected to expand quickly over the next few years. The interferon-free all oral combination of direct acting antivirals, daclatasvir and asunaprevir, is expected to be approved in September. It was recently approved for the treatment of patients with HCV GT1 in Japan.<sup>23</sup> Daclatasvir plus asunaprevir has been studied in a phase 3 multicohort study<sup>24</sup> and an open-label phase 3 study<sup>25</sup> in treatment naive patients with HCV genotype 1b. IT was also studied with or without peginterferon and ribavirin in null responders.<sup>26</sup> Daclatasvir has also been studied in combination with sofosbuvir in previously treated or untreated chronic HCV patients with genotype 1, 2, and 3 in an open-label study.<sup>27</sup>

The new direct acting antiviral ledipasvir is expected to be FDA approved by late 2014 and has been studied in combination with sofosbuvir in HCV GT 1 patients.<sup>28-30</sup>

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## Sofosbuvir (Sovaldi®)

**Goal(s) :**

- Approve cost effective treatments of chronic hepatitis C which are supported by the medical literature when there is available evidence. When evidence is lacking, consult with local specialists and the community standard.

**Length of Authorization**

- Initial trial of 8weeks
- Continuation of therapy up to 24 weeks of total therapy based on therapy regimen, genotype, and patient population

**Requires PA:**

- Sofosbuvir

Approval Criteria			
1. What diagnosis is being treated?		<b>Record ICD9 code</b>	
2. Is the request for treatment of Chronic Hepatitis C Virus?		<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh, Deny For Appropriateness
3. Is the request for continuation of therapy?		<b>Yes:</b> Go to "Continuation of Therapy"	<b>No:</b> Go to #4
4. <u>Has the patient had previous treatment (full or incomplete course) with an oral direct acting antiviral that was FDA approved after 2012 (including sofosbuvir and simeprevir)?</u>		<u><b>Yes:</b> Pass to RPh; Deny For Appropriateness</u>	<u><b>No:</b> Go to #5</u>
5. Is the medication being prescribed by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C?		<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh, Deny For Appropriateness  Forward to DMAP for further review to determine appropriateness of prescriber
6. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate severe fibrosis (stage 4) OR radiologic, laboratory, or clinical evidence of cirrhosis without ongoing progressive decompensation (MELD score between 8 and 11), and expected survival from non-HCV associated morbidity should be greater than 5 years?		<b>Yes:</b> Go to #11	<b>No:</b> Go to #7  <b>Note:</b> Patients with a MELD score >11 may be eligible for therapy, but only after review by the DMAP medical director.  Forward fee-for-service cases



		to DMAP for Medical Director Review and notify requesting provider of pending review.
7. Does the patient have one of the following extrahepatic manifestations of hepatitis C and who have formal documentation from a relevant specialist that their condition is HCV related, and expected survival from non-HCV associated morbidity should be greater than 5 years? a. Vasculitis b. Glomerulonephritis c. Cryoglobulinemia d. Lymphoma	<b>Yes:</b> Go to #11	<b>No:</b> Go to #8
8. Does the patient have a HIV coinfection with cirrhosis (Stage 4 disease), and expected survival from non-HCV associated morbidity should be greater than 5 years?	<b>Yes:</b> Go to #9	<b>No:</b> Go to #10
9. Is the patient under the supervision of an HIV specialist?	<b>Yes:</b> Go to #11	<b>No:</b> Pass to RPh; Deny (medical appropriateness)
10. Does the patient have Hepatitis C Virus in the transplant setting, including the following scenarios: a. Patient is listed for a transplant and it is essential to prevent recurrent hepatitis C infection post-transplant b. Post-transplant patients with Stage 4 fibrosis c. Post-transplant patients with fibrosing cholestatic hepatitis due to HCV infection  <b>and</b> expected survival from non-HCV associated morbidity should be greater than 5 years?	<b>Yes:</b> Go to #11  <b>Note:</b> Patients in the transplant setting may be eligible for therapy, but only after review by the DMAP medical director.  Forward fee-for-service cases to DMAP for Medical Director Review and notify requesting provider of pending review.	<b>No:</b> Pass to RPh; Deny (medical appropriateness)  <b>Note:</b> Other Scenarios not included can be brought to the Medical Director on a case by case basis
11. , Has the patient been abstinent from IV drug, illicit drugs and marijuana use, AND alcohol abuse for $\geq 6$ months?	<b>Yes:</b> Go to #12	<b>No:</b> Pass to RPh, Deny for appropriateness
12. Does the patient have significant renal impairment (CrCl < 30 ml/min) or end stage renal disease (ESRD)?	<b>Yes:</b> Pass to RPh; Deny for appropriateness	<b>No:</b> Go to #13
13. Does the patient have a baseline HCV RNA level?	<b>Yes:</b> Record value and go to #14  Note: Next HCV RNA level required at week 4 of treatment (see continuation criteria)	<b>No:</b> Pass to RPh; request provider obtain baseline lab value
14. What Hepatitis C genotype is the patient? Record Genotype:	Record Genotype and go to #15	
15. Does the patient have genotype 1 or 4 chronic hepatitis C?	<b>Yes:</b> Go to # 16	<b>No:</b> Go to #19
16. Is the medication being used as triple therapy with both ribavirin and peginterferon alfa and meets criteria for pegylated interferon-alfa and ribavirin?	<b>Yes:</b> Approve for initial 8 weeks for 12 weeks of total therapy	<b>No:</b> Go to #17
17. Is the medication being used with ribavirin or simeprevir?	<b>Yes:</b> Go to #18	<b>No:</b> Pass To RPh; Deny for Appropriateness

18. Is the patient interferon ineligible defined by having one of the following conditions: a. Previous adverse reaction or hypersensitivity to interferon b. Decompensated liver disease c. Severe or uncontrolled psychiatric disorder in consult with a psychiatrist d. Autoimmune hepatitis or other autoimmune disorders e. Unstable cardiac disease f. Severe cytopenias g. Other comorbidities that would be exacerbated by interferon use  Note: Patient's or prescribers not wanting to go through treatment with interferon does not meet the criteria for being "interferon ineligible"	<b>Yes:</b> Approve initial trial of 8 weeks for total therapy of 12 weeks for sofosbuvir + simeprevir combination <b>OR</b> a total of 24 weeks for sofosbuvir + ribavirin therapy	<b>No:</b> Pass To RPh; Deny for Appropriateness
19. Does the patient have genotype 2 chronic hepatitis C?	<b>Yes:</b> Go to #20	<b>No:</b> Go to #21
20. Is the medication being used with ribavirin?	<b>Yes:</b> Approve for initial 8 weeks for 12 weeks total therapy	<b>No:</b> Pass To RPh; Deny for Appropriateness
21. Does the patient have genotype 3 chronic hepatitis C?	<b>Yes:</b> Go to #22	<b>No:</b> Pass To RPh; Deny for Appropriateness
22. Is the medication being used with both ribavirin and peginterferon alfa and meets criteria for pegylated interferon-alfa and ribavirin?	<b>Yes:</b> Approve for initial 8 weeks for 12 weeks total therapy	<b>No:</b> Go to #23
23. Is the medication being used with only ribavirin and the patient is interferon ineligible as defined by the conditions listed above in #18?	<b>Yes:</b> Approve for 8 weeks initial fill for a total 24 weeks of therapy	<b>No:</b> Pass To RPh; Deny for Appropriateness

<b><u>Continuation of Therapy- Sofosbuvir (Assess after 4 weeks of treatment)</u></b>		
<b><u>1. Has the patient been adherent to and tolerated initial therapy?</u></b>	<b><u>Yes: Go to #2</u></b>	<b><u>No: DENY (Medical Appropriateness)</u></b>
<b><u>2. Is the HCV RNA level at week 4 detectable (HCV RNA is <math>\geq 25</math> IU/mL),?</u></b>	<b><u>Yes: reassess HCV RNA in 2 weeks. Go to #3</u></b>	<b><u>No: Go to #4</u></b>
<b><u>3. Has the HCV RNA increased (i.e., <math>&gt;1</math> log<sub>10</sub> IU/mL from nadir)?</u></b>	<b><u>Yes: Discontinue treatment</u></b>	<b><u>No: Recheck in 2 weeks (week 8 of treatment). Go to #4</u></b>

<u>4. Is the 8 week HCV RNA detectable (HCV RNA is <math>\geq 25</math> IU/mL),?</u>	<u>Yes: Discontinue treatment</u>	<u>No: Approve for additional 4-16 weeks based on genotype and regimen</u>
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*P&T Board Action: 1/30/13 (MH)  
Revision(s): 3/27/13, 7/31/13 (MH)  
Initiated:*

**Dosage and Administration:**

Genotype 1 and 4	Sofosbuvir + peginterferon alfa + ribavirin	12 weeks
Genotype 2	Sofosbuvir + ribavirin	12 weeks
Genotype 3*	Sofosbuvir + ribavirin	24 weeks
Genotype 1 and interferon ineligible	Sofosbuvir + ribavirin	24 weeks

\*Certain patients with genotype 3 (nonresponders with advanced fibrosis) can also be treated with sofosbuvir + peginterferon alfa + ribavirin for 12 weeks if deemed appropriate by physician.

## Appendix 2: Hepatitis C PA Criteria

### Hepatitis C

#### Goal(s):

- Approve cost effective treatments of chronic hepatitis C which are supported by the medical literature when there is available evidence. When evidence is lacking the approval criteria reflect a community standard developed in consultation with local specialists.
- Provide consistent patient evaluations across all hepatitis C treatments

#### Requires PA:

- All drug regimens in the Hepatitis C PDL Class

#### Approval Criteria

1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the request for treatment of Chronic Hepatitis C?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh; Deny for appropriateness.
3. Is the request for continuation of therapy?	<b>Yes:</b> Go to specific regimen PA Criteria	<b>No:</b> Go to #4
4. What regimen is requested?	<b>Document and go to #5</b>	
5. Does the regimen contain a drug not yet reviewed by P&T?	<b>Yes:</b> Pass to RPh; Deny for appropriateness.  Forward to DMAP for further review to determine appropriateness and coverage in light of most recent community standards and comorbidity.	<b>No:</b> Go to #6

Approval Criteria		
6. Is the regimen being prescribed by or in consultation with a hepatologist or gastroenterologist with experience in hepatitis C?	<b>Yes:</b> Go to #7.	<b>No:</b> Pass to RPh; Deny for appropriateness.  Forward to DMAP for further review to determine appropriateness of prescriber.
7. What genotype and stage does the patient have?	<b>Document and go to #8</b>	
8. Has the patient been abstinent from IV drugs, illicit drugs, marijuana use AND alcohol abuse for greater than or equal to 6 months?	<b>Yes:</b> Go to specific regimen PA Criteria.	<b>No:</b> Pass to RPh; Deny for medical appropriateness.

*P&T / DUR Action:*

*Revision(s):*

*Initiated:*

## Botulinum Toxins (BoNT)

### **Goal(s):**

- Approve BoNT only for funded OHP diagnoses which are supported by the medical literature (e.g. various dystonias and spasticity associated with certain neurological diseases).

### **Length of Authorization:**

- 90 days up to lifetime

### **Requires PA:**

Use of BoNT without associated dystonia or neurological disease diagnosis in last 12 months (i.e. 333.6x, 333.7x, 333.81, 333.83, 333.89, 340.xx, 341.0, 342.xx, 343.xx, 344.0x, 344.1, 344.2, 344.4x, 344.5, or 378.73)

HSN	Generic Drug Name
004867	ONABOTULINUMTOXINA (BOTOX, BOTOX COSMETIC)
036477	ABOBOTULINUMTOXINA (DYSPORT)
021869	RIMABOTULINUMTOXINB (MYOBLOC)
036687	INCOBULINUMTOXINA (XEOMIN)

ProcCode	Descriptions
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit

### **Covered Alternatives:**

Preferred alternatives listed at [www.orpdl.org](http://www.orpdl.org)

### Approval Criteria

1. What diagnosis is being treated?

Record ICD-9 Code

## Approval Criteria

<p>2. Does client have diagnosis of certain dystonias or spasticity associated with other neurological diseases that make BoNT a first-line treatment option?</p> <p>Examples:</p> <p>333.6x (genetic torsion dystonia)  333.7x (acquired torsion dystonia),  333.81 (blepharospasm)  333.83 (spasmodic torticollis)  333.89 (other fragments of torsion dystonia)  438.2x – 432.5x (paralysis associated with CVD)  340.xx (multiple sclerosis)  341.0 (neuromyelitis optica)  342.xx (spastic hemiplegia, other specified hemiplegia),  343.xx (cerebral palsy),  344.0x (quadriplegia and quadraparesis),  344.1 (paraplegia),  344.2 (diplegia of upper limbs)  344.3x (monoplegia of lower limb)  344.4x (monoplegia of upper limb)  344.5 (unspecified monoplegia)  344.89 (other specified paralytic syndrome)  359.0x – 359.2x (muscular dystrophies)  378.73 (strabismus in other neuromuscular disorders)</p>	<p>Yes: Approve for lifetime (until 12-31-2036)</p>	<p>No: Go to #3</p>
<p>3. Does client have diagnosis of chronic migraine based on clinical symptoms; at least 15 headache days per month, of which, at least 8 of those days are considered migraine days?</p>	<p>Yes: Go to #6</p>	<p>No: Go to #4</p>
<p>4. Does client have diagnosis of <u>overactive bladder detrusor over-activity (596.5x) e.g. idiopathic detrusor over-activity (IDO) also called "overactive bladder syndrome"</u> or <u>neurogenic detrusor over-activity (NDO). related to neurological causes?</u></p> <p><u>Document neurological cause</u></p>	<p>Yes: Go to #7</p>	<p>No: Go to #5</p>

## Approval Criteria

<p>5. Does client have any of the following diagnoses?</p> <p><u>Insufficient evidence of benefit:</u>  787.2x (dysphagia)  333.xx (other extrapyramidal disease and abnormal movement disorders excluding 333.6x, 333.7x, 333.81, 333.83, 333.89 and 333.82, 333. 84, 333.94-333.99)  378 excluding 378.73 (other disorders of binocular eye movements (e.g. esotropia, exotropia, mechanical strabismus, sixth nerve palsy)  307.2x (tics)  478.75 (laryngeal spasm),  723.0 and 723.4 (Spinal stenosis in cervical region or Brachial neuritis or radiculitis NOS)  728.85 (spasm of muscle [in absence of neurological diagnoses]),  727.81 (contracture of tendon – sheath [in absence of neurological diagnoses])  335.20 (amyotrophic sclerosis),  724.00-724.09, 724.4 (clinically significant spinal deformity or disorders of spine with neurological impairment)  600.xx (hyperplasia of prostate),</p> <p><u>Unfunded OHP condition:</u>  333.82, 333. 84, 333.94-333.99 (neurologic conditions with no or minimally effective treatment or not treatment is necessary)  351.xx (facial nerve disorders),  478.79 (spastic dysphonia)  565.0 (anal fissure),  705.xx (disorders of sweat glands e.g. focal hyperhidrosis),  723.xx except 723.4 (other disorders of cervical region),  705.0-705.1,705.21-705.9,780.8 (disorders of sweat glands)  724.1, 724.2, 724.4-724.6, 727.70-724.9 (acute and chronic disorders of the spine without neurologic impairment)  729.0-729.2 (disorders of soft tissue)  307.81,339.10-339.89,784. (tension headaches)  536.3 (gastroparesis),</p>	<p>Yes: Pass to RPH; Deny</p> <p>(Medical Appropriateness)</p> <p>(Condition not funded by OHP)</p>	<p>No: Go to #8</p>
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## Approval Criteria

<p>6. Has the client not responded or are they contraindicated to at least one drug in three of the following drug classes?</p> <ul style="list-style-type: none"> <li>• B-blocker (metoprolol, atenolol, nadolol, propranolol, timolol)</li> <li>• Tricyclic antidepressant (nortriptyline, amitriptyline)</li> <li>• Anticonvulsant (valproic acid, divalproate, carbamazepine, topiramate, gabapentin)</li> <li>• Calcium Channel Blocker (verapamil, diltiazem, nimodipine)</li> </ul>	<p>Yes: Approve for 180 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.</p>	<p>No: Pass to RPH; Deny (Medical Appropriateness) and recommend trial of preferred alternatives (<a href="http://www.orpdl.org">www.orpdl.org</a>).</p>
<p>7. Has the client tried or are they contraindicated to at least two of the following urinary incontinence antimuscarinic therapies? (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium)</p>	<p>Yes: Approve for 90 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.</p>	<p>No: Pass to RPH; Deny (Medical Appropriateness) and recommend trial of preferred alternatives (<a href="http://www.orpdl.org">www.orpdl.org</a>).</p>
<p>8. Pass to pharmacist to evaluate for evidence support and OHP funding level.</p>	<p>Yes: Approve for 90 days with subsequent approvals dependent on documented* positive response for annual approval. *Documented response means that follow-up and response is noted in client's chart by clinic staff.</p>	<p>No: Pass to RPH; Deny (Medical Appropriateness)</p>

P&T / DUR Action: 7/31/2014: [9/27/2014](#)  
Revision(s):  
Initiated:



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**Oregon State**  
UNIVERSITY

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## **Policy Update: RSV Antivirals - Palivizumab**

**Month/Year of Review:** September 2014

**Date of Last Review:** September 2013

**Current PA:** Prior authorization (PA) criteria are currently in place for palivizumab to align prescribing with American Academy of Pediatric (AAP) Guidelines and to allow for geographic variations of respiratory syncytial virus (RSV) activity.

### **Research Questions:**

- Is there any new evidence on the effectiveness of palivizumab on important outcomes such as mortality and hospitalizations due to RSV?
- Is there any new evidence about harms associated with palivizumab treatment?
- Are there subpopulations of patients who benefit more from palivizumab prophylaxis?

### **Conclusions:**

- There is insufficient evidence that palivizumab lowers mortality rates or subsequent wheezing after an infection in infants and children receiving palivizumab prophylaxis.<sup>1</sup>
- New AAP guidelines recommend lowering the gestational age of preterm infants who should be candidates for palivizumab prophylaxis. The determination of which infants and children are considered high risk, in addition to prematurity, and who should receive palivizumab are the following: premature infants with chronic lung disease (CLD), infants with congenital heart disease (CHD), patients with cyanotic heart defects, those undergoing cardiac transplant, neuromuscular disease or congenital anomaly and those who are immunocompromised.<sup>1</sup>

### **Recommendations:**

- Amend the current PA criteria to align recommendations with those of the AAP guideline (Appendix 1).
- Continue to allow for geographic variations in RSV activity.

### **Reason for review:**

The AAP released a revised guidance in July of 2014 for palivizumab prophylaxis among infants and young children. Review of the guidelines and analysis of data published since the last update will be included.

### **Previous Conclusions and Recommendation:**

- A policy evaluation of the palivizumab prior authorization (PA) criteria in Oregon Fee-for-Service patients was done in September of 2013 to assess palivizumab use outside of the recommended PA criteria and to determine if there was any unintended harm as a result of the policy. Results of the evaluation showed that

palivizumab was used within the established parameters of the PA criteria. This resulted in decreased palivizumab utilization and costs. No hospitalizations or emergency room visits were associated with palivizumab claims.<sup>2</sup>

- The decision was made to continue the palivizumab PA criteria for the 2013-2014 RSV season (Appendix 2).

### Background:

Palivizumab is a humanized mouse immunoglobulin (IgG1) monoclonal antibody which is indicated for prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.<sup>1,3</sup> Data demonstrating reduced RSV hospitalizations with palivizumab immunoprophylaxis, comes from two randomized controlled trials.<sup>4,5</sup> The Impact-RSV trial included children born prematurely ( $\leq 35$  weeks) or with bronchopulmonary dysplasia (BPD).<sup>4</sup> Palivizumab prophylaxis demonstrated a significant reduction in risk of RSV hospitalizations compared to placebo, 4.8% vs. 10.6%, respectively.<sup>4</sup> The Cardiac Synagis Study Group found that in children with hemodynamically significant CHD palivizumab prophylaxis also showed significant reductions in RSV hospitalization rates compared to placebo, 5.3% vs. 9.7%, respectively.<sup>5</sup> Conclusive data regarding reductions in mortality and subsequent wheezing following an infection due to palivizumab prophylaxis are lacking.<sup>1,6</sup>

### Methods:

A Medline literature search beginning July 2013 and ending July 2014 for new systematic reviews and randomized controlled trials (RCTs) that evaluated palivizumab effectiveness and/or harms was performed. 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 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. Data that is observational and/or at a high risk of bias due to study design does not meet the inclusion criteria for our analysis as outlined in the policy and procedures (i.e. Ambrose 2014, Hall 2013, Hasegawa 2013 and Winterstein 2013).<sup>7-10</sup>

### New Guidelines:

*AAP Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection*

In July 2014 the AAP updated treatment guidelines for use of palivizumab in those individuals at increased risk of RSV infection.<sup>1</sup> The goal of the updated guidelines is to streamline evidence so that those at highest risk receive prophylaxis. Recommendations are based on an analysis of the data by the Committee on Infectious Diseases (COID). Updates to the data are in the following area:

- Palivizumab pharmacokinetics
- Seasonality of RSV circulation
- Overall declining incidence of hospitalizations for bronchiolitis in the United States
- Statistically significant but clinically minimal reduction in wheezing episodes among recipients of palivizumab prophylaxis
- Reports of little benefit of palivizumab prophylaxis among patients with cystic fibrosis or Down syndrome
- Reports describing palivizumab resistant isolates from hospitalized patients who received prophylaxis
- Independently conducted cost analyses demonstrating high cost versus limited benefit from palivizumab prophylaxis

Recommendations for the consideration of palivizumab prophylaxis are for the following groups:

- Infants born before 29 weeks, 0 days' gestations that are younger than 12 months at the start of the RSV season. For infants born during the RSV season, fewer than 5 monthly doses will be needed

Author: Kathy Sentena, Pharm.D.

- Premature infants within the first 12 months of life who develop CLD of prematurity, defined by a gestational age of <32 weeks, 0 days and a requirement for >21% oxygen for at least the first 28 days after birth. These same infants may be candidates for prophylaxis in the second year of life if they continue to require medical support (chronic corticosteroid therapy, diuretic therapy or supplemental oxygen) during the 6-month period before the start of the RSV season
- Children 12 months or younger with hemodynamically significant CHD, specifically those with acyanotic heart disease who are receiving medication to control congestive heart failure (CHF) and will require cardiac surgical procedures and infants with moderate to severe pulmonary hypertension
- Infants with cyanotic heart defects, 12 months or younger, if recommended by a pediatric cardiologist
- Infants with CHD with lesions corrected by surgery and still requiring medication for CHF born within 12 months of onset of the RSV season
- Children under the age of 2 years undergoing cardiac transplantation during the RSV season
- Infants with neuromuscular disease or congenital anomaly that impairs the ability to clear secretions from the upper airway during the first year of life
- Children under the age of 24 months who are profoundly immunocompromised during the RSV season
- Infants with cystic fibrosis with clinical evidence of CLD and/or nutritional compromise in the first year of life and in those of their second year of life if manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest radiography or chest computed tomography that persists when stable) or weight or length less than the 10<sup>th</sup> percentile

In general palivizumab prophylaxis is not recommended in the second year of life based on the prematurity alone. Clinicians in Alaska may utilize RSV season surveillance data to determine needs of infant prophylaxis. Those patients receiving prophylaxis and who experience a RSV hospitalization should no longer continue to receive palivizumab. Even in areas of unpredictable onset and offset of RSV season, like Florida, only 5 doses of palivizumab are recommended. Palivizumab has not been shown to impact primary asthma prevention or reduction in subsequent episodes of wheezing.

Limitations to the guidelines include recommendations that were made on data that is subject to a high chance of bias due to study design and lack of grading of the evidence that was used within the guideline.

#### **New FDA Safety Alerts:**

In March of 2014 the Food and Drug Administration approved labeling changes to the Synagis<sup>®</sup> package insert that recommends that children undergoing cardio-pulmonary bypass should receive an additional dose of palivizumab as soon as possible, post-procedure. This recommendation is based on evidence that palivizumab serum levels are decreased after cardio-pulmonary bypass.<sup>3</sup> Additionally, language stating palivizumab provides passive immunity was also added.<sup>3</sup>

## References:

1. Committee on Infectious Diseases. From the American Academy of Pediatrics: Policy Statement – updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*. 2014; 134(2):415-420.
2. Oregon State University Drug Use Research and Management. Policy Evaluation: Palivizumab prior authorization. 2013. Available at: [http://pharmacy.oregonstate.edu/files/drug-policy/pages/dur\\_board/evaluations/articles/2013\\_09\\_26\\_Palivizumab\\_DUE.pdf](http://pharmacy.oregonstate.edu/files/drug-policy/pages/dur_board/evaluations/articles/2013_09_26_Palivizumab_DUE.pdf). Accessed August 4, 2014.
3. Synagis (Palivizumab). Prescribing Information. MedImmune. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/103770s5185lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103770s5185lbl.pdf). Accessed July 31, 2014.
4. Impact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics*. 1998;102:531-537.
5. Feltes T, Cabalka A, Meissner C, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr*. 2003;143:532-40).
6. Andabaka T, Nickerson JW, Rojas-Reyes MX, et al. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. *Cochrane Database of Syst Rev*. 2013;4:CD006602.
7. Ambrose C, Anderson E, Simoes, et al. Respiratory syncytial virus disease in preterm infants in the US Born at 32-35 weeks gestation not receiving immunoprophylaxis. *Pediatr Infect Dis J* 2014;33:576-582).
8. Hasegawa K, Tsugawa Y, Brown D, et al. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. *Pediatrics*. 2013;132(1):28-36.
9. Hall C, Weinberg G, Blumkin A, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. *Pediatrics*. 2013;132(2):e341-8.
10. Winterstein A, Knox C, Kubilis P, Hampp C. Appropriateness of age thresholds for respiratory syncytial virus immunoprophylaxis in moderate-preterm infants: a cohort study. *JAMA Pediatr*. 2013;167(12):1118-24.

**APPENDIX 1:**  
Recommended PA Criteria

## Synagis (palivizumab)

**Goal(s):**

- Promote safe and effective use of Synagis.

**Length of Authorization: Based on individual factors; may extend up to 5 months (5 doses).**

Approval Criteria											
1. What is the diagnosis being treated?	Record ICD9 code and reject/internal error code										
2. <u>Has the patient been receiving monthly palivizumab prophylaxis and been hospitalized for a breakthrough RSV infection?</u>	<b>Yes:</b> Pass to RPH: DENY (Medical Appropriateness). <b>No:</b> Go to #3										
32. Is the request for immunoprophylaxis between the months of November and March?	<b>Yes:</b> Go to #54 <b>No:</b> Go to #43										
43. Is the request for immunoprophylaxis starting in October due to an early onset* of the RSV season in the region from which the patient resides (see below)?  * Onset is defined as 2 consecutive weeks where % positive is ≥10% (data is provided by the Oregon's Weekly Respiratory Syncytial Virus Surveillance Report from the Oregon Public Health Division based on regions. Weekly updates are found at: <a href="https://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=40">https://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=40</a> )	<b>Yes:</b> Go to #54 <b>No:</b> Pass to RPH: DENY (Medical Appropriateness). Prophylaxis is indicated only during high viral activity.										
<table border="1"> <thead> <tr> <th>Region</th><th>Counties</th></tr> </thead> <tbody> <tr> <td>NW Oregon- SW Washington</td><td>Benton, Clackamas, Clatsop, Columbia, Lane, Lincoln, Linn, Marion, Multnomah, Polk, Tillamook, Washington, Yamhill</td></tr> <tr> <td>Central Oregon</td><td>Crook, Deschutes, Grant, Harney, Jefferson, Wheeler</td></tr> <tr> <td>Columbia Gorge – NE Oregon</td><td>Baker,, Gilliam, Hood River, Morrow, Sherman, Umatilla, Union, Wasco, Wallowa</td></tr> <tr> <td>Southern Oregon</td><td>Coos, Curry, Douglas, Jackson, Josephine, Klamath, Lake, Malheur</td></tr> </tbody> </table>	Region	Counties	NW Oregon- SW Washington	Benton, Clackamas, Clatsop, Columbia, Lane, Lincoln, Linn, Marion, Multnomah, Polk, Tillamook, Washington, Yamhill	Central Oregon	Crook, Deschutes, Grant, Harney, Jefferson, Wheeler	Columbia Gorge – NE Oregon	Baker,, Gilliam, Hood River, Morrow, Sherman, Umatilla, Union, Wasco, Wallowa	Southern Oregon	Coos, Curry, Douglas, Jackson, Josephine, Klamath, Lake, Malheur	
Region	Counties										
NW Oregon- SW Washington	Benton, Clackamas, Clatsop, Columbia, Lane, Lincoln, Linn, Marion, Multnomah, Polk, Tillamook, Washington, Yamhill										
Central Oregon	Crook, Deschutes, Grant, Harney, Jefferson, Wheeler										
Columbia Gorge – NE Oregon	Baker,, Gilliam, Hood River, Morrow, Sherman, Umatilla, Union, Wasco, Wallowa										
Southern Oregon	Coos, Curry, Douglas, Jackson, Josephine, Klamath, Lake, Malheur										
54. Is the current age of the patient < 24 months at start of RSV season?	<b>Yes:</b> Go to #56 <b>No:</b> Pass to RPH: DENY (Medical Appropriateness).										

		Synagis not recommended for patients $\geq 24$ months old.
<b>65. GROUP A</b> Does the patient have <del>the</del> CLD (chronic lung disease) <del>of prematurity</del> ICD9 7485x or 7486x <b>and</b> in the past 6 months has required medical treatment with at least one of the following: a. diuretics b. chronic corticosteroid therapy c. <del>supplemental</del> <del>home</del> oxygen therapy d. <del>bronchodilators</del>	<b>Yes:</b> Go to #1 <u>82</u>	<b>No:</b> Go to # <u>76</u>
<b>76. GROUP B</b> <u>Has the patient received a cardiac transplant during the RSV season?</u>  <del>Does the patient have hemodynamically significant congenital heart disease (CHD) ICD9 746xx or 747xx <b>and</b> at least one of the following:</del> <del>a. Receiving treatment for congestive heart failure <b>or</b></del> <del>b. Have moderate to severe pulmonary hypertension <b>or</b></del> <del>c. Cyanotic heart disease</del>	<b>Yes:</b> Go to #1 <u>82</u>	<b>No:</b> Go to # <u>87</u>
<b>8. GROUP C</b> <u>Is the child profoundly immunocompromised during the RSV season (i.e. solid organ transplant or hematopoietic stem cell transplantation)?</u>	<b>Yes:</b> Go to #18	<b>No:</b> Go to #9
<b>9. GROUP D</b> <u>Does the infant have cystic fibrosis and manifestations of severe lung disease or weight or length less than the 10<sup>th</sup> percentile?</u>	<b>Yes:</b> Go to #18	<b>No:</b> Go to #10
<b>10. GROUP E</b> <u>Is the request for a second season of palivizumab prophylaxis for a child born &lt;32 weeks, 0 days gestation who required at least 28 days of oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of start of second RSV season?</u>	<b>Yes:</b> Go to #18	<b>No:</b> Got to #11
<b>117.</b> Will the patient be < 12 months at start of RSV season?	<b>Yes:</b> Go to #12	<b>No:</b> Pass to RPH: DENY (Medical Appropriateness).
<b>128. GROUP F</b> <u>Was the infant born before 29 weeks, 0 days gestation?</u> <del>Is the</del>	<b>Yes:</b> Go to #1 <u>82</u>	<b>No:</b> Go to # <u>139</u>

<u>gestational age ≤ 28 weeks?</u>		
<b>139. GROUP G</b> Infants with <u>pulmonary congenital</u> abnormalities of the airway or neuromuscular disease compromising handling of secretions?	<b>Yes:</b> Go to #1 <u>82</u>	<b>No:</b> Go to #1 <u>40</u>
<b>1440. GROUP H</b> <u>Does the patient have hemodynamically significant congenital heart disease (CHD) ICD9 746xx or 747xx and at least one of the following:</u> <u>a. Acyanotic heart disease who are receiving treatment to control congestive heart failure and will require cardiac surgical procedures or</u> <u>b. Have moderate to severe pulmonary hypertension or</u> <u>c. History of lesions adequately corrected by surgery AND still requiring medication for congestive heart failure</u>  <u>Will the patient be &lt; 6 months at the start of the RSV season and the gestational age ≤ 29-31 weeks and 6 days?</u>	<b>Yes:</b> Go to #1 <u>82</u>	<b>No:</b> Go to #1 <u>54</u>
<b>154. GROUP F</b> <u>Does the patient have chronic lung disease (CLD) of prematurity defined as gestational age &lt;32 weeks, 0 days and requirement for &gt;21% oxygen for at least the first 28 days after birth?</u> <u>Will the patient be &lt; 90 days at the start of the RSV season AND have a gestational age of ≤ 32-34 weeks and 6 days AND have at least one of the following risk factors:</u> <u>a. Daycare attendance</u> <u>b. Siblings less than 5 years of age</u>	<b>Yes:</b> Go to #1 <u>82</u>	<b>No:</b> <u>Pass to RPH: DENY (Medical Appropriateness). Go to #16</u>
<b>16. GROUP I</b> <u>Does the patient have cyanotic heart defects and immunoprophylaxis is recommended by a pediatric cardiologist?</u>	<b>Yes:</b> Go to #1 <u>8</u>	<b>No:</b> Go to #1 <u>7</u>
<b>17. GROUP J</b> <u>Does the patient have cystic fibrosis with clinical evidence of CLD and/or nutritional compromise?</u>	<b>Yes:</b> Go to #1 <u>8</u>	<b>No:</b> <u>Pass to RPH: DENY (Medical Appropriateness).</u>
<b>182.</b> Is the request for more than 5 doses within the same RSV season or for dosing <28 days apart?	<b>Yes:</b> Pass to RPH: DENY (Medical Appropriateness). Prophylaxis is indicated for 5 months maximum and doses should be administered ≥28 days apart.  <b>May approve for the</b>	<b>No:</b> Go to #13



	<b>following on a case by case basis:</b> <b>a. &gt; 5 doses.</b> <b>b. Prophylaxis for a second/subsequent RSV season.</b>	
<b>193.</b> Has the patient had a weight taken within the last 30 days?	<b>Yes:</b> Document weight and date and go to #14  Weight: _____ Date: _____	<b>No:</b> Pass to RPH: obtain recent weight so accurate dose can be calculated.
<b>2014.</b> Approve palivizumab for a dose of 15mg/kg. Document number of doses received in hospital and total number approved according to <b>BIRTH DATE</b> and <b>GROUP</b> based on start of RSV season: <ul style="list-style-type: none"> <li>- Immunoprophylaxis between <u>November - March</u> refer to <b>Table 1</b></li> <li>- Immunoprophylaxis starting in <u>October</u> based on above (#3) refer to <b>Table 2</b></li> </ul> Total number of doses approved for RSV season: _____  Number of doses received in the hospital: _____		

**Table 1.** Maximum number of doses to approve for RSV prophylaxis (Based on Criteria Group from Above) – Beginning **NOVEMBER 1st**

MONTH OF BIRTH	<b>ALL GROUPS A-D</b> (Child is <24 or <12 mo. old at start of season)	<b>GROUP E</b> (Child is <6 mo. old at start of season)	<b>GROUP F</b> (Child is <3 mo. old at start of season)
November 1 – March 31 of previous RSV season	5	Zero doses; infant will be older than 6 months at start of RSV season	Zero doses; infant will be older than 90 days at start of RSV season
April	5	Zero doses; infant will be older than 6 months at start of RSV season	
May	5	5	
June	5	5	

July	5	5	
August	5	5	1*
September	5	5	2*
October	5	5	3*
November	5	5	3*
December	4	4	3*
January	3	3	3*
February	2	2	2*
March	1	1	1*

\* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

**Table 2.** Maximum number of doses to approve for RSV prophylaxis (Based on Criteria Group from Above) – Beginning **OCTOBER 1-31**

MONTH OF BIRTH	<b>ALL GROUPS A-D</b> (Child is <24 or <12 mo. old at start of season)	<b>GROUP E</b> (Child is <6 mo. old at start of season)	<b>GROUP F</b> (Child is <3 mo. old at start of season)
November 1 – March 31 of previous RSV season	5	Zero doses; infant will be older than 6 months at start of RSV season	Zero doses; infant will be older than 90 days at start of RSV season
April	5	5	
May	5	5	
June	5	5	
July	5	5	
August	5	5	1*
September	5	5	2*
October	5	5	3*
November	5	5	3*
December	4	4	3*
January	3	3	3*
February	2	2	2*
March	1	1	1*

\* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

**Notes:**

- Dose: 15 mg/kg via intramuscular injection once monthly throughout RSV season.
- The start date for Synagis is November 1 each year (or sooner when the Oregon Public Health Division has determined that RSV season onset has occurred) for a total of up to five doses.
- Approval for more than five doses or additional doses after March 31 is considered on a case-by-case basis. Results from clinical trials indicate that Synagis trough concentrations greater than 30 days after the 5<sup>th</sup> dose will be well above the protective concentration therefore five doses will provide more than 20 weeks of protection.

DUR Board Action: 05/17/11 (DO/KK), 5/26/12 (KS), 9/23/14 (KS)

Revision(s): 3/30/12 (KS)

Initiated:

## **APPENDIX 2:**

Previous PA Criteria (2013-2014 RSV season)

### Synagis (palivizumab)

#### **Goal(s):**

- Promote safe and effective use of Synagis.

**Length of Authorization: Based on individual factors; may extend up to 5 months (5 doses).**

Approval Criteria											
1. What is the diagnosis being treated?	Record ICD9 code and reject/internal error code										
2. Is the request for immunoprophylaxis between the months of November and March?	<b>Yes:</b> Go to #4 <b>No:</b> Go to #3										
3. Is the request for immunoprophylaxis starting in October due to an early onset* of the RSV season in the region from which the patient resides (see below)?  * Onset is defined as 2 consecutive weeks where % positive is $\geq 10\%$ (data is provided by the Oregon's Weekly Respiratory Syncytial Virus Surveillance Report from the Oregon Public Health Division based on regions. Weekly updates are found at: <a href="https://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=40">https://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=40</a> )	<b>Yes:</b> Go to #4 <b>No:</b> Pass to RPH: DENY (Medical Appropriateness). Prophylaxis is indicated only during high viral activity.										
<table><thead><tr><th>Region</th><th>Counties</th></tr></thead><tbody><tr><td>NW Oregon- SW Washington</td><td>Benton, Clackamas, Clatsop, Columbia, Lane, Lincoln, Linn, Marion, Multnomah, Polk, Tillamook, Washington, Yamhill</td></tr><tr><td>Central Oregon</td><td>Crook, Deschutes, Grant, Harney, Jefferson, Wheeler</td></tr><tr><td>Columbia Gorge – NE Oregon</td><td>Baker,, Gilliam, Hood River, Morrow, Sherman, Umatilla, Union, Wasco, Wallowa</td></tr><tr><td>Southern Oregon</td><td>Coos, Curry, Douglas, Jackson, Josephine, Klamath, Lake, Malheur</td></tr></tbody></table>	Region	Counties	NW Oregon- SW Washington	Benton, Clackamas, Clatsop, Columbia, Lane, Lincoln, Linn, Marion, Multnomah, Polk, Tillamook, Washington, Yamhill	Central Oregon	Crook, Deschutes, Grant, Harney, Jefferson, Wheeler	Columbia Gorge – NE Oregon	Baker,, Gilliam, Hood River, Morrow, Sherman, Umatilla, Union, Wasco, Wallowa	Southern Oregon	Coos, Curry, Douglas, Jackson, Josephine, Klamath, Lake, Malheur	
Region	Counties										
NW Oregon- SW Washington	Benton, Clackamas, Clatsop, Columbia, Lane, Lincoln, Linn, Marion, Multnomah, Polk, Tillamook, Washington, Yamhill										
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Southern Oregon	Coos, Curry, Douglas, Jackson, Josephine, Klamath, Lake, Malheur										
4. Is the current age of the patient < 24 months at start of RSV season?	<b>Yes:</b> Go to #5 <b>No:</b> Pass to RPH: DENY (Medical Appropriateness). Synagis not										

		recommended for patients $\geq 24$ months old.
<b>5. <u>GROUP A</u></b> Does the patient have the CLD (chronic lung disease) ICD9 7485x or 7486x <b>and</b> in the past 6 months has required medical treatment with at least one of the following: a. bronchodilators b. chronic corticosteroid therapy c. home oxygen therapy d. diuretics	<b>Yes:</b> Go to #12	<b>No:</b> Go to #6
<b>6. <u>GROUP B</u></b> Does the patient have hemodynamically significant congenital heart disease (CHD) ICD9 746xx or 747xx <b>and</b> at least one of the following: a. Receiving treatment for congestive heart failure <b>or</b> b. Have moderate to severe pulmonary hypertension <b>or</b> c. Cyanotic heart disease	<b>Yes:</b> Go to #12	<b>No:</b> Go to #7
<b>7.</b> Will the patient be < 12 months at start of RSV season?	<b>Yes:</b> Go to #8	<b>No:</b> Pass to RPH: DENY (Medical Appropriateness).
<b>8. <u>GROUP C</u></b> Is the gestational age $\leq 28$ weeks?	<b>Yes:</b> Go to #12	<b>No:</b> Go to #9
<b>9. <u>GROUP D</u></b> Infants with congenital abnormalities of the airway or neuromuscular disease compromising handling of secretions?	<b>Yes:</b> Go to #12	<b>No:</b> Go to #10
<b>10. <u>GROUP E</u></b> Will the patient be < 6 months at the start of the RSV season and the gestational age $\leq 29$ -31 weeks and 6 days?	<b>Yes:</b> Go to #12	<b>No:</b> Go to #11
<b>11. <u>GROUP F</u></b> Will the patient be < 90 days at the start of the RSV season AND have a gestational age of $\leq 32$ -34 weeks and 6 days AND have at least one of the following risk factors: a. Daycare attendance b. Siblings less than 5 years of age	<b>Yes:</b> Go to #12	<b>No:</b> Pass to RPH: DENY (Medical Appropriateness).
<b>12.</b> Is the request for more than 5 doses within the same RSV season or for dosing <28 days apart?	<b>Yes:</b> Pass to RPH: DENY (Medical Appropriateness). Prophylaxis is indicated for 5 months maximum and doses should be	<b>No:</b> Go to #13

	administered $\geq 28$ days apart.  <b>May approve for the following on a case by case basis:</b> <b>a. &gt; 5 doses.</b> <b>b. Prophylaxis for a second/subsequent RSV season.</b>	
13. Has the patient had a weight taken within the last 30 days?	<b>Yes:</b> Document weight and date and go to #14  Weight: _____ Date: _____	<b>No:</b> Pass to RPH: obtain recent weight so accurate dose can be calculated.
14. Approve palivizumab for a dose of 15mg/kg. Document number of doses received in hospital and total number approved according to <b>BIRTH DATE</b> and <b>GROUP</b> based on start of RSV season:  <ul style="list-style-type: none"> <li>- Immunoprophylaxis between <u>November - March</u> refer to <b>Table 1</b></li> <li>- Immunoprophylaxis starting in <u>October</u> based on above (#3) refer to <b>Table 2</b></li> </ul> Total number of doses approved for RSV season: _____  Number of doses received in the hospital: _____		

**Table 1.** Maximum number of doses to approve for RSV prophylaxis (Based on Criteria Group from Above) – Beginning **NOVEMBER 1st**

MONTH OF BIRTH	GROUP A-D (Child is <24 or <12 mo. old at start of season)	GROUP E (Child is <6 mo. old at start of season)	GROUP F (Child is <3 mo. old at start of season)
November 1 – March 31 of previous RSV season	5	Zero doses; infant will be older than 6 months at start of RSV season	Zero doses; infant will be older than 90 days at start of RSV season
April	5	Zero doses; infant will be older than 6 months at start of RSV season	
May	5	5	
June	5	5	

Author: Kathy Sentena, Pharm.D.

July	5	5	
August	5	5	1*
September	5	5	2*
October	5	5	3*
November	5	5	3*
December	4	4	3*
January	3	3	3*
February	2	2	2*
March	1	1	1*

\* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

**Table 2.** Maximum number of doses to approve for RSV prophylaxis (Based on Criteria Group from Above) – Beginning **OCTOBER 1-31**

<b>MONTH OF BIRTH</b>	<b>GROUP A-D</b> (Child is <24 or <12 mo. old at start of season)	<b>GROUP E</b> (Child is <6 mo. old at start of season)	<b>GROUP F</b> (Child is <3 mo. old at start of season)
November 1 – March 31 of previous RSV season	5	Zero doses; infant will be older than 6 months at start of RSV season	Zero doses; infant will be older than 90 days at start of RSV season
April	5	5	
May	5	5	
June	5	5	
July	5	5	
August	5	5	1*
September	5	5	2*
October	5	5	3*
November	5	5	3*
December	4	4	3*
January	3	3	3*
February	2	2	2*
March	1	1	1*

\* Infant may require less doses than listed based on age at the time of discharge from the hospital. Subtract number of doses given in hospital from total number of approved doses.

**Notes:**

- Dose: 15 mg/kg via intramuscular injection once monthly throughout RSV season.
- The start date for Synagis is November 1 each year (or sooner when the Oregon Public Health Division has determined that RSV season onset has occurred) for a total of up to five doses.
- Approval for more than five doses or additional doses after March 31 is considered on a case-by-case basis. Results from clinical trials indicate that Synagis trough concentrations greater than 30 days after the 5<sup>th</sup> dose will be well above the protective concentration therefore five doses will provide more than 20 weeks of protection.

*DUR Board Action: 05/17/11 (DO/KK), 5/26/12 (KS)*

*Revision(s): 3/30/12 (KS)*

*Initiated:*

Author: Kathy Sentena, Pharm.D.

## Class Update: Parkinson's Drugs

**Month/Year of Review:** September 2014

**PDL Class:** Parkinson's Drugs

**Literature Search End Date:** July 2014

**Date of Last Review:** September 2013

**Source Document:** OSU College of Pharmacy

Current Preferred Agents	Current Non-Preferred Agents
<b>Anticholinergics</b>	
Beztropine tablets	
Trihexyphenidyl tablets/exlir	
<b>COMT* Inhibitors</b>	
Entacapone tablets	Tolcapone (Tamsar®) tablets
<b>Dopaminergic Agents</b>	
Carbidopa/Levodopa tablets	
Carbidopa/Levodopa ER tablets	
<b>Dopamine Agonists</b>	
Amantadine capsules/syrup/tablets	Bromocriptine (Parlodel®) tablets/capsules
Pramipexole DI-HCL tablets	Ropinirole (Requip®) IR and XL tablets
	Neupro transdermal
<b>MAO- B** Inhibitors</b>	
Selegiline capsules	Rasagiline (Azilect®) tablets
<b>Combination Product</b>	
Carbidopa/Levodopa/Entacapone	

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

### Previous Conclusions and Recommendations:

- Evidence does not support a difference in efficacy or effectiveness.
- Make tolcapone non-preferred due to reported liver toxicity
- Make carbidopa/levodopa ER preferred on PDL.
- There is insufficient evidence that rotigotine is more efficacious or safer than other oral dopamine agonists in the treatment of PD. It may be a reasonable option for patients with difficulty swallowing that may be addressed by use of the patch. Make rotigotine transdermal (Neupro) non-preferred on the PDL.

**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 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.

**New Systematic Reviews:**

None

**Guidelines:**

None

**New drugs:**

None

**New FDA Indications:**

None

**New FDA safety alerts:**

None

**New Trials:**

A total of 61 citations resulted from initial literature search. After inclusion for further review, 10 were evaluated further and 5 potentially relevant comparative randomized trials were identified through abstract review for appropriate medication, indication, study design, and outcomes (**Appendix 2**). These trials are briefly described in Tablet 1.

Table 1: Potential Relevant New Trials

Study	Comparison	Population	Primary Outcome	Results
Schapira AH et al. <sup>1</sup> , 2013	Pramipexole (1.5mg/day; N = 261) vs. placebo (N = 274); then at 6 or 9 months placebo group was given pramipexole.	PD diagnosed within 2 years at time of enrollment and aged 30 to 79 years.	15-month change from baseline in total score on Unified Parkinson's Disease Rating Scale (UPDRS).	At 15 months (n=411), adjusted mean change in UPDRS total score showed no significant difference between early and delayed pramipexole (-0.4 points, 95% CI -2.2 to 1.4, p=0.65).
Mizuno Y, et al. <sup>2</sup> , 2013	Rotigotine patch (N = 82) vs. placebo (N = 90).	Early stage PD patients in Japan.	The change in UPDRS part II (activity of daily living) and part III (motor function) scores from baseline to the end of treatment (12 weeks)	The mean ( $\pm$ standard deviation) changes in UPDRS part II and III scores were $-8.4 \pm 9.7$ in the rotigotine group and $-4.1 \pm 8.2$ in the placebo group and were significantly different ( $P = 0.002$ ).
Ory-Magne F, et al. <sup>3</sup> , 2014	Wash-out study comparing continuation of amantadine (N = 27) vs. discontinuation of	Dyskinetic patients with PD on amantadine at least	The change from baseline in a UPDRS dyskinesia subscore (item 32 [duration] + 33 [severity]).	UPDRS items 32 + 33 deteriorated more in patients switched to placebo ("discontinuing" group) ( $+1.7 \pm 2.0$ units; 95% confidence interval 0.9, 2.4) as compared with those maintained on



	amantadine (N = 29).	200mg/day for at least 6 months.		amantadine ("continuing" group) (+0.2 ± 1.5 units; 95% confidence interval - 0.4, 0.8; p = 0.003).
Zhang L, et al. <sup>4</sup> , 2013	Rosagiline (1mg/day; N = 119) as adjunctive therapy to levodopa vs. placebo (N = 125).	PD patients with motor fluctuations in China.	The changes in "On" and "Off" time while awake between baseline and the week 12 visit using patient diary score cards.	The primary efficacy variable--mean adjusted total daily off time--decreased from baseline by 1.7 h in patients treated with 1.0 mg/d rasagiline compared to placebo (p < 0.05).
Zhang Z, et al. <sup>5</sup> , 2013	Ropinirole XL (N = 175) as add-on therapy to Levodopa vs. placebo (N = 170).	Advanced PD not optimally controlled with Levodopa in China.	The change from baseline in awake time spent "Off" at week 24.	Subjects receiving ropinirole XL experienced a significant reduction of "off" time (2.1 h) compared with placebo (0.4 h); mean change of -1.7hr (95% CI: -2.27, -0.26; p < 0.001).

## **References:**

1. Schapira AHV, McDermott MP, Barone P, et al. Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial. *Lancet Neurol.* 2013;12(8):747-755. doi:10.1016/S1474-4422(13)70117-0.
2. Mizuno Y, Nomoto M, Kondo T, et al. Transdermal rotigotine in early stage Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Mov Disord.* 2013;28(10):1447-1450. doi:10.1002/mds.25537.
3. Ory-Magne F, Corvol J-C, Azulay J-P, et al. Withdrawing amantadine in dyskinetic patients with Parkinson disease: the AMANDYSK trial. *Neurology.* 2014;82(4):300-307. doi:10.1212/WNL.000000000000050.
4. Zhang L, Zhang Z, Chen Y, et al. Efficacy and safety of rasagiline as an adjunct to levodopa treatment in Chinese patients with Parkinson's disease: a randomized, double-blind, parallel-controlled, multi-centre trial. *Int J Neuropsychopharmacol.* 2013;16(7):1529-1537. doi:10.1017/S1461145713000175.
5. Zhang Z, Wang J, Zhang X, et al. The efficacy and safety of ropinirole prolonged release tablets as adjunctive therapy in Chinese subjects with advanced Parkinson's disease: a multicenter, double-blind, randomized, placebo-controlled study. *Parkinsonism Relat Disord.* 2013;19(11):1022-1026. doi:10.1016/j.parkreldis.2013.07.009.

## 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

**Covered Alternatives:**

Preferred alternatives listed at [www.orpd.org](http://www.orpd.org)

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis Parkinson's disease or another chronic neurological condition?	<b>Yes:</b> Go to #5.	<b>No:</b> Go to #3
3. Is the diagnosis Restless Leg Syndrome (ICD9-333.94)?  *Baseline therapy is defined as being on $\geq 1$ stable dose of an anti-epileptic(s) drug for at least 4 weeks.	<b>Yes:</b> Pass to RPH; Deny, (Not covered by OHP)	<b>No:</b> 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	<b>Above:</b> Go to #5	<b>Below:</b> Deny, (Not covered by the OHP)
5. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> <li>• Preferred products do not require PA</li> <li>• Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&amp;T) Committee.</li> </ul>	<b>Yes:</b> Inform provider of covered alternatives in class.	<b>No:</b> 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: Randomized Clinical Trials

1. Schapira AHV, McDermott MP, Barone P, et al. Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial. *Lancet Neurol.* 2013;12(8):747-755.

### Abstract

**Background:** In models of dopaminergic neuronal loss, the dopamine agonist pramipexole has exhibited neuroprotective properties. The Pramipexole On Underlying Disease (PROUD) study was designed to identify whether early versus delayed pramipexole initiation has clinical and neuroimaging benefits in patients with Parkinson's disease (PD).

**Methods:** Between May 24, 2006, and April 22, 2009, at 98 centres, we recruited patients with PD diagnosed within 2 years and aged 30-79 years. We randomly assigned eligible patients (ratio 1:1), by a centralised, computerised randomisation schedule, to receive double-blind either placebo or pramipexole (1.5 mg a day) and followed them up for 15 months. At 9 months, or as early as 6 months if considered necessary, placebo recipients were assigned to pramipexole. In a neuroimaging substudy, striatal dopamine-transporter binding was assessed by SPECT. All patients, investigators, and independent raters were masked to study treatment. The primary endpoint was the 15-month change from baseline in total score on the unified Parkinson's disease rating scale (UPDRS).

**Findings:** Of 535 patients, 261 were randomly assigned to receive pramipexole and 274 to receive placebo. At 15 months (n=411), adjusted mean change in UPDRS total score showed no significant difference between early and delayed pramipexole (-0.4 points, 95% CI -2.2 to 1.4, p=0.65). 62 patients in the early pramipexole group and 61 patients in the delayed pramipexole group were included in the neuroimaging substudy, for which the adjusted mean 15-month change in striatal (123)I-FP-CIT binding was -15.1% (SE 2.1) for early and -14.6% (2.0) for delayed pramipexole (difference -0.5 percentage points, 95% CI -5.4 to 4.4, p=0.84). Overall, 180 (81%) of patients given early pramipexole and 179 (84%) patients given delayed pramipexole reported adverse events (most frequently nausea), and 22 (10%) patients in the early pramipexole group and 17 (8%) in the delayed pramipexole group had serious events, two of which (hallucinations and orthostatic hypotension) were deemed related to study drug.

**Interpretation:** By clinical and neuroimaging measures, pramipexole showed little evidence differentiating 15-month usage from usage delayed for 6-9 months. The results do not support the hypothesis that pramipexole has disease-modifying effects.

2. Mizuno Y, Nomoto M, Kondo T, et al. Transdermal rotigotine in early stage Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Mov Disord.* 2013;28(10):1447-1450.

### Abstract

**Background:** We conducted a randomized, double-blind, placebo-controlled trial to determine the safety and efficacy of transdermal rotigotine at doses up to 16 mg/24 hours in patients with early stage Parkinson's disease (PD) in Japan.

**Methods:** Patients received once-daily rotigotine 2 to 16 mg/24 hours (mean dose, 12.8 mg/24 hours; n = 82) or placebo (n = 90) for 12 weeks. The primary endpoint was the change in Unified Parkinson's Disease Rating Scale (UPDRS) part II (activities of daily living) and part III (motor function) scores from baseline to the end of treatment.

**Results:** The mean ( $\pm$  standard deviation) changes in UPDRS part II and III scores were  $-8.4 \pm 9.7$  in the rotigotine group and  $-4.1 \pm 8.2$  in the placebo group and were significantly different ( $P = 0.002$ ). More patients in the rotigotine group than in the placebo group had a  $\geq 20\%$  score reduction. No serious drug-related adverse events were reported.

**Conclusions:** Rotigotine at doses up to 16 mg/24 hours was well tolerated and improved function in patients with early stage PD.

3. Ory-Magne F, Corvol J-C, Azulay J-P, et al. Withdrawing amantadine in dyskinetic patients with Parkinson disease: the AMANDYSK trial. *Neurology.* 2014;82(4):300-307.

## Abstract

**Objective:** The AMANDYSK trial was designed to assess long-term efficacy of chronic treatment with amantadine in patients with Parkinson disease (PD) and levodopa-induced dyskinesia (LID).

**Methods:** This was a 3-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group, wash-out study conducted in 57 amantadine-treated ( $\geq 200$  mg/d for  $\geq 6$  months) dyskinetic patients with PD. The primary outcome measure was the change from baseline in a Unified Parkinson's Disease Rating Scale (UPDRS) dyskinesia subscore (items 32 [duration] + 33 [severity]). Secondary outcomes included other LID measurements ("responders" analysis, premature dropout for LID, Abnormal Involuntary Movement Scale). Exploratory outcomes included time with troublesome dyskinesia as measured by diaries, UPDRS Motor Examination (part III) for motor symptoms of PD, and fatigue and apathy scores for nonmotor symptoms.

**Results:** UPDRS items 32 + 33 deteriorated more in patients switched to placebo ("discontinuing" group) ( $+1.7 \pm 2.0$  units; 95% confidence interval 0.9, 2.4) as compared with those maintained on amantadine ("continuing" group) ( $+0.2 \pm 1.5$  units; 95% confidence interval -0.4, 0.8;  $p = 0.003$ ). Secondary outcomes confirmed this difference because there were significantly more responders, more dropouts for LID, greater increase in "ON" time with troublesome dyskinesia, and greater worsening of Abnormal Involuntary Movement Scale score in the discontinuing group. There were no between-group differences in the UPDRS Motor Examination, whereas apathy (as measured by caregivers) and fatigue scores tended to worsen more in patients randomized to placebo.

**Conclusion:** Wash-out of amantadine in dyskinetic patients with PD significantly worsened LID. No significant effect was observed on motor parkinsonian symptoms, while exploratory outcomes suggested that amantadine might improve apathy and fatigue in such patients.

**Classification of evidence:** This article provides Class II evidence that in patients with PD, withdrawing amantadine significantly aggravates LID in a median time of 7 days.

4. Zhang L, Zhang Z, Chen Y, et al. Efficacy and safety of rasagiline as an adjunct to levodopa treatment in Chinese patients with Parkinson's disease: a randomized, double-blind, parallel-controlled, multi-centre trial. *Int J Neuropsychopharmacol*. 2013;16(7):1529-1537.

## Abstract

Rasagiline mesylate is a highly potent, selective and irreversible monoamine oxidase type B (MAOB) inhibitor and is effective as monotherapy or adjunct to levodopa for patients with Parkinson's disease (PD). However, few studies have evaluated the efficacy and safety of rasagiline in the Chinese population. This study was designed to investigate the safety and efficacy of rasagiline as adjunctive therapy to levodopa treatment in Chinese PD patients. This was a randomized, double-blind, placebo-controlled, parallel-group, multi-centre trial conducted over a 12-wk period that enrolled 244 PD patients with motor fluctuations. Participants were randomly assigned to oral rasagiline mesylate (1 mg) or placebo, once daily. Altogether, 219 patients completed the trial. Rasagiline showed significantly greater efficacy compared with placebo. During the treatment period, the primary efficacy variable--mean adjusted total daily off time--decreased from baseline by 1.7 h in patients treated with 1.0 mg/d rasagiline compared to placebo ( $p < 0.05$ ). Scores using the Unified Parkinson's Disease Rating Scale also improved during rasagiline treatment. Rasagiline was well tolerated. This study demonstrated that rasagiline mesylate is effective and well tolerated as an adjunct to levodopa treatment in Chinese PD patients with fluctuations.

5. Zhang Z, Wang J, Zhang X, et al. The efficacy and safety of ropinirole prolonged release tablets as adjunctive therapy in Chinese subjects with advanced Parkinson's disease: a multicenter, double-blind, randomized, placebo-controlled study. *Parkinsonism Relat Disord*. 2013;19(11):1022-1026.

## Abstract

**Aim:** The first evaluation of the efficacy and safety of ropinirole prolonged release (PR) as an adjunct to L-dopa in Chinese patients with advanced Parkinson's disease (PD) not optimally controlled with L-dopa.

**Methods:** In a 24-week, double-blind, placebo-controlled, parallel-group study, subjects with advanced PD were randomized 1:1 to ropinirole PR (N = 175) or placebo (N = 170) as add-on therapy to L-dopa. Primary outcome measure was change from baseline in awake time spent "off". Starting dose of ropinirole PR was 2 mg/day, titrated based on clinical response (maximum 24 mg/day).

**Results:** At week 24, the mean dose of ropinirole PR was 11.4 mg/day with a mean reduction of L-dopa from 506.6 to 411.6 mg/day. Subjects receiving ropinirole PR experienced a significant reduction of "off" time (2.1 h) compared with placebo (0.4 h). Secondary outcome measures including hours of "on" time without troublesome dyskinesia were significantly increased in the ropinirole PR group (1.7 h) compared with placebo (0.3 h). Subjects classified as responders were significantly more frequent in the ropinirole PR (22.8%) than placebo group (2.5%). Efficacy outcomes including Unified Parkinson's disease Rating Scale and PDQ-39 subscales of mobility were significantly improved in the ropinirole PR versus placebo group. The most frequent adverse event experienced in the ropinirole PR group was dyskinesia.

**Conclusions:** This study demonstrated for the first time in Chinese subjects that ropinirole PR improved Parkinson's disease symptoms, permitting a reduction in L-dopa dose. The adverse events observed were consistent with the established safety profile of ropinirole, with no new safety signal identified.

## Class Update: Growth Hormones

**Month/Year of Review:** September 2014

**PDL Class:** Growth Hormones

**Literature Search End Date:** August 2014

**Date of Last Review:** September 2013

**Source Document:** OSU College of Pharmacy

### Current Status of PDL Class:

- Preferred Agents: SOMATROPIN (OMNITROPE®) CARTRIDGE, SOMATROPIN (SAIZEN®) CARTRIDGE & VIAL, SOMATROPIN (NORDITROPIN®)
- Non-Preferred Agents: SOMATROPIN (GENOTROPIN® MINIQUICK) VIAL, SOMATROPIN (GENOTROPIN®) VIAL, SOMATROPIN (HUMATROPE®), SOMATROPIN (NUTROPIN® AQ NUSPIN), SOMATROPIN (OMNITROPE) VIAL, SOMATROPIN (TEV-TROPIN®)

### Previous Conclusions and Recommendations:

- There is no comparative evidence that there is a difference in efficacy or safety between somatropin products.
- 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.

### Recommendations:

- No further research or review needed at this time. There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin products and formulations.
- Evaluate Comparative costs in executive session.

### Methods:

A PubMed search was conducted using 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 randomized controlled trials, systematic review and meta-analysis, English language, and conducted in humans since the date of the literature search conducted from the previous P & T review to first week of August 2014. 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.



**New Systematic Reviews:**

Since last review there was one systematic review<sup>1</sup> and one meta-analysis<sup>2</sup> that investigated the role of growth hormones (GH) in adults. Neither suggests changes and need to the GH coverage policy. Abstracts are available in Appendix 2.

**Guidelines:**

None

**New drugs:**

None

**New FDA Indications:**

None

**New FDA safety alerts:**

None

There has been growing concern about an increased cardiac and cerebrovascular risk in children treated with growth hormone. A recently published cohort study evaluated for stroke in a population-based cohort of patients in France treated with GH for short stature in childhood.<sup>3</sup> There was a significantly higher risk of stroke among patients treated with GH in childhood, most prominently hemorrhagic stroke. Further RCTs are needed to assess this plausible relationship.

**New Trials:**

A total of 45 citations resulted from initial literature search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After inclusion for further review, 7 were evaluated further and 3 potentially relevant comparative randomized trials<sup>4,5</sup> were identified through abstract review for appropriate medication, indication, study design, and outcomes (**Appendix 2**). The abstracts for these trials are in Appendix 2.

## **References:**

1. Gazzaruso C, Gola M, Karamouzis I, Giubbini R, Giustina A. Cardiovascular risk in adult patients with growth hormone (GH) deficiency and following substitution with GH--an update. *J Clin Endocrinol Metab.* 2014;99(1):18-29. doi:10.1210/jc.2013-2394.
2. Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. *J Clin Endocrinol Metab.* 2014;99(3):852-860. doi:10.1210/jc.2013-3921.
3. Poidvin A, Touzé E, Ecosse E, et al. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. *Neurology.* 2014;10.1212/WNL.0000000000000737. doi:10.1212/WNL.0000000000000737.
4. Blum WF, Ross JL, Zimmermann AG, et al. GH treatment to final height produces similar height gains in patients with SHOX deficiency and Turner syndrome: results of a multicenter trial. *J Clin Endocrinol Metab.* 2013;98(8):E1383-1392. doi:10.1210/jc.2013-1222.
5. Reus L, Pelzer BJ, Otten BJ, et al. Growth hormone combined with child-specific motor training improves motor development in infants with Prader-Willi syndrome: a randomized controlled trial. *Res Dev Disabil.* 2013;34(10):3092-3103. doi:10.1016/j.ridd.2013.05.043.

**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: [www.orpd.org](http://www.orpd.org)

**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)?	<b>Yes:</b> Pass to RPH; Deny, (Not Covered by the OHP).	<b>No:</b> Go to #2.
2. Is this a request for initiation of growth hormone?	<b>Yes:</b> Go to question #3	<b>No:</b> Go to renewal therapy
3. Is the prescriber a pediatric endocrinologist or pediatric nephrologist?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPH; Deny, (Medical Appropriateness)
4. Is the diagnosis promotion of growth delay in a child with 3 <sup>rd</sup> degree burns (ICD-9 codes 941.3-949.3)?	Yes: Document and send to DHS Medical Director for review and pending approval	<b>No:</b> Go to #5.
5. Is the diagnosis one of the following? <ul style="list-style-type: none"> <li>• Turner's Syndrome (758.6)</li> <li>• Noonan Syndrome (759.89)</li> <li>• Pre-transplant chronic renal insufficiency (CRI) (593.9)</li> <li>• Prader - Willi Syndrome(PWS) (759.81)</li> </ul>	<b>Yes:</b> Document and go to #6	<b>No:</b> Pass to RPH; Deny, (Not Covered by the OHP).

<ul style="list-style-type: none"> <li>• Neonatal Hypoglycemia associated with Growth Hormone Deficiency (775.6)</li> <li>• X-linked Hypophosphotemia</li> <li>• Pituitary Dwarfism (253.3)</li> <li>• SHOX (Short stature homeobox gene)(783.43)</li> </ul>		
6. If male, is bone age <16 years? If female, is bone age <14 years?	<b>Yes:</b> Go to #7.	<b>No:</b> Pass to RPH; Deny, (Medical Appropriateness)
7. Is there evidence of non-closure of epiphyseal plate?	<b>Yes:</b> Go to #8.	<b>No:</b> Pass to RPH; Deny, (Medical Appropriateness)
8. Is the product requested preferred?	<b>Yes:</b> Approve for 1 year.	<b>No:</b> Go to #9.
9. Will the prescriber consider a change to a preferred product?  <b>Message:</b> <ul style="list-style-type: none"> <li>• Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at:  <a href="http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml">http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml</a>.</li> </ul>	<b>Yes:</b> Inform provider of covered alternatives in class. <a href="http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml">http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml</a> . Approve for 1 year.	<b>No:</b> Approve for 1 year.
<b>Pediatric Approval Criteria (&lt;18 years old) – Renewal Therapy</b>		
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?	<b>Yes:</b> Go to #3.	<b>No:</b> Pass to RPH; Deny, (Medical Appropriateness)
3. Is male bone age <16 years and Is female bone age <14 years?	<b>Yes:</b> Approve for 1 year.	<b>No:</b> 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: Abstract of Systematic Reviews and Randomized Clinical Trials

1. Gazzaruso C, Gola M, Karamouzis I, Giubbini R, Giustina A. Cardiovascular risk in adult patients with growth hormone (GH) deficiency and following substitution with GH--an update. *J Clin Endocrinol Metab.* 2014;99(1):18-29.

### Abstract

**Context:** GH deficiency (GHD) of the adult is a clinical condition characterized by the presence of several traditional and emerging cardiovascular risk factors that can significantly increase cardiovascular morbidity and mortality. It is still an open issue whether GH replacement is able not only to improve cardiovascular risk factors but also to decrease cardiovascular morbidity and mortality.

**Evidence acquisition:** The major source of data acquisition included PubMed research strategies. Original articles, systematic reviews and meta-analyses, and included relevant citations were screened.

**Evidence synthesis:** In untreated GHD, cardiovascular risk is increased due to abnormal lipid profile (increased total and low-density lipoprotein cholesterol, increased triglycerides, and reduced high-density lipoprotein cholesterol) and impaired glucose metabolism. Emerging cardiovascular risk factors/markers such as proinflammatory cytokines, C-reactive protein, and adipokines are also increased in GHD patients. Increased cardiovascular morbidity and mortality have also been reported in GHD. GH treatment has been shown to improve both traditional and emerging cardiovascular risk factors and markers. However, evidence on the effects of GH replacement on cardiovascular events and mortality is limited.

**Conclusion:** The GHD population may be considered at high cardiovascular risk, and GH substitution may be expected to bring an added value to patients with hypopituitarism in terms of cardiovascular protection. However, there is too limited evidence (rarely coming from randomized and controlled studies) to recommend GH treatment based on the cardiovascular status of the patients.

2. Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. *J Clin Endocrinol Metab.* 2014;99(3):852-860.

### Abstract

**Objective:** GH deficiency is associated with decreased bone mineral density (BMD) and increased fracture risk. Because the effects of recombinant human GH (rhGH) therapy on BMD and bone mineral content have not been systematically investigated, we conducted a meta-analysis of pertinent studies.

**Design:** A thorough search of the literature (MEDLINE, EMBASE, and the Cochrane Register) was performed. Relevant studies were divided and analyzed according to their design (randomized/controlled or prospective/retrospective) and duration of rhGH therapy ( $\leq 12$  months and  $> 12$  months).

**Results:** Administration of rhGH led to a significant increase in lumbar spine (LS) and femoral neck (FN) BMD in randomized/controlled studies of more than 1 year [weighted mean difference (95% confidence interval)] of 0.038 g/cm<sup>2</sup> (0.011-0.065) and 0.021 g/cm<sup>2</sup> (0.006-0.037) at the LS and FN, respectively, and a nonsignificant drop at the same sites in studies of shorter duration. In prospective studies, a significant increase in the LS and FN BMD was obtained. On meta-regression, a negative association was observed between the change in LS and FN BMD and subjects' age and a positive association between the BMD change and treatment duration. In a subgroup analysis, the increase in LS and FN BMD was significant in men [0.048 g/cm<sup>2</sup> (0.033-0.064) and 0.051 g/cm<sup>2</sup> (0.003-0.098), respectively] but not in women.

**Conclusion:** This meta-analysis suggests a beneficial effect of rhGH replacement on BMD in adults with GH deficiency. This effect is affected by gender, age, and treatment duration. Larger studies are needed to evaluate the effect of rhGH on fracture risk.

3. Reus L, Pelzer BJ, Otten BJ, et al. Growth hormone combined with child-specific motor training improves motor development in infants with Prader-Willi syndrome: a randomized controlled trial. *Res Dev Disabil.* 2013;34(10):3092-3103.

## Abstract

Although severe motor problems in infants with Prader-Willi syndrome (PWS) are striking, motor development has never been studied longitudinally and the results of growth hormone (GH) treatment on motor development are contradictory. The authors studied whether GH treatment can enhance the effect of physical training on motor development in infants with PWS. Twenty-two infants were followed for two years during a randomized controlled trial. The treatment and control groups began GH after baseline or following a control period, respectively. Both groups followed a child-specific physical training program. Motor performance was measured every three months. Multi-level regression analysis revealed that motor development differed significantly between infants ( $p < .001$ ), and this could be partially explained by baseline motor developmental level ( $p < .01$ ). GH treatment enhanced the effects of child-specific physical training on both motor developmental rate and motor developmental potential. Moreover, this effect was more pronounced when GH treatment was initiated at a younger age.

4. Blum WF, Ross JL, Zimmermann AG, et al. GH treatment to final height produces similar height gains in patients with SHOX deficiency and Turner syndrome: results of a multicenter trial. *J Clin Endocrinol Metab.* 2013;98(8):E1383-1392.

## Abstract

**Context:** Growth impairment in short stature homeobox-containing gene (SHOX) deficiency and Turner syndrome share a similar etiology. Because of the established effect of GH treatment on height in patients with Turner syndrome, we hypothesized that GH therapy would also stimulate growth in patients with SHOX deficiency.

**Objective:** Our objectives were to evaluate long-term efficacy of GH treatment in short patients with SHOX deficiency and to compare the effect on final (adult) height (FH) in patients with SHOX deficiency and Turner syndrome.

**Design and setting:** A prospective, multinational, open-label, randomized 3-arm study consisting of a 2-year control period and a subsequent extension period to FH. The treatment groups were 1) SHOX-D-C/GH (untreated during the control period, GH-treated during the extension), 2) SHOX-D-GH/GH, and 3) Turner-GH/GH (GH-treated during both study periods).

**Patients:** Short-statured prepubertal patients with genetically confirmed SHOX deficiency ( $n = 49$ ) or Turner syndrome ( $n = 24$ ) who participated in the extension.

**Intervention:** Depending on the study arm, patients received a daily sc injection of 0.05 mg/kg recombinant human GH from start of the study or start of the extension until attainment of FH or study closure.

**Results:** Height SD score gain from start of GH treatment to FH was similar between the combined SHOX-deficient groups ( $n = 28$ ,  $1.34 \pm 0.18$  [least-squares mean  $\pm$  SE]) and the Turner group ( $n = 19$ ,  $1.32 \pm 0.22$ ). In this FH population, 57% of the patients with SHOX deficiency and 32% of the patients with Turner syndrome achieved a FH greater than  $-2$  SD score.

**Conclusions:** GH treatment in short children with SHOX deficiency showed similar long-term efficacy as seen in girls with Turner syndrome.

**Month/Year of Review:** September 2014

**PDL Classes:** Insulin

**Date of Last Review:** May 2010

**Source Document:** Provider Synergies

#### **Current Status of PDL Class:**

- Preferred Agents: HUM INSULIN NPH/REG INSULIN HM VIAL, HUM INSULIN NPH/REG INSULIN HM INSULN PEN (PA required), INSULIN ASPART VIAL, INSULIN ASPART CARTRIDGE (PA required), INSULIN ASPART INSULN PEN (PA required), INSULIN GLARGINE (LANTUS®) VIAL, INSULIN GLARGINE (LANTUS®) INSULN PEN (PA required), INSULIN LISPRO VIAL, INSULIN LISPRO CARTRIDGE (PA required), INSULIN NPL/INSULIN LISPRO VIAL, INSULIN REGULAR, HUMAN VIAL, INSULIN ZINC HUMAN REC VIAL, INSULN ASP PRT/INSULIN ASPART VIAL, INSULN ASP PRT/INSULIN ASPART INSULN PEN (PA required), NPH, HUMAN INSULIN ISOPHANE VIAL , NPH, HUMAN INSULIN ISOPHANE INSULIN PEN (PA required)
- Non-Preferred Agents: INSULIN DETEMIR VIAL AND PEN (LEVEMIR), INSULIN GLULISINE VIAL AND PEN (APIDRA, APIDRA SOLOSTAR), INSULIN LISPRO PEN, INSULIN NPL/INSULIN LISPRO PEN, INSULIN NPH PEN, HUM INSULIN NPH/REG INSULIN CARTRIDGE

**PA criteria:** Prior authorization criteria is currently in place for insulin to ensure appropriate drug use and safety of hypoglycemic agents by authorizing utilization in specific patient population (Appendix 1).

#### **Previous Conclusions and Recommendation:**

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Recommend inclusion of at least one agent from each subgroup:
  - Short acting
  - Rapid acting
  - Rapid/intermediate acting combination products
  - Intermediate acting
  - Long acting
- Clinical criteria to approve insulin pens/cartridges

#### **Conclusions and Recommendations:**

- There is low quality evidence of no significant differences in change in HbA1C or overall and severe hypoglycemia between insulin detemir and insulin glargine and high quality evidence that insulin detemir is associated with less weight gain and low quality evidence of more injection site reactions compared to insulin glargine.<sup>1</sup> With no clinically relevant difference in efficacy or safety of the two long acting agents, evaluate comparative costs.
- There is no significant new comparative evidence on the efficacy and safety of other agents on the PDL.
- Bring back full review of inhaled insulin (Afrezza®) once available on the market.
- Continue to include at least one agent from each subgroup (short acting, rapid acting, etc.) as preferred on the PDL and evaluate comparative costs in executive session.

#### **Methods:**

A Medline OVID search was conducted with the following search terms: NPH insulin, regular insulin, human insulin, insulin aspart, insulin lispro, insulin glargine, insulin glulisine, insulin detemir, insulin isophane, short acting insulin, long acting insulin, rapid acting insulin, diabetes, diabetes mellitus, insulin dependent diabetes, diabetes type 1, diabetes

type 2, and gestational diabetes. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to April week two 2014.

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:**

Rys et al. conducted a systematic review and meta-analysis to compare the efficacy of insulin aspart and regular human insulin in diabetic patients. Randomized controlled trials with either type 1 or 2 diabetics were eligible; individual trial duration was 4 weeks or longer for inclusion. A total of 28 trials were included; ten trials focused on type 2 diabetes, 17 on type 1 diabetes, and one study included both. The proposed primary endpoints for the analysis were morbidity and mortality; however, the authors were unable to find any trials with these types of outcomes. Instead, secondary outcomes were used such as change in glucose levels (measured by A1c, fasting glucose, or post-prandial glucose), weight loss, and quality of life from baseline. For type 1 diabetes, patients on insulin aspart experienced a significantly greater average decrease in A1c from baseline than the human insulin cohort (mean difference in change from baseline -0.11%; 95% CI: -0.16 to -0.06; N=13, n=4263). When looking at other outcomes for type 1 diabetics they found statistically significant differences in favor of treatment with insulin aspart for postprandial glucose (PPG) after breakfast (mean difference -1.43 mmol/L; 95% CI -1.75 to -1.11; N=5, n=2820), lunch (-1.11 mmol/L; 95% CI -1.61 to -0.61; N=5, n=2712) and (-0.97 mmol/L; 95% CI -1.25 to -0.69; N=6, n=3138) dinner, but not for fasting glucose (0.15 mmol/L; 95% CI -0.55 to 0.86; N=5, n=2138). For quality of life metrics, the Diabetes Treatment Satisfaction Questionnaire showed greater improvement in perception of treatment flexibility with aspart rather than human insulin (mean difference in change from baseline 0.31; 95% CI: 0.15 to 0.47). No difference was seen in episodes of severe hypoglycemia between treatments in the three studies (n=2358) that tracked the outcome (RR 0.92; 95% CI 0.75 to 1.12). In trials with type 2 diabetics, no difference (-0.4%; 95% CI: -0.10 to 0.03) was seen in change from baseline in A1c between treatments (N=9, n=1274). Mean PPG was significantly lower in the aspart cohort group (mean difference in change from baseline -1.18 mmol/L; 95% CI: -1.88 to -0.47; N=3, n=134). No studies tracking treatment satisfaction or quality of life were identified. No difference was seen between treatments in occurrence of severe hypoglycemia (RR 0.67; 95% CI 0.17 to 2.53; N=2, n=206). Individual trial quality was assessed by looking for the presence of randomization, blinding, allocation concealment, patient withdrawal reporting and rates. The majority of trials were noted to have a lack reporting reasons for withdrawals and random allocation with appropriate randomization. Four trials reported double-blinding, but only one of these was judged as having an adequate blinding method. Overall heterogeneity of data was not analyzed. Trial quality was uniformly poor.<sup>2</sup>

The Cochrane Collaboration performed a systematic review and meta-analysis to evaluate the comparative efficacy of insulin glargine and detemir for treating type 2 diabetes. Four trials (n=2250) were included; individual trial durations were between 24 and 52 weeks. The primary endpoint measured was glycemic control defined as an A1c of  $\leq 7\%$  with or without hypoglycemia. Weight gain and hypoglycemia rates by study end were secondary outcomes. The mean difference in change in A1c from baseline was not significantly different between treatment groups (0.08%; 95% CI -0.1 to 0.27). Insulin glargine was associated with a significantly lower fasting glucose by study end when compared with insulin detemir (mean difference 0.34 mmol/L; 95% CI 0.01 to 0.67). There was no difference between treatments in rates of overall hypoglycemia (RR 1.00; 95% CI 0.90 to 1.11) or severe hypoglycemia (RR 0.88; 95% CI 0.59 to 1.30). Treatment with insulin detemir was associated with less weight gain than glargine (mean difference in weight change -0.91 kg; 95% CI -1.201 to -0.61). Individual study quality was evaluated for randomization, allocation concealment, blinding, selective reporting, incomplete outcome data and other bias. Although randomization and allocation concealment descriptions were found to have a low risk of bias, all other metrics were rated as having an unclear to high rate of bias. The authors deemed the overall quality of data as having a high risk of bias and only weight gain results were graded as being high quality. All other reported results were graded as low quality.<sup>1</sup>



Szypowska et al assessed the comparative efficacy of insulin detemir with neutral protamine Hagedom (NPH) in type 1 diabetics. This systematic review and meta-analysis included ten studies with 3825 patients; trial duration was  $\geq 12$  weeks. The primary endpoint was difference in mean change in A1c at study end from baseline. Secondary outcomes included number of hypoglycemic episodes and weight gain. Patients in the detemir cohort had a significantly greater reduction in A1c compared with NPH (mean difference -0.073; 95% CI -0.135 to -0.011). Detemir patients were less likely to experience hypoglycemia during the day (RR 0.978; 95% CI 0.961 to 0.996) and at night (RR 0.877; 95% CI 0.816 to 0.942). They also had less incidence of severe hypoglycemia (RR 0.665; 95% CI 0.547 to 0.810). Weight gain was also lower for the detemir population compared with the NPH group (mean difference -0.779 kg; 95% CI -0.992 to -0.567). Individual trial quality was tracked by analyzing the study's presence of allocation concealment, blinding, randomization and whether if present these were adequate. No trials were blinded, but the majority of the studies included had adequate randomization and/or allocation concealment. Trial quality was not given a grade or rating, but the authors acknowledged that the individual trial quality was poor overall.<sup>3</sup>

Esposito et al compared the efficacy of insulin lispro protamine suspension with insulin glargine and insulin detemir in patients with type 2 diabetes. This systematic review and meta-analysis included four trials with a total of 1336 subjects; trial duration was between 24 and 36 weeks. The primary outcome of interest was mean difference in change in A1c from baseline to end of treatment. Three studies compared insulin lispro protamine with insulin glargine and one study with insulin detemir. When pooled, no significant difference between insulin lispro protamine versus insulin glargine or detemir was seen in change in A1c (0.0%; 95% CI -0.24 to 0.24%). No difference in treatment groups was seen in the proportion of subjects achieving an A1c  $\leq 7\%$  (RR 0.99; 95% CI 0.87 to 1.12), in weight gain (mean difference 0.223 kg; 95% CI -0.81 to 1.26), or in overall hypoglycemia (mean difference 0.17 events/patient/30 days; 95% CI -0.14 to 0.48) by study's end. Individual trial quality was not assessed.<sup>4</sup>

#### **Guidelines:**

In 2010, the Department of Veteran Affairs and the Department of Defense published updated guidelines regarding the management of diabetes mellitus. These guidelines provided recommendations regarding the use of insulin. Recommendations were graded for the strength of the evidence source. An A grade indicates a strong recommendation that clinicians provide the intervention to patients. It was based on good evidence which showed that benefits substantially outweighed harms. Grade B recommendations were based on fair evidence that showed the benefit outweighed any harms. Grade C interventions are neither recommended nor opposed. Evidence for this grade was judged to be fair and to show some improved outcomes; however benefits and potential harms were judged to be too close to justify an endorsement. Grade D recommendations recommend not performing the intervention and were based of fair evidence showing harms outweigh potential benefits. Finally, grade I recommendations indicate the evidence was insufficient to recommend for or against an intervention. In these instances, a grade I is given when the evidence is poor, conflicting or the balance of benefits and harms cannot be determined.<sup>5</sup>

- Use of insulin therapy should be individualized, and managed by a healthcare team experienced in managing complex insulin therapy for patients with type 1 DM. Grade I recommendation
- Use intermediate- or long-acting insulin to provide basal insulin coverage. Grade B recommendation
- Insulin glargine or detemir may be considered in the NPH insulin-treated patient with frequent or severe nocturnal hypoglycemia. Grade B recommendation
- Use regular insulin or short-acting insulin analogues for patients who require mealtime coverage.
- Alternatives to regular insulin (aspart, lispro, or glulisine) should be considered in the following settings: Grade B recommendation
  - Demonstrated requirement for pre-meal insulin coverage due to postprandial hyperglycemia AND concurrent frequent hypoglycemia
  - Patients using insulin pump.

The American Diabetes Association (ADA) issued updated guidelines in 2014 for diabetes care. Topics included recommendations for treatment. A grading system (A, B, C, or E) developed by the ADA was used to explain and categorize the evidence used for the recommendations. Grade A recommendations were based on clear evidence from

well-conducted, generalizable RCTs that were adequately powered. Recommendations given a B grade were derived from supportive evidence from well-conducted cohort studies. Grade C recommendations were based on evidence from poorly controlled or uncontrolled trials, while grade E recommendations were taken from expert consensus or experience.<sup>6</sup>

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. Grade A recommendation
- In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset. Grade E recommendation
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a glucagon-like peptide 1 (GLP-1) receptor agonist, or insulin. Grade A recommendation
- A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences. Grade E recommendation
- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. Grade B recommendation

In 2011, the American Association of Clinical Endocrinologists published updated clinical practice guidelines for diabetes comprehensive care. Recommendations were graded for the strength of the evidence source: an A grade was based on randomized clinical trials, a B on well-conducted but not randomized clinical trials, and a C grade was made despite the absence of directly applicable clinical studies. Recommendations were further classified by quality of evidence. Recommendations derived from evidence from a meta-analysis or at least one randomized control trial was rated as level 1. Level 2 recommendations were based on evidence from well-designed nonrandomized clinical trials, prospective cohort studies or retrospective case-control studies. Level 3 recommendations were based on cross-sectional or surveillance studies and case reports; level 4 recommendations were based on no clinical evidence.<sup>7</sup>

- Insulin is required in all patients with type 1 diabetes mellitus (T1DM), and it should be considered for patient with type 2 diabetes mellitus (T2DM) when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia (Recommendation Grade A; Level of Evidence 1).
- When insulin therapy is indicated in patients with T2DM to target fasting plasma glucose (FPG), therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia (Recommendation Grade A; Level of Evidence 1).
- When postprandial hyperglycemia is present, glinides and/or  $\alpha$ -glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered (Recommendation Grade A; Level of Evidence 1).
- When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia (Recommendation Grade A; Level of Evidence 1).
- Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, A1C, and weight (Recommendation Grade A; Level of Evidence 1).
- Premixed insulin (fixed combination of shorter- and longer-acting components) analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared with basal insulin or basal-bolus insulin (Recommendation Grade D; Level of Evidence 4).
- Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy (Recommendation Grade B; Level of Evidence 3).
- Physiologic insulin regimens, which provide both basal and prandial insulin, are recommended for most patients with T1DM (Recommendation Grade A; Level of Evidence 1).

- These regimens include (a) use of multiple daily injections (MDI), which usually provide 1 or 2 injections daily of basal insulin to control glycemia between meals and overnight and injections of prandial insulin before each meal to control meal-related glycemia; (b) the use of continuous subcutaneous insulin infusion (CSII) to provide a more physiologic way to deliver insulin, which may improve glucose control while reducing risks of hypoglycemia; and (c) for other patients (especially if hypoglycemia is a problem), the use of insulin analogues (Recommendation Grade A; Level of Evidence 1).
- All women with preexisting diabetes mellitus (T1DM, T2DM, or previous gestational diabetes) should have access to preconception care to ensure adequate nutrition and glucose control before conception, during pregnancy, and in the postpartum period (Recommendation Grade B; Level of Evidence 2).
- Regular or rapid-acting insulin analogues are the preferred treatment for postprandial hyperglycemia in pregnant women. Basal insulin needs can be provided by using rapid-acting insulin via CSII or by using long-acting insulin (e.g., NPH; US Food and Drug Administration [FDA] pregnancy category B) (Recommendation Grade B; Level of Evidence 2).

The International Diabetes Federation updated its practice guidelines for type 2 diabetes care in 2011. Recommendations were divided into categories labeled “recommended care,” “limited care,” or “comprehensive care”. Recommended care recommendations were considered cost-effective, evidence-based care and should be available to all people with diabetes and the aim of any health-care system should be to achieve this level of care. Limited care recommendations were labeled the lowest level of care that anyone with diabetes should receive.<sup>8</sup>

Recommended Care recommendations:

- For second-line therapy, when glucose control targets are not being achieved, add a sulfonylurea.
- A rapid-acting insulin secretagogue is an alternative option to sulfonylureas.
- For third-line therapy, when glucose control targets are no longer being achieved, start insulin or add a third oral agent.
- If starting insulin, add basal insulin or use premix insulin.
- For fourth-line therapy, begin insulin therapy when optimized oral blood glucose lowering medications (and/or GLP-1 RA) and lifestyle interventions are unable to maintain target glucose control.
- Intensify insulin therapy if already using insulin.
- Do not unduly delay the commencement of insulin.
- Maintain lifestyle measures, support for work and activities of daily living and after introduction of insulin.
- Consider every initiation or dose increase of insulin as a trial, monitoring the response.
- Explain to the person with diabetes from the time of diagnosis that insulin is one of the options available to manage their diabetes, and that it may turn out to be the best, and eventually necessary, way of maintaining glucose control, especially in the longer term.
- Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30-100 units/day.
- Continue metformin. Other oral agents may also be continued.
- Begin with:
  - A basal insulin once daily such as neutral protamine Hagedorn (NPH) insulin, insulin glargine or insulin detemir;
  - Once or twice daily premix insulin (biphasic insulin).
  - Initiate insulin using a self-titration regimen (dose increases of two units every 3 days) or with biweekly or more frequent contact with a health-care professional.
  - Aim for pre-meal glucose levels of < 6.5 mmol/l (< 115 mg/dl).
- Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen.

Limited Care recommendations:

- Less expensive human insulin can give most of the health care gains achievable with insulin therapy.
- Insulin supplies should be assured and be of consistent quality and type.

#### Comprehensive Care recommendations:

- Metformin remains the first-line therapy choice, unless contraindicated. More expensive therapies, and insulin, may be considered earlier in the treatment sequence.
- Insulin pump therapy is an additional option.

#### New drugs:

Afrezza (insulin human) Inhalation Powder was approved by the FDA in June 2014. Afrezza is a rapid acting inhaled insulin indicated to improve glycemic control in adults with diabetes mellitus. It is administered at the beginning of each meal, or within 20 minutes after starting a meal.<sup>9</sup>

In August, FDA granted tentative approval for a new insulin glargine injection (Basaglar™), indicated to improve glycemic control in adults with type 2 diabetes and in combination with mealtime insulin in adults and pediatric patients with type 1 patients. With tentative approval, the FDA cannot give final approval until the end of the automatic stay of 20 months as a result of litigation filed by Sanofi, claiming patent infringement.

#### New Formulations/Indications:

None

#### New FDA safety alerts:

None

#### New Trials:

A total of 1536 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, 20 relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 2 for the full abstracts.

Forst et al conducted an open label pilot study to compare the effect of adding a long-acting insulin to metformin on postprandial release of proinsulin. Intact proinsulin (IP) is a marker for  $\beta$ -cell dysfunction in patients with type 2 diabetes. Patients (n=28) with type 2 diabetes were randomized to receive either insulin glargine or NPH insulin once daily at bedtime for three months. All patients were previously treated with metformin and a sulfonylurea prior to study start. At baseline and at three months, patients were required to eat standardized meals and have their pre- and postprandial blood sampling to measure plasma proinsulin, total insulin, and blood glucose. Both glargine and NPH patients significantly reduced fasting blood glucose levels from baseline levels (glargine 158 vs. 121 mg/dL; NPH 156 vs. 119 mg/dL; both  $p < 0.01$ ). Fasting and postprandial glucose levels did not differ between groups. IP levels decreased in both groups ( $p < 0.05$  at all timepoints). In direct comparison, both insulin had similar levels of proinsulin with the exception of glargine after dinner which was significantly higher ( $p=0.04$ ). This was a poor quality study. It was open label design with no description of randomization and outcome data was not clearly reported.<sup>10</sup>

Swinnen et al performed a study to determine whether insulin glargine was noninferior to insulin detemir in lowering A1c in patients with type 2 diabetes. Patients (n=973) were randomized to either glargine once daily or detemir twice daily for six months. Patients were all insulin naïve but were allowed to be on oral agents during and prior to study initiation. The primary outcome was percent of patients to reach an A1c of  $\leq 7\%$ . Similar percentages of patients in both treatment groups reached the target A1c (27.5% of glargine and 25.6% of detemir patients;  $p=0.254$ ). Predetermined noninferiority margin was set at -7.68%; the difference between treatments was 1.85% (95% CI -3.78 to 7.48%), demonstrating noninferiority of glargine to detemir. Overall population improvements in A1c were also similar between treatments (1.46% A1c for glargine vs. 1.54% A1c for detemir;  $p=0.149$ ). Significantly more detemir patients achieved an A1c  $\leq 6.5\%$  (22.7 vs. 16.5%;  $p=0.017$ ). Incidence of hypoglycemia was similar between groups. Weight gain was higher in the glargine group: difference 0.77 kg,  $p \leq 0.001$ . More patients on glargine than on detemir completed the

study (95.4 and 89.9%, respectively,  $p \leq 0.001$ ). This was a fair quality study. Although an open label trial, study design methodology was well described and outcomes were well defined.<sup>11</sup>

Chacra et al conducted a study to determine the comparative efficacy of insulin lispro protamine with insulin detemir in patients with type 1 diabetes. Patients ( $n=397$ ) were randomized to receive lispro protamine or detemir twice daily; all patients received prandial insulin lispro three times daily. The primary outcome was change in A1c from baseline after 32 weeks. The change in A1c was similar between groups (least squares mean for protamine lispro 0.69%, detemir 0.59%; between treatment difference 0.1%; 95% CI -0.29 to 0.10). Predetermined noninferiority margin was set at 0.4% meaning lispro protamine is noninferior to detemir. Lispro protamine patients gained more weight than their detemir counterparts (difference between groups 1.5 kg; 95% CI 0.34 to 1.60 kg). Severe hypoglycemia was similar between groups ( $p=0.37$ ). This was a poor quality trial. Blinding, randomization and allocation concealment methodology were not described.<sup>12</sup>

Fogelfeld et al compared the efficacy of insulin detemir and insulin lispro protamine suspension in insulin naïve type 2 diabetics. Patients ( $n=442$ ) were randomized to take one of the two insulin once daily at bedtime for 24 weeks; doses were titrated to target a fasting blood glucose below 7.2 mmol/L. For up to eight weeks, an additional prebreakfast dose was given. The primary outcome was comparative improvement from baseline in A1c. Both treatment groups saw an improvement in A1c from a baseline average of 8.8% to 7.3% for lispro protamine and 7.5% detemir ( $p=0.03$ ). Predetermined noninferiority margin was set at 0.4%. The least squares mean difference between treatment A1c was -0.21% (95% CI -0.39 to 0.03%) demonstrating noninferiority. Clinical improvements in blood glucose were similar between groups. End-point mean fasting blood glucose was 7.0 vs. 6.9 mmol/L ( $p=0.85$ ) for lispro protamine and detemir respectively. The percentage of patients achieving an A1c of  $\leq 7.0\%$  were 34.9% for lispro protamine and 31.2% detemir patients ( $p<0.001$ ). Weight gain was a more significant issue for lispro protamine patients than those taking detemir (mean difference 1.52 kg;  $p<0.001$ ). As were rates of patients' hypoglycemia adjusted per year: 24.2 episodes with lispro protamine vs. 16.2 episodes with detemir ( $p=0.001$ ). This was a poor quality study. It was open label design with no description of randomization and outcome data was not clearly reported.<sup>13</sup>

Strojek et al examined the comparative efficacy of insulin glargine with insulin lispro protamine suspension in patients with type 2 diabetes. Insulin naïve patients ( $n=471$ ) were randomized to either lispro protamine or glargine for 24 weeks. Patients were allowed to continue pre-study oral diabetes medications; glargine patients were dosed once daily at bedtime, while lispro protamine patients could be dosed once or twice daily. The primary objective was comparative decrease in A1c from baseline. Decrease in baseline at endpoint was similar between groups (lispro protamine -1.46% and glargine -1.41%; least square mean difference -0.05%, 95% CI -0.21 to 0.11%). Predetermined noninferiority margin was set at 0.4% meaning lispro protamine is noninferior to glargine. Difference in weight gain was not significant (difference between treatments -0.01kg, 95% CI -0.61 to 0.59 kg). Overall hypoglycemia rates (episodes/patient/year) were similar for lispro protamine and glargine (24.2 vs. 23.0). However, severe hypoglycemia was higher for lispro protamine than glargine patients (9 vs. 2 patients;  $p=0.04$ ). This was a poor quality study. It was open label design with no description of randomization and outcome data was not clearly reported.<sup>14</sup>

Philotheou et al conducted an open label study in type 1 diabetics to compare the efficacy of insulin glulisine with insulin lispro. Children ( $n=572$ ) under 18 years old were randomized to either glulisine or lispro taken up to 15 minutes before a meal. The primary endpoint was comparative change in A1c from baseline after 26 weeks. Mean difference in A1c change from baseline was similar between the two groups: 0.10% glulisine vs. 0.16% lispro (difference 0.06%, 95% CI -0.24 to 0.12). Predetermined noninferiority margin was set at 0.4% meaning glulisine is noninferior to lispro. When stratified by age groups, the percentage of patients reaching their American Diabetes Association age specific A1c target by week 26 was significantly higher for glulisine (38.4%) than lispro (32%) patients ( $p=0.039$ ). This was a poor quality study. It was open label design with no description of randomization and outcome data was not clearly reported.<sup>15</sup>

Hsia et al compared the efficacy of adding basal insulin to poorly controlled inner city type 2 diabetics. In this small open label trial, 85 insulin naïve patients were randomized to receive once daily bedtime NPH insulin, bedtime glargine, or

morning glargine. The primary outcome was comparative change in A1c from baseline to endpoint at 26 weeks. All three groups had similar decreases in A1c; the overall mean end A1c was 7.8%, with no significant difference between treatment groups. There were also no differences in the proportions of subjects achieving  $HbA1c \leq 7.0\%$  by study end (23%, 23% and 28% for NPH, bedtime glargine, and morning glargine, respectively). There was no difference in weight gain between glargine groups: patients taking glargine at bedtime gained an average of 1.7 kg while those taking morning glargine also gained 1.7 kg. The NPH group lost an average of 0.2 kg, a significant improvement compared with both glargine groups ( $p < 0.05$ ). Overall rates of hypoglycemia were not significantly different between treatment groups. This was a poor quality trial. It was a small study, ended early due to funding issues, with poorly outlined design methodology and incomplete outcome data reported.<sup>16</sup>

Van Bon et al performed a clinical trial to compare the efficacy of three rapid acting insulin (glulisine, aspart, or lispro) administered through continuous subcutaneous insulin infusion. This was an open label cross-over study; all subjects were treated with each insulin. Type 1 diabetics were randomized to one of three treatment orders: glulisine-aspart-lispro, aspart-lispro-glulisine, or lispro-glulisine-aspart. Each insulin was used for 13 weeks. The primary outcome was to establish the superiority of glulisine over aspart or lispro on unexplained hyperglycemia and perceived infusion set occlusion. A prespecified p value of 0.025 was considered significant to correct for multiple testing. Patients with a perceived infusion set occlusion and at least one unexplained episode of hyperglycemia were not significantly different between glulisine and aspart or glulisine and lispro: 68.4% of glulisine versus 62.1% aspart patients  $p = 0.04$ ; versus lispro patients 61.3%  $p = 0.03$ . No differences were seen between insulin groups in A1c at endpoint. More patients experienced hypoglycemia in the glulisine group than in either the aspart or lispro cohorts (rates of hypoglycemia measured as episode per person per year); glulisine 73.84% versus aspart 65.01%  $p = 0.008$ ; versus lispro 62.69%  $p < 0.001$ . This was a fair quality study. Although an open label trial, study design methodology was well described and outcomes were well defined.<sup>17</sup>

Sourij et al conducted a small, open-label, crossover trial to compare postprandial hyperglycemia with short-acting insulin aspart and regular human insulin. Thirteen adult type-2 diabetics were randomized for the study; all were on preexisting insulin therapy. Subjects were given either human insulin or insulin aspart before a standardized breakfast and again before a standardized lunch four hours later. Therapy was given on two separate days with three days separating treatments. All subjects were treated with both types of insulin. The primary outcome was whether postprandial hyperglycemia is reduced with an insulin analog as opposed to human insulin. Secondary outcomes included change in free fatty acids, triglycerides, c-peptide, and intact proinsulin levels. Blood was drawn for levels every 30 minutes with a fasting level drawn prior to the first meal and continued until four hours after the second meal. The mean increase in blood glucose was significantly lower with aspart use than with regular human insulin (24.1833 vs. 34.92 mg/dl,  $P = 0.02$ ). Free fatty acid reduction was also significantly higher with aspart use (0.47 vs 0.35 mmol/l,  $P < 0.001$ ). The mean increase in intact proinsulin was significantly lower after aspart use versus human insulin (10.53 vs 15.20 pmol/l,  $P = 0.001$ ). No differences were observed in the C-peptide levels between the two groups. This was a poor quality study. It was an open label design with a very small cohort. Randomization methodology was not defined. Although the primary outcome was postprandial hyperglycemia, secondary outcomes such as free fatty acid reduction and intact proinsulin levels were promoted as the primary importance. Overall, clinical significance of findings is unclear.<sup>18</sup>

Koivisto et al compared the efficacy and safety of lispro protamine insulin suspension versus insulin glargine. Type-2 diabetics ( $n = 383$ ) were randomized to either once daily lispro protamine suspension or glargine for 24 weeks. All subjects were also given bolus lispro insulin for meals. The primary outcome was mean change in A1c at study end. Secondary outcomes included  $HbA1c < 7.0\%$ , blood glucose profiles, insulin doses, hypoglycemic episodes, adverse events and vital signs. At 24 weeks mean change in percent A1c was -1.05% for lispro protamine and -1.20% for glargine. Predetermined noninferiority margin was set at 0.4%: least-square mean between-treatment difference was 0.1%, 95% CI -0.11 to 0.31.  $HbA1c < 7.0\%$  was achieved by 21.7% of lispro protamine versus 29.4% glargine of patients ( $p = 0.01$ ). Mean basal/mealtime insulin doses at week 24 were 29.6/36.2 IU/day (ILPS) versus 32.8/42.2 IU/day (glargine); the difference was not statistically significant for total dose ( $p = 0.7$ ). For adverse events, 39% of lispro protamine versus

43% of glargine patients reported at least one event ( $p = 0.4$ ); 56.1% versus 63.6% of patients experienced hypoglycemia ( $p = 0.2$ ). No relevant differences were noted in any other variables including vital signs, blood glucose profiles, or insulin doses. This was a poor quality trial. Trial design was open label and methods for randomization and subject selection was not described.<sup>19</sup>

Thalange et al examined the difference in safety and efficacy between insulin detemir and neutral protamine Hagedorn (NPH). Children with type-1 diabetes aged two to 16 ( $n=348$ ) were randomized to one of the two long acting insulin in this multinational, open-labelled trial; only results for children aged two to five ( $n=82$ ) was reported in this paper. Results for all ages were reported elsewhere.<sup>20</sup> All subjects were given mealtime insulin aspart. The trial duration was one year. The primary endpoint was decrease in hemoglobin A1c. After 52 weeks, subjects on detemir had a greater decrease from baseline in mean A1c than those on NPH:  $-0.1\%$  vs.  $0.2\%$ ;  $p>0.05$ . Mean fasting glucose levels also decreased greater for detemir than NPH subjects ( $-1.0$  vs.  $-0.45$  mmol/L) although this was also nonsignificant. Less patients receiving detemir reported an adverse event than with NPH (69.0 vs. 77.5%; this trend was also seen in serious adverse events (12% vs. 15%). A lower rate of hypoglycemia was observed with detemir compared with NPH (50.6 vs. 78.3 episodes per patient-year). No  $p$  value was reported for adverse events. This was a poor quality trial. It was an open label design and methodology for randomization was not discussed. Although the trial recruited children up to age 16, only data for subjects under 5 years old was reported. In addition, important patient baseline characteristics were not well balanced (gender percentages were not comparable) and statistical analysis was not performed for important safety outcomes.<sup>21</sup>

Aschner et al conducted a study to compare the efficacy and safety of insulin glargine with sitagliptin a dipeptidyl peptidase-4 (DPP-4) inhibitor in patients with uncontrolled diabetes. Adults with type-2 diabetes ( $n=515$ ) were randomized to either 24 weeks insulin glargine (titrated to attain a fasting blood glucose of 4.0 to 5.5 mmol/L) or 100 mg oral sitagliptin once daily. The primary outcome was change from baseline in mean A1c after 24 weeks. At study end, adjusted mean reduction in HbA1c was greater for patients on insulin glargine ( $n=227$ ;  $-1.72\%$ ) than for those on sitagliptin ( $n=253$ ;  $-1.13\%$ ) with a mean difference of  $-0.59\%$ ; 95% CI  $-0.77$  to  $-0.42$ . The rate of all hypoglycemic episodes was greater with insulin glargine than with sitagliptin (4.21 vs. 0.50 events per patient-year;  $p<0.0001$ ). Severe hypoglycemia occurred in only three (1%) patients on insulin glargine and one ( $<1\%$ ) on sitagliptin. This was a fair quality trial. Although it was an open label design and the treatments were from different classes, the trial method and materials were well defined; as were the trial outcomes and results.<sup>22</sup>

Inagaki et al compared the efficacy of exenatide extended release with insulin glargine in lowering the hemoglobin A1c in patients with uncontrolled type-2 diabetes. Adults subjects ( $n=427$ ) were randomized to either once daily insulin glargine or once weekly exenatide for 26 weeks. Subjects were able to continue their oral diabetic medications. The primary outcome studied was mean change in A1c from baseline at trial end with a predefined noninferiority margin of 0.4%. Secondary analyses included analysis of superiority for between-group comparisons of change in weight and the proportion of patients reaching HbA1c target levels of  $<7.0\%$ . Exenatide was statistically noninferior to insulin glargine for the change in HbA1c from baseline to end point (least squares mean difference  $-0.43\%$ , 95% CI  $-0.59$  to  $-0.26\%$ ). In addition, subjects receiving exenatide had a significantly greater number of patients compared with insulin glargine achieve HbA1c target levels of  $<7.0\%$  (42.2 vs 21.0%;  $p<0.001$ ) at end point. Patient weight had a greater reduction with exenatide than with insulin glargine (least squares mean difference  $-2.01$  kg; 95% CI  $-2.46$  to  $-1.56$ ). This was a poor quality trial. Trial design was open label and methods for randomization and subject selection was not described.<sup>23</sup>

Mathieson et al conducted a trial to compare the efficacy of different long-acting insulin in pregnant patients with type-1 diabetes. Women ( $n= 310$ ) were randomized to use either insulin detemir or neutral protamine Hagedorn (NPH) for up to 12 months prior to pregnancy or started at eight to 12 weeks gestation. All patients received supplemental bolus insulin aspart. The primary endpoint was mean change from baseline in A1c at 36 weeks gestation. The predetermined noninferiority margin was set at 0.4%. The estimated A1c at 36 weeks was 6.27% for insulin detemir and 6.33% for NPH. Insulin detemir was determined to be noninferior to NPH (mean difference  $-0.06\%$ ; 95% CI  $-0.21$  to  $0.08$ ). Secondary outcome fasting plasma glucose (FPG) was significantly lower with insulin detemir rather than NPH: at 36 gestation

weeks 85.7 versus 97.4 mg/dL,  $p=0.017$ . Hypoglycemic episodes were statistically similar between the two groups: 16% of the detemir subjects versus 21% in the NPH group. There was no difference between groups in weight gain during pregnancy (11.5 kg in the detemir group and 11.0 kg in the NPH group). This was a poor quality trial. The study design was open label which can increase the risk of bias. In addition the length of time for the treatment was not fixed and not well explained.<sup>24</sup>

Thalange et al examined the difference in safety and efficacy between insulin detemir and neutral protamine Hagedorn (NPH). Children with type-1 diabetes aged two to 16 ( $n=348$ ) were randomized to one of the two long acting insulin in this multinational, open-labelled trial. The primary outcome was change in A1c from baseline after 52 weeks. Secondary outcomes included weight change and rate of hypoglycemia. At 52 weeks, insulin detemir was determined to be non-inferior to NPH insulin with regard to HbA1c (mean difference 0.13%, 95% CI  $-0.12$  to  $0.37$ ). Hypoglycemic events per subject-year were significantly lower with insulin detemir than with NPH insulin (rate ratio 0.76; 95% CI 0.60 to 0.97). Weight standard deviation (SD) scores (body weight standardized by age and gender) decreased with insulin detemir, but increased slightly with NPH insulin (change:  $-0.12$  vs.  $0.04$ ,  $P < 0.001$ ). This was a poor quality study. Trial design was open label and methods for randomization and subject selection was not described.<sup>20</sup>

Hickman et al compared the safety and tolerability of metformin to insulin for glycemic control among women with preexisting type 2 and early A2 gestational diabetes. Pregnant women ( $n=28$ ) were randomized to receive either oral metformin or long-acting insulin. The primary outcome was glycemic control compared between the two groups as defined as  $>50\%$  capillary blood glucose within target range. Mean study outcome was 11.5 weeks. No significant difference was apparent when evaluated over the entire course of study enrollment or at any of the 2-week intervals chosen for evaluation. Secondary outcomes included adverse events and weight gain. Women treated with metformin had significantly fewer subjective episodes of hypoglycemia compared with those using insulin ( $0\%$  versus  $36\%$ ;  $p=0.04$ ) as well as reported glucose values  $< 60$  mg/dL ( $7.1\%$  versus  $50\%$ ;  $p=0.03$ ). All metformin subjects continued using metformin after delivery and  $43\%$  required supplemental insulin to achieve glycemic control. This was a poor quality, very small study. There were differences in patient baseline demographics and the primary outcome was not well defined.<sup>25</sup>

Davies et al looked at the difference in efficacy and safety of exenatide extended release compared with insulin detemir. Adults with type-2 diabetes ( $n=216$ ) were randomized to receive either exenatide 2 mg once weekly or detemir once or twice daily (titrated to a fasting blood glucose of  $5.5$  mmol/mol). The primary outcome was the amount of patients achieving an A1c of  $<7.0\%$  and weight loss of  $>1$  kg after 26 weeks. Patients treated with exenatide were significantly more likely to achieve the primary outcome than insulin detemir patients ( $44.1\%$  vs.  $11.4\%$ ;  $P=0.0001$ ). Individually, exenatide use resulted in significantly greater reductions than detemir in A1C (least-square mean  $-1.30\%$  vs.  $-0.88\%$ ;  $P=0.0001$ ) and weight ( $-2.7$  kg vs.  $+0.8$  kg;  $P=0.0001$ ). Gastrointestinal-related and injection site-related adverse events occurred more frequently with exenatide than with detemir. Five ( $6\%$ ) exenatide patients and six ( $7\%$ ) detemir patients experienced minor hypoglycemia; no serious hypoglycemia events were reported. This was a fair quality study. Although an open label trial, study design methodology was well described and outcomes were well defined.<sup>26</sup>

Spaulonci et al evaluated metformin versus neutral protamine Hagedorn (NPH) insulin for glycemic control in women with gestational diabetes. Subjects ( $n=92$ ) with gestational diabetes who failed to achieve glycemic goals through nonpharmacological means (diet and exercise) were randomized to receive metformin (titrated to a goal dose of 850 three times daily) or NPH insulin ( $0.4$  units per kg in three divided doses). The primary outcomes were rates of preeclampsia, prematurity and neonatal outcomes including hypoglycemia, macrosomia, and hyperbilirubinemia. Mean glucose levels were also tracked. There was no difference between groups in rates of preeclampsia ( $p=0.420$ ), or prematurity ( $p>0.99$ ). In neonatal outcomes there were no significant differences between the two groups in frequency of macrosomia ( $p=0.242$ ). There were more occurrences of neonatal hypoglycemia in the insulin group compared with newborns from the metformin group ( $p=0.032$ ). Hyperbilirubinemia frequency was not reported. Subjects on metformin had lower mean glucose levels ( $p=0.020$ ), and less weight gain ( $p=0.002$ ) than insulin subjects. This was a poor quality study. Study design was not specified although it was most likely open label design; study methodology



(randomization, blinding, etc.) was also not described. The primary outcomes described in the body of the paper were not all reported and a secondary outcome was reported as the primary endpoint in the abstract. Study duration was not reported.<sup>27</sup>

Karagianni et al. examined the difference in efficacy between exenatide and insulin glargine in diabetes. Adults (n=47) with type two diabetes were given either exenatide twice daily or glargine once daily for 26 weeks. The primary outcome was change in hemoglobin A1c; secondary outcomes included change in body mass index (BMI), lipid profile and blood pressure. Adverse events, including episodes of hypoglycemia and gastrointestinal symptoms, were recorded. There was not a statistically significant difference in the decrease in A1c after week 26 (-1.3% in the exenatide vs. -0.5% in the glargine group; p=0.131). However, nine exenatide and six glargine patients achieved HbA1c  $\leq$  7% by the 26th week (50% vs. 21%; p=0.036). There was a significant decrease in BMI by study end for exenatide subjects but not for the insulin group (-2.5 kg/m<sup>2</sup> vs. 0.1 kg/m<sup>2</sup>; p<0.001). Exenatide subjects also had a larger decrease in triglycerides than the insulin cohort (-37 mg/dL vs. -10 mg/dL; p=0.022). There was no significant difference in blood pressure, LDL or HDL levels between treatment groups. Six patients in the insulin glargine group experienced hypoglycemia compared with no patients in the exenatide group (33.3% vs. 0%; p=0.039). Gastrointestinal adverse events were higher in the exenatide group (p=0.114). This was a poor quality study with multiple opportunities for bias. The study was a very small open label study, subjects were not randomized, and treatment groups were not equal. Patient characteristics at baseline were not provided.<sup>28</sup>

Meneghini et al. performed an open label study to assess the comparative efficacy of basal insulin initiation added to existing metformin in type 2 diabetics. Adults (n=457) were randomized to either insulin detemir or insulin glargine once daily for 26 weeks. The primary efficacy endpoint was comparison of change in A1c from baseline. Secondary endpoints included the proportion of subjects achieving HbA1c levels  $\leq$ 7% at 26 weeks, and the proportions achieving this without symptomatic hypoglycemia during the last month of treatment. At study end, there was no significant difference in mean change in A1c from baseline for either treatment group (-0.48% for detemir vs. -0.74% for glargine; p=0.30). More patients achieved an A1c of 7% or less by 26 weeks in the glargine group compared with the detemir cohort (53% vs. 38%; p=0.026). Hypoglycemia occurred less frequently with detemir rather than glargine treatment (rate ratio 0.73; 95% CI 0.54–0.98). Rates of hypoglycemia in patients who achieved an A1c of  $\leq$ 7% were not different between treatments. Weight decreased in detemir and increased in glargine subjects (-0.49 kg vs. 1.0 kg; 95% CI -2.17 to -0.89 kg). This was a fair quality trial. Although it was an open label design, the trial method and materials were well defined as were the trial outcomes and results.<sup>29</sup>

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## Appendix 1: Prior Authorization Criteria

### Insulins

#### Goal(s):

- To ensure appropriate drug use and safety of hypoglycemic agents by authorization utilization in specified patient population

#### Initiative:

- Initiative

#### Length of Authorization:

Up to 12 months

Requires PA: Non-Preferred drugs

#### Covered Alternatives:

Preferred alternatives listed at [www.orpdl.org](http://www.orpdl.org)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code	
2. Is this an OHP covered diagnosis?	Yes: Go to #3	No: Pass to RPh; Deny, (Not covered by the OHP)
3. Is the request for an Insulin Pen or Cartridge?	Yes: Go to #4	No: Go to #5
4. Is the insulin being administered by the patient or a non-professional caregiver AND any of the following criteria apply: <ul style="list-style-type: none"><li>Does the patient have physical dexterity problems/vision impairment</li><li>Comprehension related issues</li><li>Dosing errors with use of vials</li><li>The patient is on a low dose of insulin (<math>\leq 40</math> units/day)</li><li>Is the request for a child &lt; 18 years old?</li><li></li></ul>	Yes: Go to #5	No: Pass to RPh; go to #6

## Approval Criteria

5. Will the prescriber consider a change to a preferred product?

Message:

Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.

- Yes: Inform provider of covered alternatives in class. [www.oregon.gov/DHS/healthplan/tools\\_prov/dl.shtml](http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml).

For insulin pens approve for 1 year (other preferred products covered without a PA)

- No: Approve for 1 year

6. RPh only

- Requests for insulin pens and cartridges on a client-specific basis
- Refer to the PDL for the preferred pens.

AND/OR

- If the above criteria are met and the request is NOT for convenience issues alone then approve insulin pen or cartridge use.

*P&T / DUR Action: 9/16/10 (KS)*

*Revision(s): 12/16/10*

*Initiated: 1/1/11*



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### **New Drug Evaluation:** (insulin human) inhalation powder

**Month/Year of Review:** September 2014

**End date of literature search:** July 2014

**Generic Name:** (insulin human) inhalation powder

**Brand Name (Manufacturer):** Afrezza® (MannKind Corporation)

FDA Approved Indication: Insulin inhalation powder is a rapid acting inhaled insulin indicated to improve glycemic control in adult patients with diabetes mellitus.

Important limitations of use include:

- In patients with type 1 diabetes (T1DM), must use with a long-acting insulin
- Not recommended for the treatment of diabetic ketoacidosis
- Not recommended in patients who smoke

#### **Research Questions:**

- Is insulin human inhalation powder (IHIP) safe and effective in improving glycemic control in patients with T1DM and type 2 diabetes mellitus (T2DM)?
- How does IHIP differ from currently available insulin products?
- Are there certain patient subgroups that benefit from the use of IHIP?

#### **Conclusions:**

- There is low quality evidence to show that IHIP is non-inferior to insulin aspart for reducing HbA1c in patients with T1DM. Pivotal trials remain unpublished, but data from FDA briefing documents indicate that IHIP performed statistically worse than insulin aspart despite falling within non-inferiority margins.
- There is moderate quality evidence to show that IHIP is effective at reducing HbA1c in patients with type 2 diabetes. Only one phase 3 trial, of at least six months duration is published, and it shows that reductions in HbA1c are comparable between IHIP + glargine and NovoLog Mix 70/30.
- There are two unpublished phase 3 trials in which the primary endpoint was not met when compared to insulin aspart (in combination with insulin glargine) or when compared to sulfonylureas (in combination with metformin). There is one unpublished phase 3 trial in which IHIP was superior to placebo. As these trials are unpublished, the quality of the evidence cannot be assessed and results should be interpreted with caution.
- There is no evidence to show that IHIP results in an improved quality of life when compared to an active treatment alternative. One phase 3 trial evaluated quality of life as a secondary endpoint and found no difference compared to injectable insulin.

- The most common adverse events associated with IHIP were hypoglycemia, cough, and throat pain or irritation. Pulmonary adverse effects were similar in patients treated with IHIP versus placebo. A two year study shows that there is a decline in pulmonary function tests after treatment with IHIP, but it is minimal and not clinically significant.
- As this is a new route of administration, pulmonary toxicity remains a concern. The FDA has requested several post-marketing studies, including a clinical trial that evaluates the potential risk for pulmonary malignancy, cardiovascular events, and long-term effects on pulmonary function.
- Long term efficacy and safety data is necessary to better define the role of IHIP in the treatment of patients with T1DM and T2DM.

#### **Recommendations:**

- Due to low-moderate quality data in type 1 and type 2 diabetes, and a lack of long term efficacy and safety data, IHIP should be a non-preferred agent on the PDL. There is no evidence to show it offers any advantages in efficacy or safety when compared to injectable insulin products for which long term data is available.
- Prior authorization should be added to ensure appropriate use. IHIP should be limited to patients who meet the following criteria:
  - Have a diagnosis of T1DM and T2DMs and;
  - ≥18 years old and;
  - No history of asthma, COPD, or underlying lung disease and;
  - Preferred short or rapid acting injectable insulin cannot be used due to:
    - Physical dexterity problems/vision impairment
    - Comprehension related issues
    - Dosing errors with use of vials
    - Intolerable injection site reactions
  - For patients with type 1 diabetes, IHIP must be used in combination with a long-acting insulin
  - Until more data is available, it is not appropriate to use IHIP for the of purpose patient convenience alone

#### **Background:**

There were over 29 million people in the United States in 2012 who had diabetes, which was 9.3% of the population.<sup>1</sup> About 90% of individuals with diabetes worldwide have type 2 diabetes mellitus, although many remain undiagnosed.<sup>2</sup> Diabetes was the seventh leading cause of death in the United States in 2010.<sup>2</sup> People with diabetes are 1.7 times more likely to die of cardiovascular disease, 1.8 times more likely to have a heart attack, and 1.5 times more likely to have a stroke.<sup>1</sup> Diabetes is also associated with microvascular disease leading to increased kidney disease, eye problems, and amputations.<sup>1</sup>

There are two classes of medications (insulin and amylin agonists) approved for the treatment of patients with T1DM and 12 classes (insulin inclusive) of drugs approved for the treatment of T2DM in the United States.<sup>2</sup> All FDA approved insulins, besides Afrezza, are delivered via the subcutaneous route (SC) in multiple daily injections or via an insulin pump device; regular insulin can be given intravenously for short periods in the hospital setting. The current SC insulins vary in their duration of action, ranging from short to long acting. For patients in whom endogenous insulin is insufficient or not present, therapy is aimed at imitating the pattern of endogenous insulin secretion (e.g., basal to meal time ratio of 50:50 often time administered as one basal and three meal time injections).<sup>2</sup> The



American Diabetes Association recommends lowering HbA1c to below or around 7% for most nonpregnant adults. More stringent goals may be considered for some patients, depending on comorbidities and response to current therapy.<sup>2</sup>

The first inhaled insulin product, Exubera, was approved by the FDA in 2006, but was withdrawn from the market one year later due to concerns of lung cancer and a lack of acceptance by patients and prescribers. The Exubera inhaler was administered using a large device with low portability and it was difficult to train patients and providers on proper use.<sup>3</sup> The MannKind Corporation continued to develop an inhaled form of insulin, Afrezza, which was approved by the FDA in 2014.

Afrezza is a drug-device combination that consists of single-use cartridges of a dry powder formulation of recombinant regular human insulin (also referred to as technosphere insulin), and a breath-activated inhaler. Afrezza is a rapid-acting insulin that is intended to cover meal time insulin requirements for patients with T1DM and T2DM.<sup>2</sup> The Technosphere Technology platform, developed by the MannKind Corporation, is a new method for pulmonary delivery of medications, which allows proteins, like insulin, to be administered by inhalation. The Technosphere inhalation platform is made possible by the development of an excipient called fumaryl diketopiperazine (FDKP), which is an inert, small molecule. FDKP forms the particle matrix that delivers the active pharmaceutical ingredient to the lungs.<sup>4</sup>

IHIP is administered using the DreamBoat inhaler, a thumb-sized inhalation device patented by MannKind. To use a DreamBoat inhaler, patients must load the cartridge, close the device, and inhale. The inhalers are also disposable, eliminating the need to wash and dry the device, but inhalers should be discarded and replaced with a new inhaler after 15 days of use. Cartridges are available in 2 different strengths, 4 units and 8 units, so patients using higher doses of mealtime insulin (>8 units), will have to use multiple cartridges per meal. Pharmacokinetic studies show that IHIP has a more rapid absorption and elimination than subcutaneously administered regular human insulin, reaching maximum serum insulin concentrations 12-15 minutes after administration compared to 120 minutes for regular human insulin (Rave, Prescribing info).<sup>5,6</sup>

#### Clinical Efficacy:

IHIP has a complex regulatory history. Throughout the course of development, two different inhalers were used to administer IHIP, each developed by MannKind Corporation. The MedTone inhaler was the first inhaler developed and used in clinical trials. After the initial trials were completed, MannKind developed the DreamBoat inhaler (also known as the Gen2 inhaler), which is the commercially available device that was brought to market with IHIP. When MannKind initially submitted for FDA approval in 2009, the Agency required additional clinical trials, with at least one that included a head to head comparison of MedTone and DreamBoat inhalers with regards to pulmonary safety.<sup>7</sup>

#### *Studies completed using the MedTone inhaler*

In total, there were three phase 4 trials of at least 6 months duration that evaluated IHIP using the MedTone inhaler, one of which is published. One trial evaluated patients with T1DM (study 009) and three studies were completed in T2DM.

The published Phase 3 trial evaluated the efficacy and safety of IHIP in combination with insulin glargine and compared it to that of twice daily biaspart insulin (NovoLog Mix 70/30). Patients included in the trial had T2DM, a HbA1c between 7-11%, and were previously treated with insulin (with or without oral agents). Patients using metformin or sulfonylureas in combination with insulin were allowed to remain on oral therapy throughout the trial, and concomitant use was

similar across both treatment groups. Chronic pulmonary disease and unstable diabetes are among several excluded conditions. Unstable diabetes was defined as  $\geq 2$  episodes of severe hypoglycemia, or any admission to hospital or visit to an emergency department for diabetes within the preceding 6 months.<sup>8</sup>

This study found that IHIP was non-inferior to biaspart insulin for the primary endpoint of change in HbA1c from baseline to 52 weeks. This was true for all analyzed populations, including the per protocol and intent-to-treat populations [IHIP: -0.59% (95% CI -0.71, -0.47); biaspart: -0.71% (95% CI -0.83, -0.59), difference: 0.12% (95% CI -0.05, 0.29), modified intent-to-treat]. The change in fasting plasma glucose over 52 weeks was measured as a secondary endpoint, and was greater for IHIP (2mmol/L) than for biaspart insulin (1mmol/L), with a difference of 1mmol/L [ $p=0.0029$  (95% CI -1.6, -0.3)]. IHIP and biaspart insulins performed similarly for remaining secondary endpoints, including postprandial glucose AUC, and proportion of patients with HbA1c of  $\leq 7\%$ .<sup>8</sup>

Investigators evaluated quality of life using the SF-36 Quality of Life (QoL) instrument and the insulin treatment questionnaire, as additional secondary endpoints. While there were significant differences from baseline in each treatment group, there was no difference between the two treatment groups for decrease in diabetes worries ( $p=0.1825$ ), attitudes towards insulin therapy/treatment satisfaction/treatment preference ( $p=0.5276$ ). This study showed that IHIP could reduce and maintain improvements HbA1c compared to biaspart insulin, but it was not compared to a basal-bolus insulin regimen, which is commonly used in patients with diabetes, and lack of a glargine-only arm may have confounded results. Additionally, due to the differences in administration and variable dosing of study drugs, study participants were not blinded.<sup>2,8</sup>

Of the studies initially submitted for FDA approval, this study was the only one to meet the primary endpoint. The other studies remain unpublished, but additional details were available in the FDA briefing document.

Study 014 was an open-label, 24 week trial comparing IHIP + glargine to insulin aspart (SQ) + glargine in patients with T2DM, in Russia. Roughly 80% and 97% of IHIP and SC patients completed the study, respectively, with adverse events being the primary reason for discontinuation. According to the FDA briefing document, the two treatment groups were not comparable when using the intent-to-treat population with last observation carried forward, so the sponsor conducted the analysis on the intent-to-treat population without the last-observation-carried forward, which potentially biased the results. The FDA reviewer also noted that IHIP was statistically inferior to SC insulin because the upper-bound of the 95% confidence interval was 0.6%, which is above the pre-specified non-inferiority margin of 0.4% and the lower bound of the 95% confidence interval for the HbA1c treatment difference for the intent-to-treat population using last-observation-carried-forward was 0.1%.<sup>2</sup>

Study 103 was another open-label trial completed in patients with T2DM and compared IHIP vs. IHIP + metformin vs. metformin + sulfonylurea. Patients in the study had HbA1c 7.5-11% and were on a stable dose of metformin ( $\geq 1000$  mg/day) and at least half the maximum recommended dose of an insulin secretagogue (either sulfonylurea or glinide). The trial found that IHIP + metformin was not superior to the sulfonylurea + metformin. The mean reduction from baseline in HbA1c was -0.7% in the IHIP + metformin group compared to -0.8% in the sulfonylurea + metformin group ( $p=0.51$ ). The FDA reviewer identified several limitations with the trial design as the treatment duration was too short and inconsistent metformin doses were used among the different treatment groups. Lastly, investigators compared an add-on therapy to continuation therapy which could potentially overestimate the true effect of the medication.<sup>2</sup>

Study 009 was an open-label trial comparing IHIP + glargine to insulin aspart (SC) + glargine in patients with T1DM and HbA1c 7-11% ( $n=539$ ). Insulin dose titration was permitted throughout the study and the dose of IHIP was based on a conversion of 15 units IHIP for every 5 units of SC insulin, with a max dose of 90 units with meals. There was a high dropout rate during the trial with 66% and 76% of patients in the IHIP and SC groups, respectively, completing the trial. Reasons for drop out were primarily due to lack of efficacy (hyperglycemia, increase blood glucose), which occurred in 7.6% of IHIP-treated patients and 0.7% of

SC treated patients. After 52 weeks, IHIP was found to be inferior to SC insulin with a treatment difference in mean change in HbA1c of 0.2% (95%CI 0.1, 0.404), similar to study 014. FDA reviewers indicate that there was minimal titration of insulin during this study and it is possible the treatment difference between the two regimens may be more pronounced if treatments were titrated differently.<sup>2</sup>

#### *Studies completed using the DreamBoat (Gen2) inhaler*

In an effort to meet the FDA's request for additional information, two Phase 3 trials were completed using the DreamBoat inhaler, one in patients with T1DM (Study 171) and one in patients with T2DM (Study 175). Both trials titrated patients on IHIP using a dose conversion of 10 units IHIP for every 4 units of rapid acting insulin analog, which was different than the dose conversion used when the MedTone inhaler was studied. Study 171 titrated doses based on 90-minute postprandial blood glucose values, and study 171 titrated doses based on blood glucose values prior to the next meal. Both trials were randomized, multicenter trials, although study 171 was open-label, while study 175 was placebo-controlled.

Study 171 (n=518), completed in patients with T1DM and HbA1c  $\geq 7.5\%$  and  $\leq 10\%$ , evaluated the efficacy of IHIP + basal insulin versus insulin aspart + basal insulin, and the effects on pulmonary safety between the DreamBoat and MedTone inhalers. Patients were randomized to one of three treatment groups: SC insulin (SC), IHIP administered using the DreamBoat inhaler (IHIP-DB), or IHIP administered using the MedTone inhaler (IHIP-MT); each treatment arm received basal insulin. After 24 weeks, the mean reduction in HbA1c from baseline was -0.21% for patients treated with IHIP-DB and -0.4% for patients treated with SC insulin, for a treatment difference of 0.19% (95% CI 0.02-0.36). Efficacy results were not reported for patients in the IHIP-MT group, as this data was used only to assess safety endpoints for each of the inhalers. Non-inferiority was met, as the upper bound of the 95% CI was lower than the prespecified margin of 0.4%, however IHIP performed statistically worse than insulin aspart. Additionally, more patients treated with insulin aspart achieved HbA1c  $\leq 7\%$  at the end of the trial (30.7% vs 18.3%,  $p=0.0158$ ).<sup>2</sup>

Study 175 (n=353), completed in patients with T2DM and HbA1c  $\geq 7.5\%$  and  $\leq 10\%$ , evaluated the efficacy of IHIP compared to placebo when added to oral antidiabetic medications in insulin-naïve patients. To be included in the trial, patients had to be on a stable dose of metformin as monotherapy, or at least 2 oral antidiabetic medications. After 24 weeks, investigators found that patients receiving IHIP + background therapy experienced a greater reduction in HbA1c (-0.82%) compared to those receiving placebo + background therapy (-0.42%) for a treatment difference of -0.4% (95% CI -0.57, -0.23),  $p<0.0001$ . More patients treated with IHIP achieved HbA1c  $\leq 7\%$  at the end of the trial, than with placebo (37.7% vs 19%,  $p=0.0005$ ).<sup>2</sup>

#### Clinical Safety:

In the Rosenstock et al trial, safety was assessed in all patients who received at least one dose of the study drug. Adverse events occurred in 85% of patients using IHIP and 89% of those using SC insulin. Hypoglycemia was the most commonly reported treatment-related adverse event, occurring in 31% of patients on IHIP and 49% of patients on subcutaneous insulin. The rate of mild to moderate hypoglycemia per patient months was significantly lower in patients who received IHIP ( $p=0.0029$ ), but the difference in event rate of severe hypoglycemia was not significantly different ( $p=0.0591$ ). Cough was commonly reported in the IHIP group (32% vs 4% in the subcutaneous group), and most cases occurred within 10 minutes of inhalation. Changes in pulmonary function tests were similar between treatment groups. More patients in the IHIP group discontinued treatment due to adverse events (9% vs 4%), primarily due to adverse events affecting the respiratory tract.<sup>8</sup>

In the FDA review, information from all submitted clinical trials was pooled, analyzed, and reported. Death rates in clinical trials were low, and appeared to be unrelated to treatment with IHIP. In total 0.4% of IHIP-treated patients died (9/2409). The rate of patients dropping out due to adverse events was higher in

patients treated with IHIP compared to other groups, with adverse events related to cough or pulmonary effects and lack of efficacy being the most common reasons for discontinuation. The cumulative incidence of discontinuations due to adverse events was 6.9% for IHIP and 0.6% for comparator groups. These rates are also similar when comparing patients using the DreamBoat inhaler for administration (7.3%) to those using the MedTone inhaler for administration (6.2%). Although the discontinuation rate was higher with the DreamBoat inhaler, the FDA did not feel that the difference was substantial enough to be clinically meaningful. Although four IHIP-treated patients developed malignancy, there is still an unclear association with IHIP and cancer. The most common adverse event was cough, with an incidence of 30%, and this typically occurred within 10 minutes and tended to decrease over time.<sup>2</sup>

Pulmonary adverse effects are a concern with inhaled insulin and were evaluated in a randomized, open-label, two-year study. In total, 1,699 patients with T1DM or T2DM were randomized to prandial IHIP or a usual care regimen without IHIP for 24 months. Investigators also enrolled a cohort of individuals without diabetes to examine changes in lung function over two years. Baseline lung function was comparable across all three treatment groups. After two years, a small decline from baseline FEV<sub>1</sub> was seen in all three groups, with the smallest change in the group without diabetes. IHIP was non-inferior to usual care for mean Forced Expiratory Volume in 1 second (FEV<sub>1</sub>) change from baseline (mean treatment group difference was 0.037, 95% CI 0.014 to 0.060). There was an early decline in pulmonary function tests noted after month 3, but after the initial decline, the annual rates of decline in FEV<sub>1</sub>, Forced Vital Capacity (FVC), and Diffusing Lung Capacity (DLco) from months 3-24 were not statistically different between groups, indicating that Pulmonary Function Test (PFT) changes associated with IHIP were non-progressive for up to two years.<sup>9</sup>

While the prior study evaluated the effects of IHIP administered using the MedTone inhaler, the FDA briefing document compared lung function of patients using IHIP administered via the MedTone versus DreamBoat inhalers. In patients with T1DM, there was no significant difference in the mean change from baseline in FEV<sub>1</sub> between the DreamBoat and MedTone inhaler groups [difference=0.01L (95%CI 0.02, 0.04)]. In patients with T2DM, the change in FEV<sub>1</sub> from baseline was similar to that of the MedTone inhaler in the original submission to the FDA (-0.13 L for the DreamBoat and the MedTone inhaler). Coughing was commonly reported, with similar rates occurring in patients using the DreamBoat and MedTone inhalers (incidence of cough using DreamBoat inhaler: 32% in T1DM, 24% in T2DM vs 2% in insulin aspart vs 20% with placebo). Patients with asthma, COPD, or other underlying lung disease were excluded from clinical trials and IHIP should not be used in these patients. The FDA is requiring postmarketing studies to evaluate efficacy and safety in pediatric patients, the risk of pulmonary malignancy, and to further refine the pharmacokinetic profile of IHIP.<sup>2</sup>

## **COMPARATIVE CLINICAL EFFICACY**

### **Relevant Endpoints:**

- 1) Mortality
- 2) Morbidity
- 3) Difference in mean change in HbA1c from baseline

### **Primary Study Endpoint:**

- 1) Difference in mean change in HbA1c from baseline

Ref./Study Design	Drug Regimens/ Duration	Patient Population	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
Rosenstock et al. 2010 <sup>9</sup>  R, OL, PG  52 weeks	<p>1. inhaled human insulin powder + insulin glargine (IHIP) (n= 302)</p> <p><i>~50% of total daily insulin dose was given as basal insulin. The remainder was given as inhaled insulin, adjusted in 15U increments, max 90 U per meal</i></p> <p>2. Subcutaneous biaspert insulin (SCI) (n=316)</p> <p><i>Premixed, 70% insulin aspart protamine suspension and 30% insulin aspart (rDNA origin)</i></p>	<p>Demographics (IHIP, SC):</p> <ul style="list-style-type: none"> <li>• Age: 55.9, 55.9</li> <li>• Weight (kg): 88.3, 85.8</li> <li>• BMI (kg/m<sup>2</sup>): 31.6, 31.1</li> <li>• HbA1c: 8.7%, 8.7%</li> <li>• Fasting plasma glucose (mmol/L): 9.4, 9.8</li> <li>• Duration of diabetes (years): 13, 13.7</li> </ul> <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Age 18-80</li> <li>• Type 2 diabetes</li> <li>• HbA1c 7-11%</li> <li>• Non-smoking for ≥6 months prior</li> <li>• FEV<sub>1</sub> and DL<sub>CO</sub> ≥ 70% of predicted</li> <li>• Total lung capacity ≥ 80% of predicted</li> <li>• BMI ≤ 40kg/m<sup>2</sup></li> <li>• Required &lt; 1.4IU insulin/kg</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>• Clinical significant diabetes complication</li> <li>• Hepatic or renal disease</li> <li>• Current drug or alcohol abuse</li> <li>• Severe or several allergies</li> <li>• Chronic pulmonary disease</li> <li>• Major psychiatric disorders</li> <li>• Unstable diabetes</li> </ul>	<p><u>Δ in HbA1c at 52 weeks (modified ITT, LOCF):</u></p> <p>IHIP: -0.59%</p> <p>SCI: -0.71%</p> <p>Pbo: 54.9%</p> <p>Difference: 0.12% (95%CI -0.05, 0.29)</p> <p><u>Δ in HbA1c at 52 weeks (per protocol):</u></p> <p>IHIP: -0.68%</p> <p>SCI: -0.76%</p> <p>Pbo: 54.9%</p> <p>Difference: 0.07% (95%CI -0.13, 0.27)</p>	N/A	<p><u>Treatment withdrawal:</u></p> <p>IHIP: 32%</p> <p>SCI: 24%</p> <p><u>Withdrawal due to adverse events:</u></p> <p>IHIP: 9%</p> <p>SCI: 4%</p>	N/A	<p><b>Quality Rating: Fair</b></p> <p><b>Internal Validity:</b>  <u>Selection:</u> Adequate randomization assignment (computer interactive voice response); groups similar at baseline.  <u>Performance:</u> This was an unblinded study using two different routes of administration.  <u>Detection:</u> Unclear if outcome assessors were blinded.  <u>Attrition:</u> 7 of the 334 patients randomized to IHIP were lost to follow-up. 22 of the 343 patients randomized to subcutaneous insulin were lost to follow-up</p> <p><b>External Validity:</b>  <u>Recruitment:</u> This is a multicenter study that recruited patients from hospitals and clinics in Argentina, Brazil, Canada, Chile, Mexico, Poland, Russia, Spain, UK, and USA  <u>Patient Characteristics:</u> Adult patients with type 2 diabetes moderately uncontrolled on insulin therapy without comorbidities  <u>Setting:</u> Patients received care at hospitals or outpatient clinics.  <u>Outcomes:</u> Primary endpoint (change in HbA1c), and secondary endpoints were measured after 52 weeks Change in HbA1c is an appropriate surrogate outcome for this study. No health outcomes, such as mortality, were studied..</p>
R: randomized, OL: open-label, PG: parallel group, FEV <sub>1</sub> : Forced expiratory volume in 1 second, DL <sub>CO</sub> : diffusing lung capacity, BMI: body mass index, ITT: intention-to-treat, LOCF: last observation carried forward							

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## Appendix 1: Specific Drug Information

### CLINICAL PHARMACOLOGY

#### PHARMACOKINETICS<sup>6</sup>

Parameter	Result
Time to maximum serum concentration	12-15 minutes
Duration of action	160-180 minutes
Half-Life	28-39 minutes
Metabolism	Phase I and II reactions in hepatocytes

- Based on inhaled Afrezza 4-32 units in 12 type 1 diabetes patients

This inhaled insulin has a lower bioavailability compared to subcutaneous insulin. The relative bioavailability is 20-30% that of subcutaneous insulin. The studies accounted for this lower bioavailability in the pivotal trials using the following dose algorithm (10 units of Afrezza for 4 units of SC insulin).<sup>6</sup>

#### DOSE & AVAILABILITY<sup>6</sup>

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
4 and 8 unit cartridges	Inhaled	With meals	Varies by patient	Monitor blood sugars closely, may cause hypoglycemia. Dose reduction may be required.	Monitor blood sugars closely, may cause hypoglycemia. Dose reduction may be required.	Not been studied in patients younger than 18 years of age	No overall differences in safety or effectiveness were observed in trials.	Must be use the IHIP inhaler to administer the doses

#### DRUG SAFETY<sup>6</sup>

*Serious (REMS, Black Box Warnings, Contraindications):*

Black Box Warning: Risk of acute bronchospasm in patients with chronic lung disease.

Contraindications: During episodes of hypoglycemia; chronic lung disease, such as asthma, or chronic obstructive pulmonary disease; hypersensitivity to regular human insulin or any of the excipients

*Warnings and Precautions:*

- Acute bronchospasm- Observed in patients with asthma and COPD.
- Change in insulin regimen- carry out under close medical supervision

- 
- Hypoglycemia- May be life-threatening. Monitor glucose more frequently when making changes to insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity, and in patients with renal or hepatic impairment.
  - Decline in pulmonary function- Assess pulmonary function before initiating, after 6 months of therapy, and annually
  - Lung cancer- Do not use in the setting of active lung cancer
  - Diabetic ketoacidosis- More patients experienced diabetic ketoacidosis in clinical trials.
  - Hypersensitivity reactions- Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products.
  - Hypokalemia- May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated.
  - Fluid Retention and heart failure with concomitant use with thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs.



**Month/Year of Review:** September 2014

**PDL Classes:** Alzheimer's Drugs

**Date of Last Review:** September 2013

**Source Document:** OSU College of Pharmacy

**Current Status of PDL Class:**

- Preferred Agents: DONEPEZIL TABLET (10mg only), GALANTAMINE TABLET, GALANTAMINE ER CAPSULE, MEMANTINE (NAMENDA®), RIVASTIGMINE (EXELON PATCH®),
- Non-Preferred Agents: RIVASTIGMINE CAPSULES, DONEPEZIL ODT (ARICEPT ODT®), DONEPEZIL TABLET (OTHER THAN 10 MG), MEMANTINE XR (NAMENDA XR®)

**Previous Conclusions and Recommendation:**

- There remains insufficient evidence for the treatment of Alzheimer's disease (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.
- Make Aricept 23mg non-preferred due to increased adverse drug events.

**PA Criteria:** None

**Methods:**

The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.<sup>1</sup>

**Conclusions and Recommendations:**

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

**References:**

1. Peterson, Kim. Drug Effectiveness Review Project: Drug Class Review on Alzheimer's Drugs. Preliminary Scan Report #5, August 2014.

# Drug Class Review

## Alzheimer's Drugs

### Preliminary Scan Report #5

August 2014

Last Report: June 2006

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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## OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, new systematic reviews, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

### Date of Last Report

Update #1, June 2006 (searches through December 2005)

### Date of Last Preliminary Update Scan Report

Preliminary Scan Report #4, October 2013

### Scope and Key Questions

Researchers at the University of North Carolina Chapel Hill wrote preliminary key questions and the eligibility criteria for studies based on the populations, interventions, and outcomes of interest. These were reviewed by representatives of organizations participating in the Drug Effectiveness Review Project (DERP) and posted to the DERP website for public comment. The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. How do donepezil, galantamine, rivastigmine, tacrine, and memantine or combinations of these drugs (i.e., acetylcholinesterase inhibitor plus memantine) compare in their efficacy or effectiveness for stabilizing symptoms and treating behavioral disturbances in patients with AD?
2. How do donepezil, galantamine, rivastigmine, tacrine, and memantine (or combinations of these drugs) compare in their time to effect and in the time required to assess the clinical response?
3. What are the comparative incidence and severity of complications of donepezil, galantamine, rivastigmine, tacrine, and memantine (or combinations of these drugs)?
4. Does efficacy, effectiveness, or adverse events of donepezil, galantamine, rivastigmine, tacrine, or memantine (or combinations of these drugs) differ in subgroups of patients with (1) different demographic profiles (age, race, or gender), (2) Parkinsonian features or vascular dementia, or (3) use of other commonly prescribed drugs?

## Inclusion Criteria

### Populations

- Patients with Alzheimer's disease

### Interventions

**Table 1. Included interventions**

Class	Generic Name	US Trade Name	Dosage Forms	Labeled Uses
AChEI	Donepezil	Aricept®	5, 10, 23 mg tabs 1x/day 5mg/5mL solution	Mild, moderate, and severe dementia of the Alzheimer's type
	Tacrine	Cognex®	discontinued by manufacturer	Mild to moderate dementia of the Alzheimer's type
AChEI, BuChEI	Rivastigmine	Exelon®	1.5, 3, 4.5, 6 mg tabs 2x/day 2 mg/mL solution 4.6 mg/24 hours or 9.5 mg/24 hours or 13.3 mg/24 hours patch 1x/day	Mild, moderate, and severe dementia of the Alzheimer's type
AChEI, NRM	Galantamine	Razadyne® Razadyne ER®	4, 8, 12 mg tabs 2x/day <sup>a</sup> 4mg/mL solution <sup>a</sup> 8, 16, 24 tabs 1x/day <sup>b</sup>	Mild to moderate dementia of the Alzheimer's type
NMDA antagonist	Memantine	Namenda™ Namenda XR®	5, 10 mg tabs 2x/day <sup>c</sup> 2 mg/mL solution <sup>c</sup> 7, 14, 21, 28 mg tabs 1x/day <sup>d</sup>	Moderate to severe dementia of the Alzheimer's type

Abbreviations: AChEI, acetylcholinesterase inhibition; BuChEI, butyrylcholinesterase inhibition; NRM, nicotinicreceptor modulator; NMDA, N-methyl d-aspartate

<sup>a</sup> Razadyne

<sup>b</sup> Razadyne ER

<sup>c</sup> Namenda

<sup>d</sup> Namenda XR

### Study designs

- RCTs only
- Sample size  $n \geq 100$
- Study duration  $\geq 12$  weeks

### Comparators

- Any other Alzheimer's medication listed above
- Combination of any Alzheimer's medications listed above
- Placebo

### Efficacy and effectiveness outcomes

- Stabilizing or slowing the rate of decline in health outcome measures:
  - Activities of daily living
  - Instrumental activities of daily living

- Level of care changes
  - Quality of life
  - Behavioral symptoms (e.g., aggression, agitation, psychosis, mood disorders)
- Stabilizing or slowing the rate of decline in intermediate outcome measures:
  - Cognition
  - Global assessment
- Discontinuation effects (i.e., temporary or permanent changes in behavioral symptoms, functional capacity, or cognition as a result of discontinuing treatment)
- Reducing caregiver burden
- Hospitalizations or nursing home placement
- Mortality

**Harms/adverse events outcomes**

- Overall adverse effect reports
- Withdrawals because of adverse effects
- Serious adverse event reports
- Adverse events due to discontinuation
- Specific adverse events, including:
  - Gastrointestinal symptoms
  - Hepatotoxicity
  - Weight loss

**METHODS****Literature Search**

To identify relevant citations for randomized controlled trials published since the last full report, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from March 2005 through July 7, 2014 using terms for included drugs. We also searched the FDA website (<http://www.fda.gov/medwatch/safety.htm>) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>), the Canadian Agency for Drugs and Technology in Health (<http://www.cadth.ca/>), the VA Evidence-based Synthesis Program (<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>), and University of York Centre for Reviews and Dissemination (<http://www.york.ac.uk/inst/crd/crdreports.htm>). All citations were imported into an electronic database (EndNote X4) and duplicate citations were removed.

**Study Selection**

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## RESULTS

### New Drugs

#### ***New drugs identified in this Preliminary Update Scan***

None identified.

#### ***New drugs identified in previous Preliminary Update Scan(s)***

6/21/2010: Namenda XR™ (memantine), an extended release version of Namenda™, was approved for the treatment of moderate to severe dementia of the Alzheimer's type.

5/01/2012: Cognex® (tacrine), was discontinued by the manufacturer, Shionogi Inc., and withdrawn from the US market.

9/1/2012: Exelon® (rivastigmine), a higher dose of the rivastigmine transdermal patch was approved by the FDA, the transdermal patch is now available in 3 doses: 4.6 mg/24 hours or 9.5 mg/24 hours or 13.3 mg/24 hours.

### New Indications

#### ***New indications identified in this Preliminary Update Scan***

None identified.

#### ***New indications identified in previous Preliminary Update Scan(s)***

6/27/2006: Exelon® (rivastigmine), a reversible cholinesterase inhibitor, was approved for the treatment of mild to moderate dementia associated with Parkinson's Disease.

10/13/2006: Aricept® (donepezil hydrochloride), an acetylcholinesterase inhibitor, was approved for the treatment of dementia of the Alzheimer's type in patients with severe Alzheimer's Disease.

### New Safety Alerts

#### ***Identified in this Preliminary Update Scan***

None identified.

#### ***Identified in previous Preliminary Update Scan(s)***

None identified.

### Comparative Effectiveness Reviews

#### ***Reviews identified in this Preliminary Update Scan***

None identified.

**Reviews identified in previous Preliminary Update Scan(s)**

None identified.

**Randomized Controlled Trials*****Trials identified since the most recent Full Report***

We identified 17 new publications through recent Medline searches. After screening titles and abstracts, we identified 2 new potentially relevant placebo-controlled trials for one of the included medications (memantine). This increases the total of new citations for randomized controlled trials found through Medline searches to 313 since the last full report. Of those, there are 37 potentially relevant new publications, including 4 head-to-head trials, 32 publications of 26 placebo-controlled trials, and 1 subgroup or secondary analysis of 1 trial included in an existing report (see Appendix A for abstracts). Characteristics of these trials are shown in Tables 2, 3, and 4, below. Table 5 is a matrix showing head-to-head trials.

**Table 2. New head-to-head trials**

Study	N, Duration	Population	Comparison	Focus
Choi, 2011	172, 24 weeks	Mild-to-moderate AD	Rivastigmine vs. memantine + rivastigmine	Tolerability and efficacy of combination therapy of memantine plus rivastigmine patch compared to rivastigmine patch monotherapy in patients with mild-to-moderate AD
Han, 2012	206, 24 weeks	Probable AD	Rivastigmine vs. memantine + rivastigmine	Effect of the apolipoprotein E genotype on the clinical response to rivastigmine transdermal patch monotherapy or memantine plus rivastigmine patch in patients with mild-to-moderate AD
Parnetti, 2011	144, 1 year	AD	Rivastigmine vs. galantamine vs. donepezil	Cerebrospinal fluid activity of acetylcholinesterase and butyrylcholinesterase in patients with AD, before and after long-term treatment with different AChEIs
Howard, 2012	295, 52 weeks	Moderate or severe AD	Donepezil vs. memantine vs. donepezil + memantine	Treatment benefits of cholinesterase inhibitors after the progression to moderate-to-severe AD

Abbreviations: AD, Alzheimer's disease; AChEI, acetylcholinesterase inhibitor

**Table 3. New placebo-controlled trials**

Study	N, Duration	Population	Comparison	Focus
Andersen, 2012	187, 12 months	Recent diagnosis of mild or moderate AD	Donepezil vs. Placebo	Effect of stimulation therapy and donepezil on cognitive function in AD
Black, 2007	343, 24 weeks	Severe AD	Donepezil vs. Placebo	Efficacy and safety of donepezil for severe AD
Frolich, 2011	567, 12 weeks	Mild-to-moderate AD	Donepezil vs. Placebo	Effects of AZD3480 on cognition in patients with mild-to-moderate AD

Study	N, Duration	Population	Comparison	Focus
Gold, 2010	693, 24 weeks	Mild-to-moderate AD	Donepezil vs. Placebo	Efficacy and safety of rosiglitazone XR in mild-to-moderate AD
Homma, 2008	325, 24 weeks	Severe AD	Donepezil vs. Placebo	Efficacy and tolerability of donepezil in severe AD
Howard, 2007	272, 12 weeks	Patients with AD who had clinically significant agitation and no response to a brief psychosocial treatment program	Donepezil vs. Placebo	Benefits of cholinesterase inhibitors for behavioral disturbances in patients with AD
Mazza, 2006	NR, 24 weeks	Mild-to-moderate Alzheimer's dementia	Donepezil vs. Placebo	Efficacy of Ginkgo biloba special extract EGb 761 compared with second-generation cholinesterase inhibitors in the treatment of mild-to-moderate Alzheimer's dementia
Burns, 2009	407, NR	Severe AD	Galantamine vs. Placebo	Efficacy of galantamine in patients with severe AD
Rockwood, 2006	130, 4 months	Mild-to-moderate AD	Galantamine vs. Placebo	Clinical meaningfulness of cholinesterase inhibitors in AD
Scarpini, 2011	NR, 24 months	Mild-to-moderate AD	Galantamine vs. Placebo	Examination of long-term outcomes of galantamine treatment in patients with AD
Suh, 2008	138, 52 weeks	Mild-to-moderate AD	Galantamine vs. Placebo	Impact of galantamine treatment on the function, caregiver time, and resources used in the treatment of patients with mild-to-moderate AD
Ashford, 2011	NR, 52 weeks	Probable AD diagnosis with mild-to-moderate dementia	Memantine vs. Placebo	To test whether memantine would slow or prevent the loss of neurons in mild-to-moderate AD patients
Bakchine, 2007	470, 24 weeks	Mild-to-moderate AD	Memantine vs. Placebo	Efficacy and tolerability of 20mg/day memantine in patients with mild-to-moderate AD
Cummings, 2006	NR, 24 weeks	Moderate-to-severe AD on stable donepezil treatment	Memantine vs. Placebo	Investigation of the behavioral effects of memantine in moderate-to-severe AD
Dyksen, 2014	613, mean (SD) follow up 2.27 (1.22) years	Mild to moderate AD	Memantine vs. Placebo	To determine if vitamin E (alpha tocopherol), memantine, or both slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitor
Fox, 2012	149, 12 weeks	Moderate-to-severe AD	Memantine vs. Placebo	Efficacy of memantine in treating clinically significant agitation in patients with moderate-to-severe AD
Grossberg, 2013	667, 24 weeks	Moderate-to-severe AD	Memantine XR vs. Placebo	Evaluate the efficacy, safety, and tolerability of a higher-dose, once-daily, extended-release formulation in patients with moderate-to-severe AD concurrently taking cholinesterase inhibitors



Study	N, Duration	Population	Comparison	Focus
Peskind, 2006	403, 24 weeks	Mild-to-moderate AD	Memantine vs. Placebo	Efficacy and safety of memantine versus placebo in patients with mild-to-moderate AD
Porsteinsson, 2008	433, 24 weeks	Probable AD	Memantine vs. Placebo	Efficacy and safety of memantine in patients with mild-to-moderate AD receiving cholinesterase inhibitor treatment
Saxton, 2012	257, 12 weeks	AD	Memantine vs. Placebo	Communication-related benefits of memantine treatment in patients with AD
van Dyck, 2007	350, 24 weeks	Moderate-to-severe AD	Memantine vs. Placebo	Efficacy and safety of memantine monotherapy in patients with moderate-to-severe AD
Wilkinson, 2012	278, 52 weeks	Probable AD	Memantine vs. Placebo	Rate of total brain atrophy with serial magnetic resonance imaging using the Brain Boundary Shift Integral in patients with probable AD over the course of 52 weeks of treatment with memantine or placebo
Feldman, 2007	678, 26 weeks	Probable AD	Rivastigmine vs. Placebo	Efficacy and safety of rapidly titrated rivastigmine administered twice or three times daily in patients with mild-to-moderate AD
Grossberg, 2009	870, 28 weeks	AD	Rivastigmine vs. Placebo	Long-term safety and tolerability of a transdermal rivastigmine patch up to 1 year, as a novel approach to treatment in AD
Mowla, 2007	122, 12 weeks	Mild-to-moderate Alzheimer's dementia	Rivastigmine vs. Placebo	Survey of the effect of serotonin augmentation on cognition and activities of daily living in patients with AD
Blesa, 2007 Cummings, 2010 Grossberg, 2011 Grossberg, 2011 Lee, 2011 Winblad, 2007 Winblad, 2007 Winblad, 2007	1,195, 24 weeks	Probable AD	Rivastigmine vs. Placebo	Efficacy, safety and tolerability of a novel rivastigmine transdermal patch with conventional rivastigmine capsules and placebo in patients with AD

Abbreviations: AD, Alzheimer's disease

**Table 4. Secondary analyses of included primary trial publications**

Study	N, Duration	Population	Comparison	Focus
Gaudig, 1622	841, 6 weeks	Mild-to-moderate AD	Galantamine vs. placebo	Effects of galantamine withdrawal and comparison with uninterrupted therapy

Abbreviations: AD, Alzheimer's disease

**Table 5. Breakdown of potentially relevant head-to-head comparisons by drug:**

	<b>Donepezil</b>	<b>Tacrine</b>	<b>Rivastigmine</b>	<b>Galantamine</b>	<b>Memantine</b>	<b>Memantine + donepezil</b>	<b>Memantine + rivastigmine</b>
<b>Donepezil</b>			1	1	1	1	
<b>Tacrine</b>							
<b>Rivastigmine</b>	1			1			2
<b>Galantamine</b>	1		1				
<b>Memantine</b>	1					1	
<b>Memantine + donepezil</b>	1				1		
<b>Memantine + rivastigmine</b>			2				

## Summary

We found 2 new placebo-controlled trials for one of the included medications (memantine) through recent searches. Cumulatively, all scans since the last full report identified 37 potentially relevant new publications (4 head-to-head trials, 26 placebo controlled trials [32 publications], and 1 subgroup or secondary analyses of 1 trial). Previous scans identified additional doses or formulations for two of the included medications (rivastigmine and memantine), and found that one included medication (tacrine) has been discontinued and withdrawn from the US market. The current scan yielded no new drugs, safety alerts, or systematic reviews.

## Appendix A. Abstracts of potentially relevant new trials of second generation antidepressants

### Head-to-head trials

Choi, S. H., K. W. Park, et al. (2011). "Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomized, open-label, parallel-group study." *Curr Med Res Opin* **27**(7): 1375-83.

**OBJECTIVE:** To compare the tolerability and efficacy of combination therapy of memantine plus rivastigmine patch with rivastigmine patch monotherapy in patients with mild to moderate Alzheimer's disease (AD). **RESEARCH DESIGN AND METHODS:** In this multicenter, randomized, open-label study, patients entered an 8-week run-in period (a 5 cm 2 rivastigmine patch for 4 weeks, then a 10 cm(2) patch for 4 weeks) followed by 16 weeks of memantine plus rivastigmine patch or rivastigmine patch monotherapy. The primary outcome measure was the retention rate at the end of the trial. Clinical trial registration: clinicaltrials.gov. NCT01025466. **RESULTS:** Overall, 88 and 84 patients received rivastigmine patch with and without memantine, respectively, and of these, 77 (87.5%) and 70 (83.3%) patients completed the study. The difference in retention rate was not significant (95% confidence interval: -6.3-14.7%). The incidence of adverse events (AEs) (53.4 vs. 50.6%) and discontinuation due to AEs (6.8 vs. 4.8%) were not different between patients with and without memantine. The most frequent AEs were skin irritation in patients with and without memantine (42.0 vs. 34.9%,  $p = 0.71$ ), but discontinuation due to skin irritation was rare (4.5 vs. 2.4%,  $p = 0.74$ ). The incidence of gastrointestinal AEs was very low in patients with and without memantine (nausea, 2.3 vs. 1.2%; vomiting, 1.1 vs. 1.2%). The Korean Version of the Cohen Mansfield Agitation Inventory scores favored rivastigmine patch monotherapy at the end of treatment ( $p = 0.01$ ). Changes in other efficacy measures were similar between the groups.

**CONCLUSION:** There were no significant differences in tolerability and safety between the treatment groups. The combination therapy of memantine plus rivastigmine patch did not show an advantage over rivastigmine patch monotherapy on efficacy analyses. The sample size for comparing tolerability may have been too small to detect a difference of efficacy between the two groups.

Han, H. J., B. C. Kim, et al. (2012). "Response to rivastigmine transdermal patch or memantine plus rivastigmine patch is affected by apolipoprotein E genotype in Alzheimer patients." *Dement Geriatr Cogn Disord* **34**(3-4): 167-73.

**BACKGROUND/AIMS:** The apolipoprotein E (APOE) genotype in response to pharmacological treatments in patients with Alzheimer's disease (AD) remains a matter of controversy. This analysis investigated the effect of the APOE genotype on the clinical response to rivastigmine transdermal patch monotherapy or memantine plus rivastigmine patch in patients with mild to moderate AD. **METHODS:** Two hundred and six ( $n = 206$ ) patients with probable AD and Mini-Mental State Examination (MMSE) scores of 10-20 were randomized to rivastigmine patch monotherapy or memantine plus rivastigmine patch for 24 weeks. Of the 206 patients with probable AD, 146 patients who consented to genetic testing for APOE were included and assessed for this subgroup study. **RESULTS:** There were no significant differences on MMSE, NPI, ADAS-cog, ADCS-ADL, CDR-

SB, NPI and FAB between rivastigmine patch monotherapy and memantine plus rivastigmine patch according to the APOE genotype. However, patients with moderately severe AD (MMSE  $\leq 15$ ) who were APOE epsilon4 carriers showed higher responder rates on ADOS-ADL with memantine plus rivastigmine patch compared to rivastigmine patch monotherapy. **CONCLUSION:** Moderately severe AD patients with the APOE epsilon4 allele may respond more favorably to memantine plus rivastigmine patch than epsilon4 noncarriers.

Howard, R., R. McShane, et al. (2012). "Donepezil and memantine for moderate-to-severe Alzheimer's disease." *N Engl J Med* **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.).

Parnetti, L., D. Chiasserini, et al. (2011). "Changes in CSF acetyl- and butyrylcholinesterase activity after long-term treatment with AChE inhibitors in Alzheimer's disease." *Acta Neurol Scand* **124**(2): 122-9.

**OBJECTIVES:** To measure cerebrospinal fluid (CSF) activity of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) in patients with Alzheimer's disease (AD) participating in randomized clinical trials from three European centers, before and after long-term treatment with different AChE inhibitors (AChEIs). **MATERIALS AND**

**METHODS:** Of the 144 patients included in the study, 104 were treated with donepezil, 15 with galantamine, 16 with rivastigmine, and nine with placebo. CSF AChE and BChE activities were measured at baseline and after 1- year treatment. **RESULTS:** Donepezil and galantamine groups showed a significant increase in CSF AChE activity at follow-up, while no changes for BChE activity were observed; in donepezil group, a positive correlation between plasma concentration and AChE activity was documented. Conversely, in rivastigmine group, a decrease in CSF activity of both enzymes was observed. CSF AChE and BChE activities were not correlated with the clinical outcome in any group considered. CSF biomarkers did not show any change after treatment. **CONCLUSIONS:** AChEIs differently influence the activity of target enzymes in CSF independent of their pharmacodynamic effects.

### Placebo-controlled trials

Andersen, F., M. Viitanen, et al. (2012). "The effect of stimulation therapy and donepezil on cognitive function in Alzheimer's disease. A community based RCT with a two-by-two factorial design." *BMC Neurol* **12**(59).

**BACKGROUND:** Progressive neurodegeneration in Alzheimer's disease (AD) induces cognitive deterioration, and there is controversy regarding the optimal treatment strategy in early AD. Stimulation therapy, including physical exercise and cholinesterase inhibitors are both reported to postpone cognitive deterioration in separate studies. We aimed to study the effect of stimulation therapy and the additional effect of donepezil on cognitive function in early AD. **METHOD:** Design: A two-by-two factorial trial comprising stimulation therapy for one year compared to standard care to which a randomized double-blinded placebo controlled trial with donepezil was added. **Setting:** Nine rural municipalities in Northern Norway. **Participants:** 187 participants 65 years and older with a recent diagnosis of mild or moderate AD were included in the study of which 146 completed a one-year follow-up. **INTERVENTIONS:** In five municipalities the participants received stimulation therapy whereas participants in four received standard care. All participants were randomised double-blindly to donepezil or placebo and tested with three different cognitive tests four times during the one-year study period. **Main outcome:** Changes in MMSE sum score. **Secondary outcome:** Changes in ADAS-Cog and Clock Drawing Test. **RESULTS:** MMSE scores remained unchanged amongst AD participants receiving stimulation therapy and those receiving standard care. The results were consistent for ADAS-Cog and Clock Drawing Test. No time trend differences were found during one-year follow-up between groups receiving stimulation therapy versus standard care or between donepezil versus placebo. **CONCLUSION:** In rural AD patients non-pharmacological and pharmacological therapy did not improve outcome compared with standard care but all groups retained cognitive function during one year follow-up. Other studies are needed to confirm these results. **TRIAL REGISTRATION:** ClinicalTrials.gov (Identifier: NCT00443014). EudraCT database (no 2004-002613-37).

Ashford, J. W., M. Adamson, et al. (2011). "MR spectroscopy for assessment of memantine treatment in mild to moderate Alzheimer dementia." *J Alzheimers Dis* **26 Suppl 3**(331-6).

**OBJECTIVES:** Magnetic Resonance Spectroscopy (MRS) may provide a precise and reliable assessment of the extent and severity of neural tissue loss caused by various

diseases. In particular, the N-Acetyl Aspartate (NAA) and Creatine (Cr) ratio has been found to be an indicator of the degree of neuronal loss in Alzheimer's disease (AD). Memantine is thought to benefit the AD brain by stabilizing the NMDA receptors on neurons in turn reducing excitotoxicity. Despite its effectiveness in treating moderate to severe AD, memantine has not had similar success in the treatment of mildly demented AD patients. The objective of this study was to test whether memantine would slow or prevent the loss of neurons in mild to moderate AD patients. **METHODS:** A double-blind placebo-controlled study was designed to measure the effect of a year-long course of memantine in patients with a probable AD diagnosis with mild to moderate dementia. The primary outcome measure was stipulated to be change in MRS NAA/Cr ratio in inferior parietal cortex in memantine relative to the placebo treatment condition. The secondary outcome measures were changes in cognitive and function scale scores. **RESULTS:** This pilot study failed to demonstrate a benefit of memantine on the primary outcome measure, the inferior parietal NAA/Cr ratio, or the secondary outcome measures. **CONCLUSIONS:** More studies are needed to determine the effect of memantine on regions of the brain significantly affected by AD pathology.

Bakchine, S.H. Loft. (2007). "Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study." *J Alzheimers Dis* **11**(4): 471-9.

Memantine is a moderate affinity, uncompetitive NMDA receptor antagonist currently approved for the treatment of moderate to severe Alzheimer's disease (AD). A 24-week, double-blind, placebo-controlled, study (Study 99679) conducted in Europe evaluated the efficacy and tolerability of 20mg/day memantine in patients with mild to moderate AD. Patients were randomised to either memantine or placebo in a 2:1 ratio. Efficacy was primarily assessed as change from baseline in ADAS-cog and CIBIC-plus score. Of 470 patients randomised and treated (memantine, n=318; placebo, n=152), 85% and 91% completed the study. Memantine-treated patients showed statistically significant improvement relative to placebo at weeks 12 and 18, and numerical superiority at week 24 on both efficacy scales. The lack of significance at week 24 was attributed to an unexpectedly high placebo response. Memantine was well tolerated with an adverse event profile similar to placebo. The data presented support the efficacy of memantine in mild to moderate AD.

Black, S. E., R. Doody, et al. (2007). "Donepezil preserves cognition and global function in patients with severe Alzheimer disease." *Neurology* **69**(5): 459-69.

**OBJECTIVE:** To evaluate the efficacy and safety of donepezil for severe Alzheimer disease (AD). **METHODS:** Patients with severe AD (Mini-Mental State Examination [MMSE] scores 1 to 12 and Functional Assessment Staging [FAST] scores  $\geq$  6) were enrolled in this multinational, double-blind, placebo-controlled trial at 98 sites. Patients were randomized to donepezil 10 mg daily or placebo for 24 weeks. Primary endpoints were the Severe Impairment Battery (SIB) and Clinician's Interview-Based Impression of Change-Plus caregiver input (CIBIC-Plus). Secondary endpoints included the MMSE, the Alzheimer Disease Cooperative Study-Activities of Daily Living-severe version (ADCS-ADL-sev), the Neuropsychiatric Inventory (NPI), the Caregiver Burden Questionnaire (CBQ), and the Resource Utilization for Severe Alzheimer Disease

Patients (RUSP). Efficacy analyses were performed in the intent-to-treat (ITT) population using last post-baseline observation carried forward (LOCF). Safety assessments were performed for patients receiving  $\geq$  or  $=1$  dose of donepezil or placebo. **RESULTS:** Patients were randomized to donepezil (n = 176) or placebo (n = 167). Donepezil was superior to placebo on SIB score change from baseline to endpoint (least squares mean difference 5.32; p = 0.0001). CIBIC-Plus and MMSE scores favored donepezil at endpoint (p = 0.0473 and p = 0.0267). Donepezil was not significantly different from placebo on the ADCS-ADL-sev, NPI, CBQ, or RUSP. Adverse events reported were consistent with the known cholinergic effects of donepezil and with the safety profile in patients with mild to moderate AD. **CONCLUSION:** Patients with severe AD demonstrated greater efficacy compared to placebo on measures of cognition and global function.

Blesa, R., C. Ballard, et al. (2007). "Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease." *Neurology* **69**(4 Suppl 1): S23-8.

Alzheimer disease (AD) has a significant impact on caregivers. Administering and managing medications is one of their many daily tasks. More effective modes of drug administration may benefit patient and caregiver, and may improve compliance. A prospective outcome of the IDEAL (Investigation of TransDermal Exelon in ALzheimer's disease) trial was to evaluate caregiver preference for rivastigmine patches compared with capsules. The 24-week, randomized, double-blind, double-dummy, placebo- and active-controlled IDEAL trial investigated once-daily rivastigmine patches vs twice-daily capsules in moderate AD patients. Caregivers rated patch adhesion throughout. The AD Caregiver Preference Questionnaire (ADCPQ) assessed patch vs capsule from caregivers' perspective, based on expectations, preferences, and satisfaction with treatment. A total of 1,059 caregivers completed the ADCPQ while their respective patients were on study drug. More than 70% of caregivers preferred the patch to capsules overall. The patch was preferred to capsules with respect to ease of use (p < 0.0001) and ease of following the schedule (p < 0.0001). Caregivers indicated greater satisfaction overall (p < 0.0001) and less interference with daily life (p < 0.01) with the patch vs capsules. The preference substudy of the IDEAL trial demonstrated that caregivers of AD patients preferred patches to capsules for drug delivery. Preference for the patch may indicate reduced caregiver stress, substantiated by greater satisfaction and less interference with daily life. These benefits may lead to improved compliance.

Burns, A., R. Bernabei, et al. (2009). "Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial." *Lancet Neurol* **8**(1): 39-47.

**BACKGROUND:** The efficacy of galantamine has been shown in patients with mild, moderate, and advanced moderate Alzheimer's disease (AD). Here we report its efficacy in patients with severe AD. **METHODS:** Between December, 2003, and March, 2007, patients aged 84 (SD 6) years with severe AD (mini-mental state examination [MMSE] score 5-12 points), in a nursing home setting were randomly assigned to receive galantamine (n=207), titrated initially to 24 mg/day, or placebo (n=200). Co-primary efficacy measures for cognitive function and ability to undertake normal daily activities were the severe impairment battery (SIB) and the seven-item minimum data set-activities

of daily living (MDS-ADL), respectively. Adverse events, vital signs, laboratory parameters, and electrocardiograms were monitored. This trial is registered with ClinicalTrials.gov, number NCT00216593. FINDINGS: 168 of 207 (81%) patients in the galantamine group and 161 of 200 (81%) in the placebo group completed the study. Mean SIB scores increased (improved) by 1.9 (95% CI -0.1 to 3.9) points with galantamine and decreased (worsened) by 3.0 (-5.6 to -0.5) points with placebo (between-group least squares mean difference 4.36, 1.3 to 7.5;  $p=0.006$ ). Mean MDS-ADL self-performance score worsened by 1.2 (0.6 to 1.8) points and 1.6 (0.8 to 2.3) points, respectively (between-group least squares mean difference -0.41, -1.3 to 0.5;  $p=0.383$ ). Nominally significant between-group differences in favour of galantamine occurred for the SIB domains of memory ( $p=0.006$ ), praxis ( $p=0.010$ ), and visuospatial ability ( $p=0.002$ ), and for the MDS-ADL subitem locomotion on unit ( $p=0.021$ ). 183 of 207 patients (88%) who received galantamine and 177 of 200 (89%) who received placebo had adverse events, which were mostly mild to moderate. Eight patients (4%) in the galantamine group and 21 patients (11%) in the placebo group died. ECG abnormalities were similar between the two groups. INTERPRETATION: Galantamine can be started and used safely in elderly patients with severe AD. Galantamine improved cognitive function but failed to significantly improve the co-primary parameter of overall activities of daily living.

Cummings, J. L., M. R. Farlow, et al. (2010). "Rivastigmine transdermal patch tolerability: results of a 1-year clinical trial in patients with mild-to-moderate Alzheimer's disease." *Clin Drug Investig* **30**(1): 41-9.

**BACKGROUND AND OBJECTIVES:** Transdermal patches provide non-invasive, continuous drug delivery, and offer significant potential advantages over oral treatments. With all transdermal treatments a proportion of patients will experience some form of skin reaction. The rivastigmine patch has been approved for the treatment of mild-to-moderate Alzheimer's disease (AD) since July 2007 in the US. The aim of the component of the trial reported here was to evaluate the skin tolerability of the rivastigmine transdermal patch in patients with mild-to-moderate AD. **METHODS:** The pivotal IDEAL trial was a 24-week, randomized, double-blind, placebo-controlled, multicentre trial of the efficacy and tolerability of the rivastigmine transdermal patch in 1195 patients with mild-to-moderate AD. This was followed by a 28-week open-label extension. Although not prospectively defined as a secondary assessment, during both phases of the study the condition of the patients' skin at the application site was evaluated. These data are reviewed in this article. **RESULTS:** During the 24-week, double-blind phase of the study, 89.6% of patients in the target 9.5 mg/24 h patch treatment group had recorded 'no, slight or mild' signs or symptoms for their most severe application-site reaction. Erythema and pruritus were the most commonly reported reactions. No patient in any patch treatment group experienced a skin reaction that was reported as a serious adverse event. In the 9.5 mg/24 h treatment group, 2.4% of patients discontinued treatment due to an application-site reaction. During the 28-week open-label extension, the skin tolerability profile was similar to that seen in the double-blind phase. Overall, 3.7% of patients discontinued treatment due to application-site skin reactions. There was no indication that the severity of the skin reactions increased over time. **CONCLUSION:** Overall, the data support a favourable skin tolerability profile for the rivastigmine



transdermal patch, and provide reassurance that the benefits of rivastigmine patch therapy for patients with AD are not confounded by significant skin irritation problems. Nevertheless, care should be taken to follow manufacturer's advice about patch application, such as daily rotation of the application site, to minimize the risk of skin reactions.

Cummings, J. L., E. Schneider, et al. (2006). "Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment." *Neurology* **67**(1): 57-63.

**OBJECTIVE:** To investigate the behavioral effects of memantine in moderate to severe Alzheimer disease (AD). **METHODS:** The authors conducted a hypothesis-generating, exploratory analysis of a 24-week, double-blind, placebo-controlled trial comparing memantine (20 mg/day) with placebo in subjects with moderate to severe AD on stable donepezil treatment. They employed the Neuropsychiatric Inventory (NPI; 12-item), administered at baseline, week 12, and week 24, to assess the effects of memantine on behavior. Global, cognitive, and functional measures were collected and relationships between these assessments and changes in behavior were determined. The intent-to-treat population was examined using last-observation-carried-forward and observed-cases approaches. **RESULTS:** Patients treated with memantine had significantly lower NPI total scores than patients treated with placebo. Analyses of the 12 NPI domains revealed significant effects in favor of memantine on agitation/aggression, eating/appetite, and irritability/lability. Of patients who exhibited agitation/aggression at baseline, those treated with memantine showed significant reduction of symptoms compared with placebo-treated patients. Memantine-treated patients without agitation/aggression at baseline evidenced significantly less emergence of this symptom compared with similar patients receiving placebo. Caregivers of patients receiving memantine registered significantly less agitation-related distress. There were significant relationships between the NPI and the global rating scale and performance of activities of daily living, but not between changes in the NPI and cognition. **CONCLUSION:** Treatment with memantine reduced agitation/aggression, irritability, and appetite/eating disturbances. Memantine reduced agitation/aggression in patients who were agitated at baseline and delayed its emergence in those who were free of agitation at baseline.

Dysken, M. W., et al. (2014). "Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial." *JAMA* **311**(1): 33-44.

**IMPORTANCE:** Although vitamin E and memantine have been shown to have beneficial effects in moderately severe Alzheimer disease (AD), evidence is limited in mild to moderate AD. **OBJECTIVE:** To determine if vitamin E (alpha tocopherol), memantine, or both slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitor. **DESIGN, SETTING, AND PARTICIPANTS:** Double-blind, placebo-controlled, parallel-group, randomized clinical trial involving 613 patients with mild to moderate AD initiated in August 2007 and concluded in September 2012 at 14 Veterans Affairs medical centers. **INTERVENTIONS:** Participants received either 2000 IU/d of alpha tocopherol (n = 152), 20 mg/d of memantine (n = 155), the combination (n = 154), or placebo (n = 152). **MAIN OUTCOMES AND MEASURES:** Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory score (range, 0-78). Secondary outcomes included cognitive, neuropsychiatric,

functional, and caregiver measures. **RESULTS:** Data from 561 participants were analyzed (alpha tocopherol = 140, memantine = 142, combination = 139, placebo = 140), with 52 excluded because of a lack of any follow-up data. Over the mean (SD) follow-up of 2.27 (1.22) years, ADAS-ADL Inventory scores declined by 3.15 units (95% CI, 0.92 to 5.39; adjusted  $P = .03$ ) less in the alpha tocopherol group compared with the placebo group. In the memantine group, these scores declined 1.98 units less (95% CI, -0.24 to 4.20; adjusted  $P = .40$ ) than the placebo group's decline. This change in the alpha tocopherol group translates into a delay in clinical progression of 19% per year compared with placebo or a delay of approximately 6.2 months over the follow-up period. Caregiver time increased least in the alpha tocopherol group. All-cause mortality and safety analyses showed a difference only on the serious adverse event of "infections or infestations," with greater frequencies in the memantine (31 events in 23 participants) and combination groups (44 events in 31 participants) compared with placebo (13 events in 11 participants). **CONCLUSIONS AND RELEVANCE:** Among patients with mild to moderate AD, 2000 IU/d of alpha tocopherol compared with placebo resulted in slower functional decline. There were no significant differences in the groups receiving memantine alone or memantine plus alpha tocopherol. These findings suggest benefit of alpha tocopherol in mild to moderate AD by slowing functional decline and decreasing caregiver burden. **TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00235716.

Feldman, H. H.R. Lane. (2007). "Rivastigmine: a placebo controlled trial of twice daily and three times daily regimens in patients with Alzheimer's disease." *J Neurol Neurosurg Psychiatry* 78(10): 1056-63.

**OBJECTIVE:** To evaluate the efficacy and safety of rapidly titrated rivastigmine administered twice (BID) or three times (TID) daily in patients with mild to moderate Alzheimer's disease (AD). **METHODS:** This was a 26 week international, randomised, double blind, placebo controlled study in which 678 patients with probable AD received placebo or rivastigmine 2-12 mg/day BID or TID. Primary outcome measures included the cognitive subscale of the AD Assessment Scale (ADAS-cog) and categorical analysis of the Clinician Interview Based Impression of Change incorporating caregiver information (CIBIC-Plus). Secondary outcomes were the CIBIC-Plus change from baseline, Progressive Deterioration Scale, ADAS-cogA, Mini-Mental State Examination and Global Deterioration Scale. **RESULTS:** At week 26, mean rivastigmine dose was 9.6 (2.76) mg/day in the TID group and 8.9 (2.93) mg/day in the BID group. Mean ADAS-cog changes from baseline in the TID and BID rivastigmine treated groups were -0.2 (SD 7.3) and 1.2 (SD 7.2) versus 2.8 (SD 7.2) for the placebo group ( $p < 0.05$ ). Differences between rivastigmine TID and placebo on the CIBIC-Plus categorical responder analysis were significant (31% vs 19%;  $p < 0.05$ , intention to treat). No significant differences were seen between BID and placebo for this outcome measure. Adverse events were predominantly gastrointestinal, occurring mainly during dose titration. Withdrawal because of adverse events accounted for 17% of BID, 11% of TID and 9% of placebo patients. **CONCLUSIONS:** Rivastigmine administered as a BID or TID regimen significantly benefited cognitive, function and global performances in AD patients. The TID regimen showed a tendency for superior tolerability and permitted titration to higher doses, an outcome that is significant as the efficacy of rivastigmine is dose related.

Fox, C., M. Crugel, et al. (2012). "Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial." *PLoS One* 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. **TRIAL REGISTRATION:** ClinicalTrials.gov NCT00371059. **TRIAL REGISTRATION:** International Standard Randomised Controlled Trial 24953404.

Frolich, L., T. Ashwood, et al. (2011). "Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: a phase IIb dose-finding study." *J Alzheimers Dis* 24(2): 363-74.

AZD3480 is a selective agonist of the central alpha4beta2 and alpha2beta2 neuronal nicotinic cholinergic receptors (NNRs). Its effects on cognition were investigated in 567 patients with mild-to-moderate Alzheimer's disease (AD) (Mini Mental State Examination [MMSE] 12-26). Mean baseline MMSE was 21 (SD +/- 3.7), with 61% of patients having mild disease (MMSE 21-26). Mean age was 74 (range 58-85) years. Patients were randomized to one of 5 treatment groups: AZD3480 5 mg, 20 mg or 35/100 mg, donepezil 10 mg (active comparator) or placebo, and treated once daily for 12 weeks. The primary outcome measure was change from baseline at Week 12 on the AD Assessment Scale-Cognitive Subscale (ADAS-Cog). Neither AZD3480 nor donepezil showed a statistically significant improvement versus placebo on ADAS-Cog. Improvements in a number of secondary outcome measures (MMSE, AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) and Disability Assessment for Dementia [DAD]) were observed for AZD3480 and for donepezil. A post-hoc analysis on ADAS-Cog, excluding patients with very mild AD (MMSE 25-26) indicated

improvement versus placebo for AZD3480 20 mg (-1.4, 95% CI: -3.0; 0.2) and donepezil (-1.0, 95% CI: -2.3; 0.3). AZD3480 was well tolerated. The study did not meet proof of concept criteria: since neither AZD3480 nor donepezil were statistically significantly superior to placebo on ADAS-Cog and was considered to be inconclusive. Further studies are required to determine the therapeutic potential of stimulating alpha4beta2 receptors with NNRs in AD patients.

Gold, M., C. Alderton, et al. (2010). "Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study." *Dement Geriatr Cogn Disord* **30**(2): 131-46.

**BACKGROUND/AIMS:** A phase II study of the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone extended release (RSG XR) in mild-to-moderate Alzheimer's disease (AD) detected a treatment benefit to cognition in apolipoprotein E(APOE)-epsilon4-negative subjects. The current phase III study with prospective stratification by APOE genotype was conducted to confirm the efficacy and safety of RSG XR in mild-to-moderate AD. An open-label extension study assessed the long-term safety and tolerability of 8 mg RSG XR. **METHODS:** This double-blind, randomized, placebo-controlled study enrolled 693 subjects. Within 2 APOE allelic strata (epsilon4-positive, epsilon4-negative), subjects were randomized (2:2:2:1) to once-daily placebo, 2 mg RSG XR, 8 mg RSG XR or 10 mg donepezil (control). Coprimary endpoints were change from baseline to week 24 in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) score, and week 24 Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC+). **RESULTS:** At week 24, no significant differences from placebo in change from baseline in coprimary endpoints were detected with either the RSG XR dose in APOE-epsilon4-negative subjects or overall. For donepezil, no significant treatment difference was detected in ADAS-Cog; however, a significant difference was detected ( $p = 0.009$ ) on the CIBIC+. Peripheral edema was the most common adverse event for 8 mg RSG XR (15%) and placebo (5%), and nasopharyngitis for 2 mg RSG XR (7%). **CONCLUSION:** No evidence of efficacy of 2 mg or 8 mg RSG XR monotherapy in cognition or global function was detected in the APOE-epsilon4-negative or other analysis populations. The safety and tolerability of RSG XR was consistent with its known pharmacology.

Grossberg, G., X. Meng, et al. (2011). "Impact of rivastigmine patch and capsules on activities of daily living in Alzheimer's disease." *Am J Alzheimers Dis Other Dement* **26**(1): 65-71.

**BACKGROUND:** Rivastigmine patches provide similar efficacy to rivastigmine capsules with a lower incidence of gastrointestinal side effects in patients with probable Alzheimer's disease (AD). **METHODS:** Post hoc analysis of a 24-week, prospective, international, randomized, double-blind, placebo- and active-controlled trial. Patients ( $n = 892$ ) with probable AD received rivastigmine transdermal patches (9.5 mg/24 hours [10 cm(2)]), rivastigmine capsules (6 mg twice daily), or placebo, and impact on activities of daily living (ADLs) was assessed utilizing 3 subscales: basic, high-level function, and autonomy. **RESULTS:** At week 24, both rivastigmine groups demonstrated significantly superior performance in Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Total Score versus placebo (rivastigmine patch,  $P = .013$ ; capsules,  $P = .039$ ). Overall, both rivastigmine formulations provided benefits in ADL subscales.

For basic ADLs, rivastigmine capsules performed significantly better than placebo ( $P = .012$ ). For high-level function ADLs, rivastigmine patch performed better than placebo ( $P = .056$ ). For autonomy ADLs, rivastigmine patch performed significantly better than placebo ( $P = .017$ ). **CONCLUSION:** Rivastigmine patches and capsules provide significant effects in both total and subscale ADLs in patients with probable AD.

Grossberg, G., C. Sadowsky, et al. (2009). "Safety and tolerability of the rivastigmine patch: results of a 28-week open-label extension." *Alzheimer Dis Assoc Disord* **23**(2): 158-64.

The primary objective of the open-label extension was to evaluate the long-term safety and tolerability of a transdermal rivastigmine patch up to 1 year, as a novel approach to treatment in Alzheimer disease. This was a 28-week extension to a 24-week, double-blind, double-dummy, placebo-controlled, and active-controlled study evaluating rivastigmine patches [9.5 mg/24 h (10 cm<sup>2</sup>) and 17.4 mg/24 h (20 cm<sup>2</sup>)] and oral capsules (3 to 6 mg twice-daily). Patients entering the extension were switched directly to 9.5 mg/24 h rivastigmine patch and increased to 17.4 mg/24 h patch, irrespective of their double-blind study treatment. Primary measures included safety and tolerability assessments, including adverse events and serious adverse events. Of 1195 patients randomized to treatment, 870 (72.8%) completed the double-blind study and entered the open-label extension. During weeks 1 to 4 of the extension, 9.5 mg/24 h rivastigmine patch was well tolerated overall by patients formerly randomized to rivastigmine capsule or patch groups:  $\leq 2.5\%$  reported nausea and  $\leq 1.9\%$  reported vomiting. No unexpected safety issues arose, and skin tolerability was good; similar to the double-blind study. During the 28-week, open-label extension phase, the patch seemed to be well tolerated with a favorable safety profile.

Grossberg, G. T., J. T. Olin, et al. (2011). "Dose effects associated with rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease." *Int J Clin Pract* **65**(4): 465-71.

**AIM:** The cholinesterase inhibitor rivastigmine is available in both oral and transdermal forms. The efficacy of oral rivastigmine appears to be dose-dependent. The current analysis investigates the effect of dose on the efficacy of the rivastigmine transdermal patch. **METHODS:** This was a retrospective analysis of a large, international, 24-week, randomised, placebo- and active-controlled trial (IDEAL, CENA713D2320) of rivastigmine in patients with mild-to-moderate Alzheimer's disease (AD). Patients received the 9.5 mg/24 h rivastigmine patch, the 17.4 mg/24 h rivastigmine patch, 12 mg/day rivastigmine capsules or placebo. Changes from baseline at week 24 on the AD Assessment Scale-cognitive subscale (ADAS-cog), AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) and the AD Cooperative Study-Activities of Daily Living (ADCS-ADL) scale were calculated based on the patient's mode and last prescribed patch dose. The analysis included the 4.6 mg/24 h and 13.3 mg/24 h patch doses, for which efficacy data have not previously been reported. **RESULTS:** Significant differences ( $p < 0.05$  vs. placebo) were seen on the ADAS-cog and ADCS-ADL for all mode rivastigmine patch doses (except 4.6 mg/24 h) and all last prescribed rivastigmine patch doses (except 4.6 mg/24 h and 13.3 mg/24 h). Patients with a last prescribed/mode patch dose of 9.5 mg/24 h and 13.3 mg/24 h showed significant improvements ( $p < 0.05$  vs. placebo) on the ADCS-CGIC. **CONCLUSION:** Rivastigmine patch doses higher than

9.5 mg/24 h may offer additional benefits. The 13.3 mg/24 h patch is worthy of further investigation.

Grossberg, G. T., et al. (2013). "The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors." *CNS Drugs* **27**(6): 469-478.

**INTRODUCTION:** Immediate-release memantine (10 mg, twice daily) is approved in the USA for moderate-to-severe Alzheimer's disease (AD). This study evaluated the efficacy, safety, and tolerability of a higher-dose, once-daily, extended-release formulation in patients with moderate-to-severe AD concurrently taking cholinesterase inhibitors. **METHODS:** In this 24-week, double-blind, multinational study (NCT00322153), outpatients with AD (Mini-Mental State Examination scores of 3-14) were randomized to receive once-daily, 28-mg, extended-release memantine or placebo. Co-primary efficacy parameters were the baseline-to-endpoint score change on the Severe Impairment Battery (SIB) and the endpoint score on the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus). The secondary efficacy parameter was the baseline-to-endpoint score change on the 19-item Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL19); additional parameters included the baseline-to-endpoint score changes on the Neuropsychiatric Inventory (NPI) and verbal fluency test. Data were analyzed using a two-way analysis of covariance model, except for CIBIC-Plus (Cochran-Mantel-Haenszel test). Safety and tolerability were assessed through adverse events and physical and laboratory examinations. **RESULTS:** A total of 677 patients were randomized to receive extended-release memantine (n = 342) or placebo (n = 335); completion rates were 79.8 and 81.2 %, respectively. At endpoint (week 24, last observation carried forward), memantine-treated patients significantly outperformed placebo-treated patients on the SIB (least squares mean difference [95 % CI] 2.6 [1.0, 4.2]; p = 0.001), CIBIC-Plus (p = 0.008), NPI (p = 0.005), and verbal fluency test (p = 0.004); the effect did not achieve significance on ADCS-ADL19 (p = 0.177). Adverse events with a frequency of  $\geq 5.0$  % that were more prevalent in the memantine group were headache (5.6 vs. 5.1 %) and diarrhea (5.0 vs. 3.9 %). **CONCLUSION:** Extended-release memantine was efficacious, safe, and well tolerated in this population.

Homma, A., Y. Imai, et al. (2008). "Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24-week, double-blind, placebo-controlled, randomized trial." *Dement Geriatr Cogn Disord* **25**(5): 399-407.

**BACKGROUND/AIMS:** A 24-week, randomized, parallel-group, double-blind placebo-controlled study was conducted to evaluate the efficacy and tolerability of donepezil in severe Alzheimer's disease (AD). **METHODS:** Patients with severe AD (Mini-Mental State Examination score 1-12; modified Hachinski Ischemic Score  $\leq 6$ ; Functional Assessment Staging  $\geq 6$ ) were enrolled in this study in Japan. A total of 325 patients were randomized to donepezil 5 mg/day (n = 110), donepezil 10 mg/day (n = 103) or placebo (n = 112). Primary outcome measures were change from baseline to endpoint in the Severe Impairment Battery (SIB) and Clinician's Interview-Based Impression of Change-plus caregiver input (CIBIC-plus) at the endpoint visit. **RESULTS:** Donepezil 5

mg/day and 10 mg/day were significantly superior to placebo on the SIB, with a least-squares mean treatment difference of 6.7 and 9.0, respectively ( $p < 0.001$  compared with placebo). CIBIC-plus analyses showed significant differences in favor of donepezil 10 mg/day over placebo at endpoint ( $p = 0.003$ ). A statistically significant dose-response relationship was demonstrated with the SIB and CIBIC-plus. Donepezil was well tolerated. **CONCLUSION:** This study confirmed the effectiveness of donepezil 10 mg/day in patients with severe AD and demonstrated a significant dose-response relationship. Donepezil at dosages of both 5 mg/day and 10 mg/day is safe and well tolerated in Japanese patients with severe AD.

Howard, R. J., E. Juszcak, et al. (2007). "Donepezil for the treatment of agitation in Alzheimer's disease." *N Engl J Med* **357**(14): 1382-92.

**BACKGROUND:** Agitation is a common and distressing symptom in patients with Alzheimer's disease. Cholinesterase inhibitors improve cognitive outcomes in such patients, but the benefits of these drugs for behavioral disturbances are unclear. **METHODS:** We randomly assigned 272 patients with Alzheimer's disease who had clinically significant agitation and no response to a brief psychosocial treatment program to receive 10 mg of donepezil per day (128 patients) or placebo (131 patients) for 12 weeks. The primary outcome was a change in the score on the Cohen-Mansfield Agitation Inventory (CMAI) (on a scale of 29 to 203, with higher scores indicating more agitation) at 12 weeks. **RESULTS:** There was no significant difference between the effects of donepezil and those of placebo on the basis of the change in CMAI scores from baseline to 12 weeks (estimated mean difference in change [the value for donepezil minus that for placebo], -0.06; 95% confidence interval [CI], -4.35 to 4.22). Twenty-two of 108 patients (20.4%) in the placebo group and 22 of 113 (19.5%) in the donepezil group had a reduction of 30% or greater in the CMAI score (the value for donepezil minus that for placebo, -0.9 percentage point; 95% CI, -11.4 to 9.6). There were also no significant differences between the placebo and donepezil groups in scores for the Neuropsychiatric Inventory, the Neuropsychiatric Inventory Caregiver Distress Scale, or the Clinician's Global Impression of Change. **CONCLUSIONS:** In this 12-week trial, donepezil was not more effective than placebo in treating agitation in patients with Alzheimer's disease. (ClinicalTrials.gov number, NCT00142324 [ClinicalTrials.gov].).

Lee, J. H.J. Seigny. (2011). "Effects of body weight on tolerability of rivastigmine transdermal patch: a post-hoc analysis of a double-blind trial in patients with Alzheimer disease." *Alzheimer Dis Assoc Disord* **25**(1): 58-62.

The rationale for the development of the rivastigmine transdermal patch was to improve upon an efficacious therapy by mitigating certain adverse events, such as nausea and vomiting. This may be particularly important in Alzheimer disease patients with low body weights, who may be more susceptible to these adverse events. This analysis compared the effect of body weight on tolerability in Alzheimer disease patients receiving rivastigmine capsules or rivastigmine patch. Using data from a 24-week trial, adverse events and discontinuations were evaluated in patients stratified on the basis of extreme low weight (<50 kg), medium weight (50 to 80 kg), and high weight (>80 kg) at baseline. Rivastigmine patch was generally well tolerated, regardless of patient body weight. Among patients receiving rivastigmine patch, lower body weight, as stratified,

was not associated with a higher adverse event rate; however, there was an association between a higher adverse event rate and low body weight among patients receiving rivastigmine capsules. Discontinuations because of adverse events were not directly related to weight. A lower incidence of adverse events was apparent with transdermal delivery of rivastigmine compared with oral administration.

Mazza, M., A. Capuano, et al. (2006). "Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study." *Eur J Neurol* **13**(9): 981-5.

The Ginkgo biloba special extract EGb 761 seems to produce neuroprotective effects in neurodegenerative diseases of multifactorial origin. There is still debate about the efficacy of Ginkgo biloba special extract EGb 761 compared with second-generation cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's dementia. Our aim is to assess the efficacy of the Ginkgo biloba special extract E.S. in patients with dementia of the Alzheimer type in slowing down the disease's degenerative progression and the patients' cognitive impairment compared with donepezil and placebo. The trial was designed as a 24-week randomized, placebo-controlled, double-blind study. Patients aged 50-80 years, suffering from mild to moderate dementia, were allocated into one of the three treatments: Ginkgo biloba (160 mg daily dose), donepezil (5 mg daily dose), or placebo group. The degree of severity of dementia was assessed by the Syndrom Kurz test and the Mini-Mental State Examination. Clinical Global Impression score was recorded to assess the change in the patients' conditions and the therapeutic efficacy of tested medications. Our results confirm the clinical efficacy of Ginkgo biloba E.S. (Flavogin) in the dementia of the Alzheimer type, comparable with donepezil clinical efficacy. There are few published trials that have directly compared a cholinesterase inhibitor with Ginkgo for dementia. This study directly compares a cholinesterase inhibitor with Ginkgo biloba for dementia of the Alzheimer type and could be a valid contribution in this debate. Our study suggests that there is no evidence of relevant differences in the efficacy of EGb 761 and donepezil in the treatment of mild to moderate Alzheimer's dementia, so the use of both substances can be justified. In addition, this study contributes to establish the efficacy and tolerability of the Ginkgo biloba special extract E.S. in the dementia of the Alzheimer type with special respect to moderately severe stages.

Mowla, A., M. Mosavinasab, et al. (2007). "Does serotonin augmentation have any effect on cognition and activities of daily living in Alzheimer's dementia? A double-blind, placebo-controlled clinical trial." *J Clin Psychopharmacol* **27**(5): 484-7.

**OBJECTIVE:** Recent studies suggest that cholinergic dysfunction does not provide a complete account of age-related cognitive deficits, and other neuronal systems like monoaminergic hypofunction are involved. In several studies, selective serotonin reuptake inhibitors demonstrated promotion in neurogenesis in the hippocampus and enhanced memory and cognition. The aim of this study is to survey the effect of serotonin augmentation on cognition and activities of daily living in patients with Alzheimer's disease. **METHOD:** The trial was designed as a 12-week randomized, placebo-controlled, double-blind study. One hundred twenty-two patients aged 55 to 85 years with mild-to-moderate Alzheimer's dementia were randomly allocated in 1 of the 3 treatment groups:



fluoxetine plus rivastigmine, rivastigmine alone, or placebo group. Efficacy measures comprised assessments of cognition, activities of daily living, and global functioning. Hamilton Depression Scale also was used to assess changes in mood throughout the study. **RESULT:** Fluoxetine plus rivastigmine and rivastigmine groups demonstrated improvement on measures of cognitive and memory without any significant difference; however, the former group did better in their activities of daily living and global functioning. Patients taking placebo had significant deterioration in all the efficacy measures. Patients taking rivastigmine or rivastigmine plus fluoxetine had improvements in Hamilton Depression Scale without significant differences. **CONCLUSIONS:** Concomitant use of selective serotonin-enhancing agents and acetyl cholinesterase inhibitors can provide greater benefit in activities of daily living and global functioning in patients with cognitive impairment. Because our study is preliminary, larger double-blind studies are needed to confirm the results.

Peskind, E. R., S. G. Potkin, et al. (2006). "Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial." *Am J Geriatr Psychiatry* **14**(8): 704-15.

**OBJECTIVE:** The objective of this study was to compare the efficacy and safety of the moderate-affinity, uncompetitive N-methyl-d-aspartate receptor antagonist, memantine, versus placebo in patients with mild to moderate Alzheimer disease (AD). **METHOD:** This was a randomized, double-blind, placebo-controlled clinical trial conducted at 42 U.S. sites. Participants were 403 outpatients with mild to moderate AD and Mini-Mental State Examination scores of 10-22 randomized to memantine (20 mg/day; N=201) or placebo (N=202) for 24 weeks. Primary outcomes were change from baseline at 24 weeks on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), a measure of cognition, and on the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), a global measure. Secondary outcomes included change on the Neuropsychiatric Inventory (NPI) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL(23)), measures of behavior and function, respectively. **RESULTS:** Most (82.4%) participants completed the trial. Memantine resulted in significantly better outcomes than placebo on measures of cognition, global status, and behavior when based on the protocol-specified primary last observation carried forward imputation as well as a mixed-models repeated-measures approach applied to the continuous outcomes. Treatment discontinuations because of adverse events for memantine versus placebo were 19 (9.5%) and 10 (5.0%), respectively. **CONCLUSIONS:** These results support the safety and efficacy of memantine for the treatment of mild to moderate AD.

Porsteinsson, A. P., G. T. Grossberg, et al. (2008). "Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial." *Curr Alzheimer Res* **5**(1): 83-9.

**OBJECTIVE:** To evaluate the efficacy and safety of memantine in patients with mild to moderate Alzheimer's disease (AD) receiving cholinesterase inhibitor (ChEI) treatment. **METHODS:** Participants (N= 433) with probable AD, Mini-Mental State Exam (MMSE) scores between 10-22 (inclusive), and concurrent stable use of ChEIs (donepezil, rivastigmine, galantamine) were randomized to placebo or memantine (20 mg once daily) for 24 weeks. Primary outcomes were changes from baseline on the Alzheimer's Disease

Assessment Scale-cognitive subscale (ADAS-cog) and on Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) score. Secondary measures comprised the 23-item Alzheimer Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL(23)), Neuropsychiatric Inventory (NPI), and MMSE. RESULTS: At the end of the trial, there were no statistically significant differences between the memantine- and placebo group on primary and secondary outcome measures. The incidence of adverse events (AEs) was similar between the two groups, with no AE occurring in more than 5% of memantine-treated patients and at a rate twice that of the placebo group. CONCLUSIONS: In this trial, memantine did not show an advantage over placebo based on protocol-specified primary or secondary analyses in patients with mild to moderate AD on stable ChEI regimens. There were no significant differences in tolerability and safety between the memantine- and placebo groups.

Rockwood, K., S. Fay, et al. (2006). "Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial." *Cmaj* **174**(8): 1099-105.

BACKGROUND: Although cholinesterase inhibitors have produced statistically significant treatment effects, their clinical meaningfulness in Alzheimer's disease is disputed. An important aspect of clinical meaningfulness is the extent to which an intervention meets the goals of treatment. METHODS: In this randomized controlled trial, patients with mild to moderate Alzheimer's disease were treated with either galantamine or placebo for 4 months, followed by a 4-month open-label extension during which all patients received galantamine. The primary outcome measures were Goal Attainment Scaling (GAS) scores from assessments by clinicians and by patients or caregivers of treatment goals set before treatment and evaluated every 2 months. Secondary outcome measures included the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), the Clinician's Interview-based Impression of Change plus Caregiver Input (CIBIC-plus), the Disability Assessment for Dementia (DAD) and the Caregiving Burden Scale (CBS). To evaluate treatment effect, we calculated effect sizes (as standardized response means [SRMs]) and p values. RESULTS: Of 159 patients screened, 130 (mean age 77 [standard deviation (SD) 7.7]; 63% women) were enrolled in the study (64 in the galantamine group and 66 in the placebo group); 128 were included in the analysis because they had at least one post-baseline evaluation. In the intention-to-treat analysis, the clinician-rated GAS scores showed a significantly greater improvement in goal attainment among patients in the galantamine group than among those in the placebo group (change from baseline score 4.8 [SD 9.6]) v. 0.9 [SD 9.5] respectively; SRM = 0.41, p = 0.02). The patient- caregiver-rated GAS scores showed a similar improvement in the galantamine group (change from baseline score 4.2 [SD 10.6]); however, because of the improvement also seen in the placebo group (2.3 [SD 9.0]), the difference between groups was not statistically significant (SRM = 0.20, p = 0.27). Of the secondary outcome measures, the ADAS-cog scores differed significantly between groups (SRM = -0.36, p = 0.04), as did the CIBIC-plus scores (SRM = -0.40, p = 0.03); no significant differences were in either the DAD scores (SRM = 0.28, p = 0.13) or the CBS scores (SRM = -0.17, p = 0.38). INTERPRETATION: Clinicians, but not patients and caregivers, observed a significantly greater improvement in goal attainment among patients with mild to moderate Alzheimer's disease who were taking galantamine than among those who were taking placebo.

Saxton, J., R. K. Hofbauer, et al. (2012). "Memantine and functional communication in Alzheimer's disease: results of a 12-week, international, randomized clinical trial." *J Alzheimers Dis* **28**(1): 109-18.

Post hoc analyses suggest that memantine treatment may provide communication-related benefits in patients with Alzheimer's disease (AD). In this 12-week, international, randomized, double-blind, placebo-controlled trial of memantine (10 mg bid), the functional communication abilities of patients with AD (MMSE range: 10-19) were assessed using the Functional Linguistic Communication Inventory (FLCI; primary measure). Two combined subscales (Social Communication and Communication of Basic Needs) from the American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults (ASHA FACS; secondary measure) were administered to caregivers. Treatment-emergent adverse events were also recorded. After 12 weeks, memantine-treated patients (n = 133) demonstrated a non-significant improvement on the FLCI (placebo: -0.6; memantine: 0.7; p = 0.070, LOCF) and a significant improvement on the ASHA FACS (placebo: -5.3; memantine: 0.5; p = 0.022), compared with placebo-treated patients (n = 124). Memantine had a low incidence of adverse events. In patients with moderate AD, memantine treatment improved functional communication, as recognized by caregivers.

Scarpini, E., G. Bruno, et al. (2011). "Cessation versus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial." *J Alzheimers Dis* **26**(2): 211-20.

Galantamine improved symptoms in Alzheimer's disease (AD) patients after 5 to 6 months of treatment. To examine long-term outcomes, this study assessed if continuing of galantamine treatment beyond 12 months delayed further cognitive deterioration. It consisted of two phases: an open label (OL) phase (12 months), followed by a double blind, randomized, placebo controlled withdrawal phase (up to 24 months). Subjects with mild to moderate AD were included in the study and titrated up to 16 mg/day of galantamine. Subjects were eligible to enter the double blind phase if a cognitive decline of <4 points on AD Assessment Scale-cognitive subscale (ADAS-cog)/11 was recorded at the end of the OL phase. The differences between galantamine and placebo in time to dropout were estimated using the Cox proportional hazard model. 47.4% of galantamine and 31.7% of placebo subjects completed the double blind phase. Placebo subjects were more likely to discontinue prematurely than galantamine subjects for any reason (hazard ratio [HR] 1.76, 95% confidence interval [CI] 1.10-2.81, p = 0.02), or lack of efficacy (HR 1.80, 95% CI 1.02-3.18, p = 0.04); no statistically significant difference was seen for a change in ADAS-cog  $\geq 4$  between treatment groups (HR 1.66, 95% CI 0.78-3.54, p = 0.19). Subjects who responded to 12 months of galantamine treatment benefited from continued drug therapy for up to 36 months. Galantamine was effective in delaying time to cognitive deterioration in subjects with mild to moderate AD. Treatment was generally safe and well tolerated.

Suh, G. H., H. Y. Jung, et al. (2008). "Economic and clinical benefits of galantamine in the treatment of mild to moderate Alzheimer's disease in a Korean population: a 52-week prospective study." *J Korean Med Sci* **23**(1): 10-7.

To evaluate the impact of galantamine treatment on the function, caregiver time, and resource used in the treatment of patients with mild to moderate Alzheimer's disease (AD), costs and outcomes were evaluated during a 52-week prospective, randomized, double-blind, community-controlled trial of galantamine. Patients received either galantamine treatment (n=72) or no treatment (n=66). The analysis was performed from a societal perspective. Galantamine treatment reduced time spent caring for the patients and maintained improved functional capacity, whereas, when no treatments were given, a great increase in caregiver time and progressive functional deteriorations were observed. Saved caregiver time was equivalent to 113 working days per year. After 52 weeks, mean total annual costs per patient were 14,735,000 Korea Won (KRW) (USD 12,315) for patients with galantamine treatment and 25,325,000 KRW (USD 21,166) for patients without treatment. Adjusted annual cost saving of galantamine treatment was 6,428,000 KRW (USD 5,372) when compared to no treatment (p=0.0089). Galantamine had a beneficial effect not only to slow functional decline in patients with mild to moderate AD, but also to save a substantial amount of costs, closely related to reduction in caregiver burden and decrease in caregiver time.

van Dyck, C. H., P. N. Tariot, et al. (2007). "A 24-week randomized, controlled trial of memantine in patients with moderate-to-severe Alzheimer disease." *Alzheimer Dis Assoc Disord* **21**(2): 136-43.

This study examined the efficacy and safety of memantine monotherapy in patients with moderate-to-severe Alzheimer disease (AD). Patients not receiving a cholinesterase inhibitor (N=350) were randomized to receive memantine (20 mg/d) or placebo during this 24-week, double-blind, placebo-controlled trial. Prospectively defined analyses failed to demonstrate a statistically significant benefit of memantine treatment compared with placebo on the Severe Impairment Battery (SIB) at week 24 end point, although a significant advantage was observed for memantine at weeks 12 and 18. The 19-item Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL19) did not differ significantly between groups in any analysis. Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus) did not significantly favor memantine at week 24 despite a significant advantage for memantine at weeks 12 and 18. Other secondary outcomes showed no significant treatment differences. Post hoc analyses of potentially confounding covariates and alternative methods of imputing missing data did not substantially alter the results. Because of the violations of normality assumptions for the SIB and ADCS-ADL19, nonparametric analyses were performed; statistically significant benefit of memantine over placebo was demonstrated at week 24 for the SIB but not the ADCS-ADL19. The type and incidence of adverse events were similar in both groups.

Wilkinson, D., N. C. Fox, et al. (2012). "Memantine and brain atrophy in Alzheimer's disease: a 1-year randomized controlled trial." *J Alzheimers Dis* **29**(2): 459-69.

The primary objective of this study was to evaluate the rate of total brain atrophy (TBA) with serial magnetic resonance imaging (MRI), using the Brain Boundary Shift Integral (BBSI), in patients with probable Alzheimer's disease (AD) over the course of 52 weeks of treatment with memantine or placebo. This was a multi-national, randomized, double-blind, placebo-controlled, fixed-dose 1-year study. Patients were randomized (1 : 1) to

treatment with placebo or memantine. Patients randomized to memantine were up-titrated to the target dose of 20 mg/day over 4 weeks. MRI scans were collected at screening and at Weeks 4, 42, and 52. Secondary efficacy assessments included several cognitive and behavioral scales. 518 patients were screened, 278 patients were randomized, and 217 patients completed the study. In the primary efficacy analysis, the differences in TBA rates between memantine (15.2 mL/year) and placebo (15.3 mL/year) were not statistically significant (-0.04 mL/year [(95% CI: -2.60, 2.52),  $p = 0.98$ ]). There was a statistically significant correlation between change in TBA and change in most cognitive and behavioral scale scores. Patients who were not treated with acetyl cholinesterase inhibitors (AChEIs) showed a significantly lower TBA rate than patients treated with AChEIs. Memantine had a placebo-level incidence of adverse events. There were no statistically significant differences between memantine and placebo in total brain or hippocampal atrophy rates in patients with probable AD treated for 1 year. The biological relevance of cerebral atrophy was supported by a significant correlation between rate of atrophy and decline in cognitive and behavioral outcomes.

Winblad, B., J. Cummings, et al. (2007). "A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease--rivastigmine patch versus capsule." *Int J Geriatr Psychiatry* **22**(5): 456-67.

**OBJECTIVES:** To compare the efficacy, safety and tolerability of a novel rivastigmine transdermal patch with conventional rivastigmine capsules and placebo in patients with Alzheimer's disease (AD). **METHODS:** In this 24-week, multicenter, double-blind, double-dummy, placebo- and active-controlled trial, patients with probable AD were randomized to one of four treatment groups: 12 mg/day rivastigmine capsules; 10 cm<sup>2</sup> (9.5 mg/24 h) rivastigmine patch; 20 cm<sup>2</sup> (17.4 mg/24 h) rivastigmine patch; or placebo. Primary efficacy measures were the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and Alzheimer's Disease Cooperative Study--Clinical Global Impression of Change (ADCS-CGIC). **RESULTS:** One thousand one hundred and ninety five AD patients from 21 countries participated in the study. Treatment differences (vs placebo) on the ADAS-Cog at Week 24 in 10 cm<sup>2</sup> patch, 20 cm<sup>2</sup> patch and capsule groups were 1.6 ( $p=0.005$ ), 2.6 ( $p<0.001$ ) and 1.6 ( $p=0.003$ ). Treatment differences on the ADCS-CGIC were 0.3 ( $p=0.01$ ), 0.2 ( $p=0.054$ ) and 0.3 ( $p=0.009$ ). Comparison between the 10 cm<sup>2</sup> patch and the capsule revealed non-inferiority. Rates of nausea in the 10 cm<sup>2</sup> patch and capsule groups were 7.2% and 23.1%, respectively; rates of vomiting were 6.2% and 17.0%, respectively. Moderate or severe skin irritation occurred in  $\geq 10\%$  patients across the four patch sizes (5, 10, 15 and 20 cm<sup>2</sup>). **CONCLUSIONS:** The target dose of 10 cm<sup>2</sup> rivastigmine patch provides efficacy similar to the highest doses of capsules with a superior tolerability profile. The transdermal patch with rivastigmine may offer convenience important to many caregivers and patients.

Winblad, B., G. Grossberg, et al. (2007). "IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease." *Neurology* **69**(4 Suppl 1): S14-22.

The rivastigmine patch is the first transdermal treatment for Alzheimer disease (AD). By providing continuous delivery of drug into the bloodstream over 24 hours, transdermal delivery may offer benefits superior to those of oral administration. This study compared the efficacy, safety and tolerability of rivastigmine patches with capsules and placebo.

IDEAL (Investigation of transDermal Exelon in ALzheimer's disease) was a 24-week, double-blind, double-dummy, placebo- and active-controlled study. Patients with AD were randomized to placebo or one of three active treatment target dose groups: 10-cm(2) rivastigmine patch (delivering 9.5 mg/24 hours); 20-cm(2) rivastigmine patch (17.4 mg/24 hours); or 6-mg BID rivastigmine capsules. Primary efficacy measures were the Alzheimer's Disease Assessment Scale-Cognitive subscale and Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. Secondary outcome measures assessed a range of domains, including behavior, cognitive performance, attention, executive functions, and activities of daily living. A total of 1,195 AD patients participated. All rivastigmine treatment groups showed significant improvement relative to placebo. The 10-cm(2) patch showed similar efficacy to capsules, with approximately two-thirds fewer reports of nausea (7.2% vs 23.1%) and vomiting (6.2% vs 17.0%), incidences statistically not significantly different from placebo (5.0% and 3.3% for nausea and vomiting, respectively). The 20-cm(2) patch showed earlier improvement and numerically superior cognitive scores vs the 10-cm(2) patch with similar tolerability to capsules. Local skin tolerability was good. The transdermal patch with rivastigmine may offer additional therapeutic benefits and may prove to be the best delivery system for this drug to treat AD.

### Secondary analyses of included primary trial publications

Gaudig, M., U. Richarz, et al. (2011). "Effects of galantamine in Alzheimer's disease: double-blind withdrawal studies evaluating sustained versus interrupted treatment." *Curr Alzheimer Res* 8(7): 771-80.

To evaluate the effects of galantamine withdrawal, and compare this with uninterrupted therapy, two 6-week double-blind withdrawal studies (Studies 1 and 2) were performed. These enrolled individuals who had completed one of two 3- or 5-month randomized clinical trials (parent trials) involving patients with mild to moderate Alzheimer's disease (AD). In Study 1 (GAL-USA-11; n=723), patients continuously treated with galantamine 16 mg/day exhibited a mean (+/- standard error [SE]) improvement in 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale score of 1.8 (+/- 0.46) points at Week 6 compared with the parent trial baseline, ( $p < 0.001$  vs placebo; observed cases analysis). Over the same period, patients switched from galantamine to placebo and those who had received continuous placebo, exhibited mean (+/- SE) deteriorations of 0.7 (+/- 0.49) and 1.2 (+/- 0.49) points, respectively. Similar trends were apparent in Study 2 (GAL-USA-5; n=118). In Study 1, subgroup analyses demonstrated cognitive benefits with continuing galantamine treatment and deterioration associated with galantamine withdrawal in patients with advanced moderate AD (baseline Mini-Mental State Examination score  $\leq 14$ ) and in individuals deemed non-responsive in terms of Clinician's Interview-Based Impression of Change-plus Caregiver Input (CIBIC-plus) evaluation at the end of the parent trial (CIBIC-plus score  $> 4$ ). No safety issues were identified. In patients with mild to moderate AD who have exhibited cognitive benefits from up to 5 months' galantamine treatment, continuing therapy reinforces previously achieved benefit, whereas in patients in whom galantamine is discontinued, although no safety concerns arise, the natural progression of AD is apparent.

**Month/Year of Review:** September 2014

**PDL Classes:** Other Lipotropics

**Date of Last Review:** September 2013

**Source Document:** OSU College of Pharmacy

**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), ICOSAPENT ETHYL (VASCEPA®)

**PA criteria:** Prior Authorization Criteria is in place for Omega-3 Fatty Acids (Lovaza® and Vascepa®) to promote the safe and effective use of these lipid lowering agents (Appendix 1).

**Previous Conclusions and Recommendation:**

- Make cholestyramine a preferred bile acid sequestrant, which has shown improved cardiovascular (CV) related or stroke outcomes.
- There is moderate quality evidence that gemfibrozil may reduce the risk for stroke and CV mortality. Include gemfibrozil as a preferred medication.
- There is no clinical evidence of superiority of one fenofibrate agent over another.
- Make Niaspan and Niacor preferred due to a demonstrated reduction in CV outcomes.
- Make ezetimibe a non-preferred agent due to insufficient outcome data, and implement the non-PDL prior authorization criteria for use.
- 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. Maintain as non-preferred and prior authorize omega-3 fatty acids including the following:
  - Clinically diagnosed hypertriglyceridemia with triglyceride levels > 500
  - Failure or contraindication to a fibric acid derivative and niacin OR
  - The patient is taking a statin and is unable to take a fibric acid derivative or niacin due to an increased risk of myopathy.

**Conclusions and Recommendations:**

- There remains insufficient evidence for improved Atherosclerotic Cardiovascular Disease (ASCVD) outcomes for non-statin lipid lowering agents.
- For high risk patients, it may be reasonable to add a nonstatin cholesterol-lowering medication in high-risk patients who have a less than anticipated response to statins, who are unable to tolerate a less than recommended intensity of a statin or who are completely statin intolerant.
- There is no new relevant evidence supporting changes to PDL; evaluate comparative costs 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.<sup>1</sup> 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.<sup>2</sup> High risk individuals include those with established CHD, other clinical atherosclerotic CVD, or multiple risk factors. These individuals have a 10-year 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.<sup>1</sup> There has also been a demonstrated correlation between raised triglycerides and CV disease.<sup>3</sup> 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.<sup>2,4-6</sup> 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.<sup>7</sup> 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.<sup>8</sup>

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.<sup>9</sup> 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.<sup>10</sup> The Helsinki Heart Study looked at gemfibrozil and prevention of CHD risk in patients with borderline high TGs.<sup>11,12</sup> Patients who were originally placed on gemfibrozil had significantly less risk of CHD mortality, but all-cause mortality was not statistically significant.<sup>11,12</sup> 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.<sup>11</sup> The ACCORD trial examined CV risk in patients on combination statin and fenofibrate therapy vs statin alone.<sup>9</sup> 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.<sup>2,7</sup> 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.<sup>13</sup>

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.<sup>14,15</sup> 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.<sup>15,16</sup> 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.<sup>16</sup> 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.<sup>17</sup> 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 including the medications and diagnoses as search terms. The search was limited to English language articles of controlled trials and systematic reviews conducted on humans published from 2013 to August week two 2014.

The Cochrane Collection, Dynamed, National Institute for Health and Care Excellence (NICE) and Agency for Healthcare Research and Quality (AHRQ) 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:**

*Agency for Healthcare Research and Quality:*

A 2014 AHRQ review compared 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.<sup>18,19</sup> 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.

Another publication focused only on adults at high risk for atherosclerotic cardiovascular disease (ASCVD).<sup>19</sup> This review was done in response to the new ACC/AHA guidelines recommending moderate- or high-intensity statin monotherapy as first line therapy. For patients who cannot tolerate the recommended intensity of statin therapy, lower-intensity combination therapy could still be an option. Thirty six RCTs were included in this analysis. Overall, there was insufficient evidence to compare long-term clinical outcomes, including mortality acute coronary events, cerebrovascular events, and revascularization procedures, for all combination therapy and statin intensity comparisons. 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 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.

#### **Guidelines:**

In November, 2013, the ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic CV risk in adults was released.<sup>20,21</sup> The new guidelines abandon specific cholesterol treatment goals and instead focus on four high-risk groups that are most likely to benefit from statin therapy. The new guidelines also emphasize that overall risk of heart disease and stroke should be evaluated on an individual basis and recommend only using medications that have been proven to reduce ASCVD risk. Therefore, moderate- to high-intensity statins are the focus of the recommendations. The panel could not find data supporting the routine use of nonstatin drugs combined with statin therapy to further reduce ASCVD events and no RCTs that assessed ASCVD outcomes in statin-intolerant patients were found. In regards to other lipid-modifying agents, the 2013 ACC/AHA guidelines suggest that clinicians consider “moderated” combination therapy with a lower-intensity statin and another lipid-modifying medication among high-risk

patients (LDL cholesterol level  $\geq 4.91$  mmol/L [ $\geq 190$  mg/dL], preexisting ASCVD, or DM) who are intolerant of or unresponsive to statins. This recommendation is only based on expert opinion (Evidence grade E). Other recommendations regarding non-statin therapies include:

- Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are greater than or equal to 500 mg/dl are judged to outweigh the potential risk for adverse events (Expert opinion; E).
- Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis (Moderate SOE; B).

The Institute for Clinical Systems Improvement (ICSI) released guidelines for the lipid management in adults in November 2013.<sup>22</sup> Evidence-based recommendations, which could only be provided for statin use and lifestyle habits. Recommendations for other lipid-lowering agents were provided throughout the document, but only as a result of work group consensus and not evidence-based.

**New drugs:**

None

**New Formulations/Indications:**

None

**New FDA safety alerts:**

None

**New Trials:**

No head to head trials or relevant placebo-controlled trials were identified.

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## Appendix 1: Prior Authorization Criteria

### Omega-3 Fatty Acids

#### Goal(s):

- Promote safe and effective therapies for lipid lowering agent.

**Length of Authorization: 1 year**

**Requires PA :** Omega-3-Acid Ethyl Esters (Lovaza®)  
Icosapent Ethyl (Vascepa®)

**Covered Alternatives:** Listed at: [http://www.oregon.gov/DHS/healthplan/tools\\_prov/pdl.shtml](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?	<b>Yes:</b> Go to #3. <b>No:</b> Pass to RPh, Deny for OHP Coverage.
3. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> <li>Preferred products do not require PA.</li> <li>Preferred products have received evidence-based reviews for comparative effectiveness and safety by the Pharmacy &amp; Therapeutics Committee</li> </ul>	<b>Yes:</b> Inform provider of covered alternatives in class <a href="http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html">http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html</a> <b>No:</b> Go to #4
4. Does the patient have clinically diagnosed hypertriglyceridemia with triglyceride levels $\geq 500$ mg/dl?	<b>Yes:</b> Go to #5 <b>No:</b> Pass to RPh; Deny for Medical Appropriateness
5. Has the patient failed or have a contraindication to an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil) at maximum tolerable dose (as seen in dosing table below). <b>AND</b> niacin 1-2 mg/day <b>OR</b> Is patient taking a statin and is unable to take a fibric acid derivative or niacin due to an increased risk of myopathy.	<b>Yes:</b> Approve up to 1 year. <b>No:</b> Deny for Medical Appropriateness. Recommend untried agent(s).

**Table 1: Dosing of fenofibrate and derivatives for hypertriglyceridemia**

Drug	Recommended dose	Maximum dose
Antara (micronized)	43-130 mg once daily	130 mg once daily
Fenoglide	40-120 once daily	120 mg once daily
Fibricor	25-105 mg once daily	105 mg once daily
Lipofen	50-150 mg once daily	150 mg once daily
Lofibra (micronized)	67-200 mg once daily	200 mg once daily
Lofibra (tablets)	54-160 mg once daily	160 mg once daily
TriCor	48-145 mg once daily	145 mg once daily
Triglide	50-160 mg once daily	160 mg once daily
Trilipix	45-135 mg once daily	135 mg once daily
Gemfibrozil	600 mg twice daily	600 mg twice daily

P&T Action: 3-27-2014 (MH/KK)

Revision(s):

Initiated:

### **Abbreviated Class Update: Diabetes Medications**

**Month/Year of Review:** September 2014

**Last Class Update:** September 2013

**PDL Classes:** See Appendix 2

**End date of literature search:** August 2014

**Source:** OSU DURM

#### **Research Questions:**

- Is there any new comparative evidence for diabetes treatments?
- Is there any new evidence about comparative harms among the available diabetes treatments?
- Are there subpopulations of patients with diabetes for which a specific diabetes therapy may be more effective or associated with less harm?

#### **Conclusions:**

- A recent systematic review found insufficient evidence to compare health outcomes of the newer diabetes medications and combinations. Intermediate endpoints, including hemoglobin A1c (HbA1c) and weight, found low strength of evidence (SOE) that exenatide XR weekly was superior to exenatide daily, liraglutide was superior to exenatide and sitagliptin, exenatide was superior to sitagliptin, and canagliflozin was similar in efficacy to metformin. In a comparison between metformin and dapagliflozin there was low SOE of a trend favoring dapagliflozin for HbA1c lowering, but it was not deemed clinically significant, -.11% and -.12%, respectively. There was moderate SOE that metformin was superior to linagliptin, alogliptin and sitagliptin. The addition of metformin to alogliptin, linagliptin or sitagliptin resulted in greater glucose lowering than monotherapy dose comparisons.<sup>1</sup>
- In a phase 4, placebo-controlled, randomized trial of over 16,000 patients there was moderate evidence that saxagliptin therapy neither conferred a cardiovascular risk or benefit compared to placebo (HR 1.00 [95% CI, 0.89 to 1.12, P<0.001 for noninferiority). Only small benefits in HbA1c were seen with saxagliptin compared to placebo at 2 years, 7.5% vs. 7.8%, respectively. Hospitalization rates in patients with heart failure were found to be higher in those patients treated with saxagliptin (HR 1.27 [95% CI, 1.07 to 1.51, P=0.007]).<sup>2</sup>
- A systematic review and meta-analysis on sodium-glucose cotransporter 2 (SGLT2) inhibitors, including canagliflozin and dapagliflozin, demonstrated HbA1c lowering when compared to placebo (mean difference -0.66% [95% CI, -0.73% to -0.58%]) and to active comparators (mean difference -0.06% [95% CI, -0.18% to 0.05%]). The most common adverse events were urinary infections (odds ratio, 1.42 [95% CI, 1.06 to 1.90]) and genital tract infections (odds ratio, 5.06 [95% CI, 3.44 to 7.45]).<sup>3</sup>
- Oral hypoglycemic scan summary from the Drug Effectiveness Review Project (DERP) found limited new evidence since the last review; no further review or research needed.<sup>4</sup>

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**Recommendations:**

- The current PA criteria (Appendix 1) align with the conclusions of a recent systematic review by the Drug Effectiveness Review Project. No changes to the PDL are recommended.
- Continue to require a prior authorization for saxagliptin therapy. No changes to the PDL are recommended.
- Evidence on SGLT2 inhibitors supports the current PA criteria. Dapagliflozin should be added to the criteria and made non-preferred. No changes to the PDL are recommended.
- There is no new evidence on the comparative efficacy/effectiveness or safety for the oral hypoglycemic PDL class. Evaluate comparative costs in executive session

**Reason for Review:**

Therapies for the treatment of diabetes were reviewed in September of 2013. Annual class review updates allow for the incorporation of new literature and ensure prior recommendations are current and accurate. This review will analyze the comparative effectiveness of the newer medications for diabetes, including a recent report from the DERP, and incorporate important updates and revisions as they are related to this class since the last review. There was also a recent DERP Scan for the oral hypoglycemic class.<sup>4</sup>

**Previous Conclusions and Recommendations:**

- There is moderate evidence that canagliflozin is more effective than placebo in lowering HbA1C (-0.77% to -1.06%) in patients with type 2 DM. Designate canagliflozin as non-preferred. Canagliflozin will be available as a fourth-line treatment option for patients unable to tolerate or have contraindications to metformin, sulfonylurea therapy and other third-line treatments.
- There is moderate evidence that alogliptin lowered HbA1C in patients with type 2 diabetes by 0.4%-0.9% compared to placebo. Make alogliptin a non-preferred treatment. Alogliptin is available by PA as a third-line treatment option for patients unable to tolerate or have contraindications to metformin and/or sulfonylurea therapy.
- 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. Sulfonylurea therapies should be considered a preferred second-line treatment option for patients without contraindications or tolerance issues.

**Background:**

Type 2 diabetes is a prevalent disease which affects an estimated 25.6 million people in the United States.<sup>5</sup> 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.<sup>6</sup> 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  $\leq 6.5\%$  to  $\leq 7\%$  but in all cases should be tailored according to patient specific factors, such as concomitant comorbidities.<sup>7,8</sup> A number of therapeutic options are available for management of glycemic variances associated with diabetes.<sup>9</sup> Classes of anti-hyperglycemic agents (AHA) currently available are: alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, insulins, meglitinides, sulfonylureas, thiazolidinediones (TZD), 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. Hemoglobin 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.<sup>8</sup> 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.<sup>8</sup> 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.<sup>8</sup> The long-term effect of many of the AHAs on complications of diabetes is unknown.

### **Methods:**

A Medline literature search ending in August 2014 for new systematic reviews and randomized controlled trials (RCTs) for diabetic treatments was conducted. The Agency for Healthcare Research and Quality (AHRQ), Drug Effectiveness Review Project (DERP), 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, and will be limited to head to head trials.

### **Systematic Reviews:**

#### *DERP – Drug Class Review: Newer Diabetes Medications and Combinations*

The Drug Effectiveness Review Project (DERP) reviewed newer antihyperglycemic treatments; amylin agonists, DPP-4 inhibitors, GLP-1 analogs, SGLT2 inhibitors (including dapagliflozin), and drug combinations in individuals with type 2 diabetes and in those with type 1 diabetes for pramlintide only.<sup>1</sup> This streamlined report includes comparisons of head-to-head studies between the classes of newer diabetes medications and newer diabetes medications compared to metformin. Comparisons of the newer diabetes agents to pioglitazone or sulfonylureas were not included. Patients on background therapy with insulin or other oral medications were allowed if the study met other eligibility criteria. Thirty trials met the inclusion criteria, all were randomized controlled trials. The intermediate outcomes, HbA1c and weight, were analyzed in all trials. Health outcomes were rarely reported and a majority of trial durations were 6 months or less. The comparative evidence is presented below.

#### Within Class Comparisons

##### Exenatide XR vs. Exenatide

A meta-analysis of three trials found low SOE that exenatide XR weekly lowered HbA1c to a greater extent than twice daily exenatide (WMD -0.46%| 95% CI, -0.69 to -0.23). No differences were found in their effect on weight. Injection site reactions were higher in the exenatide weekly group (moderate SOE).<sup>1</sup>

##### Liraglutide vs. Exenatide

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Liraglutide 1.8 mg daily was compared to exenatide 10 µg twice daily in 464 patients and found to have greater HbA1c lowering (between-group difference: -0.33%; 95% CI, -0.47 to -0.18) based on low SOE. Minor hypoglycemia was higher in the exenatide group (RR 0.55; 95% CI, 0.34 to 0.88). Effect on weight was not different between the groups.<sup>1</sup>

#### Sitagliptin vs. Saxagliptin

One trial of unknown quality was found to be insufficient to determine the comparative efficacy or harms between sitagliptin and saxagliptin.<sup>1</sup>

#### Separate Class Comparisons

##### Exenatide XR vs Sitagliptin

Exenatide XR was found to be more effective than sitagliptin 100mg at lowering HbA1c in a pooled data analysis of two trials (n=753) (WMD -0.48; 95% CI, -0.69 to -0.26) (low SOE). Exenatide was also associated with more weight loss compared to sitagliptin (WMD -1.32; 95% CI, -1.87 to -0.76) based on low SOE. Nausea, vomiting and diarrhea were higher in with exenatide XR compared to sitagliptin.<sup>1</sup>

##### Liraglutide vs. Sitagliptin

One trial of 665 patients found liraglutide 1.2mg and liraglutide 1.8mg to be more effective than sitagliptin 100mg in mean HbA1c reduction, -0.34 and -60%, respectively (low SOE). More nausea was reported with liraglutide than with sitagliptin.<sup>1</sup>

##### Canagliflozin vs. Sitagliptin

Canagliflozin 100mg and 300mg was compared to sitagliptin and no differences in HbA1c lowering were seen based on low SOE. Canagliflozin (100mg and 300mg) was associated with more weight loss than sitagliptin (low SOE). Women allocated to canagliflozin were found to have a higher incidence of genital mycotic infections compared to sitagliptin in one trial (low SOE).<sup>1</sup>

##### DPP-4 vs. Metformin

Eight trials compared a DPP-4 inhibitor to metformin. Half of the trials were sitagliptin and metformin comparisons. One study of linagliptin and alogliptin and two saxagliptin studies were included. Metformin 1000 mgs or more was found to be more effective than linagliptin 5 mg, alogliptin 25 mg and sitagliptin 100 mg (between-group differences range from -0.30% to -0.60%) (moderate SOE). When “up-titration” of metformin (patients not at goal on submaximal doses of metformin) were compared to saxagliptin, no difference in efficacy was found based on low SOE. The addition of saxagliptin resulted in more hypoglycemia events compared to metformin alone (low SOE). Adverse events for the DPP-4 inhibitors and metformin were similar between groups except for the incidence of diarrhea, which was higher for metformin compared to alogliptin and sitagliptin (low SOE). Greater weight reduction was found with metformin 1000 mg per day when compared head-to-head with DPP-4 inhibitors.<sup>1</sup>

##### GLP-1 Analogs vs. Metformin

Exenatide and exenatide XR were compared to metformin in two studies, however there was insufficient evidence to compare efficacy.<sup>1</sup>

##### Dapagliflozin vs. Metformin

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In a comparison between dapagliflozin and metformin, no difference in HbA1c lowering was found. There was a trend favoring dapagliflozin but it was not deemed clinically significant (-.11% and -.12%). Low SOE found dapagliflozin to be associated with more weight loss than metformin. Rates of hypoglycemia and nausea were similar between groups (low SOE).<sup>1</sup>

#### Fixed Dose Combination/Dual Therapy Product Comparisons

##### Alogliptin plus Metformin

There was moderate SOE that alogliptin plus metformin was more effective, HbA1c lowering of -0.44% to -0.99%, than monotherapy for all dose comparisons. Similar changes in weight were observed for all groups (moderate SOE).<sup>1</sup>

##### Linagliptin plus Metformin

The combination of linagliptin plus metformin was shown to lower HbA1c more than component therapy of each. Differences in HbA1c lowering ranged from -0.50% to -1.10%. The combination of linagliptin 2.5 mg and metformin 1000 mg twice daily was found to cause greater weight loss than linagliptin 5 mg daily (low SOE).<sup>1</sup>

##### Sitagliptin plus Metformin

Sitagliptin 100 mg plus metformin 2000 mg daily was associated with greater HbA1c reductions compared to metformin monotherapy in a meta-analysis of two trials of short duration (WMD -0.60 %; 95% CI, -0.75 to -0.45). No differences in weight reductions between the groups were seen.<sup>1</sup>

#### *Vasilakou, et al- Sodium-Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes*

A systematic review and meta-analysis was performed on the new AHA class sodium-glucose cotransporter 2 (SGLT2) inhibitors.<sup>3</sup> Forty five placebo-controlled and 13 active comparator studies of canagliflozin 100 or 300mg (12 trials), dapagliflozin 5 or 10 mg (21 trials), ipragliflozin (8 trials), empagliflozin (3 trials), luseogliflozin (2 trials), tofogliflozin (1 trial), ertugliflozin (1 trial), and remogliflozin (1 trial). Of the agents studied canagliflozin and dapagliflozin are the only US approved SGLT2 inhibitors. In the active comparator studies, SGLT2 inhibitors were compared to metformin (6 studies), sitagliptin (5 studies), and sulfonylureas (2 studies). The majority of studies lasted between 12-26 weeks.

A majority of studies were found to have a high risk of publication bias due to incomplete outcome data and use of last-observation-carried-forward (LOCF) methodology, which can overstate results. For most efficacy outcomes the evidence was graded as low. Studies of placebo-controlled trials showed SGLT2 inhibitors to lower A1c (mean difference, -0.66% [95% CI, -0.73% to -0.58%]).<sup>3</sup> Comparison of SGLT2 inhibitors versus active treatments also slightly favored SGLT2 inhibitors (mean difference -0.0.6% [95% CI -0.18% to -0.05%]). SGLT2 inhibitors as add-on treatment also demonstrated A1c lowering (WMD, -0.61%, 95% CI -0.69% to -0.53%). SGLT2 inhibitors were found to have similar lowering as other AHAs when used as monotherapy or as add-on treatment in studies included in the analysis. Changes in A1c seen with dapagliflozin compared to placebo were -0.59% (95% CI, -0.67% to -0.50%) and for canagliflozin -0.78% (95% CI, -0.90% to -0.66%). Changes in body weight from baseline favored SGLT2 inhibitors compared to placebo (WMD -1.74 kg, 95% CI -2.03 to -1.45 kg) and percent change (WMD -2.27%, 95% CI, -2.73% to -2.02%).<sup>3</sup> Comparison in body weight changes with active comparators demonstrated only small weight reductions favoring SGLT2 inhibitors. Greater blood pressure reductions were seen with SGLT2 inhibitors compared to placebo and active control, -3.77 mmHg and -4.45 mmHg, respectively. SGLT2 inhibitors were associated with an increased risk of genital and urinary tract infections. Hypoglycemia risk was similar to other treatments. There was insufficient evidence on cardiovascular outcomes and mortality. Dapagliflozin was shown to have a higher incidence of bladder and breast cancer compared to control, however, data is insufficient to draw firm conclusions.

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### **New Guidelines:**

#### *IDF – Managing Older People with Type 2 Diabetes Global Guideline*

In response to the need for specific advice for older individuals with diabetes the International Diabetes Foundation (IDF) released a global guideline in 2013.<sup>10</sup> Recommendations include glucose and management targets that are individualized and based on patient's functional status and comorbidities (established CVD, history and risk of hypoglycemia, and presence of microvascular complications).

Treatment selection should be based on the overall risk-to-benefit ratio to the patient.<sup>10</sup> First-line therapy, in patients without contraindications, is metformin. Sulfonylureas are recommended for those unable to take metformin, however, glyburide/glibenclamide should be avoided due to risk of hypoglycemia. DPP-4 inhibitors may be considered if an economically viable option for the patient. For patients with an unpredictable eating schedule and those with postprandial hyperglycemia, glinides may be an appropriate choice.

For second-line treatment, sulfonylureas are recommended and DPP-4 inhibitors can also be considered.<sup>10</sup> Long-acting basal insulin is appropriate in patients who cannot tolerate or have contraindications to oral agents. Third line treatments include: triple oral therapy, basal or pre-mixed insulins and GLP-1 agonists. If patients are still not meeting glycemic goals in triple therapy then switching one of the oral agents to a different class, initiating basal or pre-mixed insulin, using GLP-1 agonists, changing to or adding insulin if on a GLP-1 agonists or maximizing current insulin regimen is recommended. Basal insulin, long-acting insulin or once or twice daily premixed insulin should be used in patients requiring further glucose lowering.

#### *NICE – Dapagliflozin in Combination Therapy for Treating Type 2 Diabetes*

A 2013 technology report on the use of dapagliflozin in combination with other AHA was created by the National Institutes for Health and Care Excellence (NICE).<sup>11</sup> Five, good-quality, randomized controlled trials were included in the analysis. Recommendations were to consider the use of dapagliflozin with metformin if there is a significant risk of hypoglycemia and if there are contraindications to a sulfonylurea. Dapagliflozin could also be considered as an addition to sulfonylurea therapy if metformin is contraindicated or not tolerated. Dapagliflozin and insulin in combination is a recommended option for type 2 diabetes patients. The combination of dapagliflozin and insulin is also recommended. Using dapagliflozin as a third agent, with metformin and a sulfonylurea, is not recommended at this time.

#### *NICE – Canagliflozin in Combination Therapy for Treating Type 2 Diabetes*

A 2014 technology report from NICE reported on the evidence of six, good-quality, randomized controlled trials on the use of canagliflozin.<sup>12</sup> Canagliflozin is recommended as dual therapy when sulfonylureas are contraindicated or not tolerated and in patients at significant risk of hypoglycemia. Canagliflozin use may also be considered in patients taking metformin and a sulfonylurea or metformin and pioglitazone as part of a three-drug regimen. The use of canagliflozin and insulin may also be an appropriate treatment option.

### **New Safety Alerts:**

*FDA to Review Heart Failure Risk with Diabetes Drug Saxagliptin (marketed as Onglyza and Kombiglyze XR)*

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In February of 2014 the FDA announced that they will be investigating heart failure associated with saxagliptin.<sup>13</sup> The FDA action was in response the SAVOR-TIMI 53 trial<sup>2</sup> in New England Journal of Medicine (NEJM), presented below, which showed an increased risk of hospitalizations for heart failure in those patients randomized to saxagliptin.

### **New Primary Literature:**

#### **Saxagliptin and Cardiovascular Outcomes**

In order to further define the risks and benefits of saxagliptin therapy on cardiovascular outcomes, a phase 4, placebo-controlled, good quality, randomized controlled trial was conducted in 16,492 patients in the SAVOR-TIMI 53 trial.<sup>2</sup> Patients were randomized in a 1:1 fashion to saxagliptin 5 mg daily (patients with an estimated glomerular filtration rate [GFR] of  $\leq 50$  ml/minute received saxagliptin 2.5mg daily) or placebo for median of 2.1 years. Majority of patients were male (67%) and were a mean age of 65 years. The mean HbA1c was 8% and median duration of diabetes was 10 years. To be eligible for study participation patients had to have type 2 diabetes and history of established cardiovascular disease or multiple risk factors for vascular disease. Other treatments for diabetes and cardiovascular disease were permitted, however, the use of incretin-based therapy currently or within the previous 6 months was not allowed. The primary efficacy and safety endpoint was the composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal ischemic stroke. Key secondary endpoints were the primary composite endpoint and hospitalization for heart failure, coronary revascularization, or unstable angina.

There is moderate SOE that saxagliptin was not superior but was non-inferior to placebo for the incidence of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal ischemic stroke (HR: 1.00 [95% CI, 0.89 to 1.12,  $P < 0.001$  for noninferiority).<sup>2</sup> For the secondary endpoint of the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, coronary revascularization or heart failure was found to be similar between saxagliptin and placebo, 12.8% and 12.4%, respectively (HR: 1.02 [95%CI, 0.94 to 1.11,  $P = 0.66$ ). The results for the primary and secondary endpoints in the saxagliptin groups were similar for patients with heart failure and without. Saxagliptin was associated with more hospitalizations for heart failure compared to placebo (HR1.27 [95% CI, 1.07 to 1.51,  $P = 0.007$ ). Hemoglobin A1c levels were significantly lower in patients treated with saxagliptin compared to placebo at year 1 (7.6% vs 7.9%), year 2 (7.5% vs. 7.8%) and end of the treatment period (7.7% and 7.9%).

Hypoglycemia was more in common in patients treated with saxagliptin compared to placebo and major hypoglycemia occurred in 2.1% of saxagliptin patients and 1.7% of placebo treated patients ( $P = 0.047$ ). The rate of pancreatitis was similar between groups (0.3%). The risk of pancreatic cancer was higher in the placebo group ( $n = 12$ ) compared to saxagliptin ( $n = 5$ ). Overall discontinuation rates were slightly lower with saxagliptin versus placebo, 18.4% and 20.8%, respectively.<sup>2</sup>

In patients with type 2 diabetes, saxagliptin therapy was associated with no cardiovascular benefit or risk. Hemoglobin A1c reductions favored saxagliptin but the change was small and clinical significance is unknown. The optional use and titration of other medications for diabetes could account for small differences in HbA1c between the groups but also raises the question if the benefit of saxagliptin is worth the potential for additional adverse events. Saxagliptin association with an increased risk of hospitalizations in patients with heart failure needs to be further investigated.

#### **Drug Class Scans**

The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.<sup>4</sup> There is limited new evidence since the last review; no further review or research needed.

Previous research found the following:

- There is no clinically significant difference between any of the agents in these two drug classes (oral sulfonylureas and non-sulfonylurea secretagogues) in their ability to lower hemoglobin HbA1c.
- There is no statistically significant difference between glyburide and chlorpropamide in the progression or occurrence of clinically relevant outcomes with the exception of retinopathy. Patients on glyburide had greater risk reduction of progression of retinopathy than those on chlorpropamide.
- There is insufficient evidence on other sulfonylureas and nonsulfonylureas secretagogues to identify a difference in progression or occurrence of clinically relevant outcomes.
- Chlorpropamide has a less favorable adverse effect profile compared to glyburide. There is no difference in safety or adverse effect profiles for other oral sulfonylureas and non-sulfonylureas secretagogues. Glimepiride, glipizide, glyburide, micronized glyburide and repaglinide do not differ in safety or adverse effect profile. No evidence exists for evaluation of tolbutamide, tolazamide or nateglinide.

#### **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
- 3.) Composite of cardiovascular death, MI or ischemic stroke

#### **Evidence Table**

Study Design	Drug Regimen/ Duration	Patient Population	N	Outcomes/Efficacy Results (CI, p- values)	ARR/NNT	Safety Results (CI, p-values)	ARR/NNH	Quality Rating
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<sup>1</sup>**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.

<sup>2</sup>**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

<sup>3</sup>**NNT/NNH** are reported only for statistically significant results

<sup>4</sup>**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

**Clinical Abbreviations:** AHA = antihyperglycemic agent, A1c = hemoglobin A1c, MI = myocardial infarction

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## APPENDIX 1: Current PA Criteria

### Incretin Enhancers (DPP-4 Inhibitors)

#### Initiative:

- Optimize correct use that corresponds to National Guidelines of incretin enhancers.

#### Length of Authorization:

Up to 12 months

#### Covered Alternatives:

Preferred alternatives listed at [www.orpd.org](http://www.orpd.org).

#### 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: <ul style="list-style-type: none"><li>Renal disease or renal dysfunction</li><li>Known hypersensitivity to therapies</li><li>Acute or chronic metabolic acidosis</li><li>Patients at increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function)</li><li>Increased risk of hypoglycemia</li></ul>	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

- 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.

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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:* 9/23/14 (HM/KS), 9/26/13 (KS), 4/26/12 (KS), 3/17/11 (KS)

*Revision(s):*

*Initiated:* 7/16/12, 1/1/12

## Sodium-Glucose Co-Transporter 2 (SGLT2)

### **Initiative:**

- Optimize appropriate prescribing of SGLT2s.

### **Length of Authorization:**

Up to 12 months

### **Requires PA:**

- Non-preferred drugs

### **Covered Alternatives:**

Preferred alternatives listed at [www.orpd.org](http://www.orpd.org)

### 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: <ul style="list-style-type: none"> <li>• Renal disease or renal dysfunction</li> <li>• Known hypersensitivity to therapies</li> <li>• Acute or chronic metabolic acidosis</li> <li>• Patients at increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function)</li> <li>• Increased risk of hypoglycemia</li> </ul>	Yes: Go to #3	No: Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
3. Has the patient tried and failed other third-line treatments for diabetes or have contraindications to third-line treatments?	Yes: Approve for up to 12 months.	No: Deny. Require a trial of third-line agents.

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### 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.*

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*P&T / DUR Action:* 9/23/14 (KS), 9/26/13 (KS)

*Revision(s):*

*Initiated:* 9/26/13

## Incretin Mimetics (GLP-1 Analog)

### Initiative:

- To optimize the correct use of insulin mimetics.

### Length of Authorization:

Up to 12 months

### Requires PA:

- Non-preferred drugs

### Preferred Alternatives:

Preferred alternatives listed at [www.orpdl.org](http://www.orpdl.org)

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	<b>No:</b> Pass to RPH; Deny (medical appropriateness)
2. Will the prescriber consider a change to a preferred product?  Message: <ul style="list-style-type: none"> <li>• Preferred products do not require PA.</li> <li>• Preferred products are evidence-based reviewed for comparative effectiveness &amp; safety by the Health Resources Commission (HRC).</li> </ul> Reports are available at: <a href="http://www.oregon.gov/OHPPR/HRC/EvidenceBased_Reports.shtml">http://www.oregon.gov/OHPPR/HRC/EvidenceBased_Reports.shtml</a> .	<b>Yes:</b> Inform provider of covered alternatives in class. <a href="http://www.orpdl.org">www.orpdl.org</a>	<b>No:</b> Go to #3.
3. Has the patient tried and failed metformin <b>and</b> sulfonylurea therapy or have contraindications to these treatments?  Contraindications to metformin: <ul style="list-style-type: none"> <li>- Renal disease or renal dysfunction</li> </ul>	<b>Yes:</b> Go to #4.	<b>No:</b> Pass to RPH; Deny (medical appropriateness). <b>Recommend trial of metformin or sulfonylurea. See</b>

<ul style="list-style-type: none"> <li>- Known hypersensitivity</li> <li>- Acute or chronic metabolic acidosis</li> <li>- Increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function)</li> </ul> <p>Contraindications to sulfonylureas:</p> <ul style="list-style-type: none"> <li>- Known hypersensitivity</li> <li>- Increased risk of hypoglycemia</li> </ul>		<b>below for metformin titration schedule.</b>
<b>4.</b> Is the patient currently taking insulin?	<b>Yes:</b> Go to #5	<b>No:</b> Approve for up to 1 year.
<b>5.</b> Is the patient requesting exentatide (Byetta) and is taking insulin glargine?	<b>Yes:</b> Approve for up to 12 months	<p><b>No:</b> Pass to RPH; Deny (medical appropriateness).</p> <p>The safety and efficacy of other insulin formations and GLP-1 Agonists have not been studied.</p>

#### 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.

DUR Board Action: 9/23/14 (KS), 9/26/13(KS), 3/17/11 (KS), 4/26/12 (KS)

Revision(s): 1/31/12 (KS)

Initiated:

## Appendix 2 – Preferred Drug List Classes and Drug Status

### Incretin Enhancers (DPP-4 Inhibitors and SGLT2 Inhibitors)

Brand	Generic	FormDesc	PDL
JANUMET	SITAGLIPTIN PHOS/METFORMIN HCL	TABLET	Y
JANUVIA	SITAGLIPTIN PHOSPHATE	TABLET	Y
FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	TABLET	N
INVOKANA	CANAGLIFLOZIN	TABLET	N
JENTADUETO	LINAGLIPTIN/METFORMIN HCL	TABLET	N
KAZANO	ALOGLIPTIN BENZ/METFORMIN HCL	TABLET	N
NESINA	ALOGLIPTIN BENZOATE	TABLET	N
ONGLYZA	SAXAGLIPTIN HCL	TABLET	N
TRADJENTA	LINAGLIPTIN	TABLET	N
JANUMET XR	SITAGLIPTIN PHOS/METFORMIN HCL	TBMP 24HR	N
KOMBIGLYZE XR	SAXAGLIPTIN HCL/METFORMIN HCL	TBMP 24HR	N
OSENI	ALOGLIPTIN BENZ/PIOGLITAZONE	TABLET	N

### Incretin Mimetics (GLP-1 Analog)

Brand	Generic	FormDesc	PDL
BYDUREON	EXENATIDE MICROSPHERES	VIAL	N
BYDUREON PEN	EXENATIDE MICROSPHERES	PEN INJCTR	N
BYETTA	EXENATIDE	PEN INJCTR	N
SYMLINPEN 120	PRAMLINTIDE ACETATE	PEN INJCTR	N
SYMLINPEN 60	PRAMLINTIDE ACETATE	PEN INJCTR	N
TANZEUM	ALBIGLUTIDE	PEN INJCTR	N
VICTOZA 2-PAK	LIRAGLUTIDE	PEN INJCTR	N
VICTOZA 3-PAK	LIRAGLUTIDE	PEN INJCTR	N

### Thiazolidinediones

Brand	Generic	FormDesc	PDL
ACTOS	PIOGLITAZONE HCL	TABLET	Y
PIOGLITAZONE HCL	PIOGLITAZONE HCL	TABLET	Y
ACTOPLUS MET	PIOGLITAZONE HCL/METFORMIN HCL	TABLET	N
AVANDAMET	ROSIGLITAZONE/METFORMIN HCL	TABLET	N
PIOGLITAZONE-METFORMIN	PIOGLITAZONE HCL/METFORMIN HCL	TABLET	N
ACTOPLUS MET XR	PIOGLITAZONE HCL/METFORMIN HCL	TBMP 24HR	N
AVANDARYL	ROSIGLITAZONE/GLIMEPIRIDE	TABLET	
DUETACT	PIOGLITAZONE HCL/GLIMEPIRIDE	TABLET	
PIOGLITAZONE-GLIMEPIRIDE	PIOGLITAZONE HCL/GLIMEPIRIDE	TABLET	

## Oral Hypoglycemics

Brand	Generic	FormDesc	PDL
FORTAMET	METFORMIN HCL	TAB ER 24	Y
METFORMIN HCL ER	METFORMIN HCL	TAB ER 24	Y
GLUCOPHAGE XR	METFORMIN HCL	TAB ER 24H	Y
METFORMIN HCL ER	METFORMIN HCL	TAB ER 24H	Y
AMARYL	GLIMEPIRIDE	TABLET	Y
DIABETA	GLYBURIDE	TABLET	Y
GLIMEPIRIDE	GLIMEPIRIDE	TABLET	Y
GLIPIZIDE	GLIPIZIDE	TABLET	Y
GLUCOPHAGE	METFORMIN HCL	TABLET	Y
GLUCOTROL	GLIPIZIDE	TABLET	Y
GLYBURIDE	GLYBURIDE	TABLET	Y
METFORMIN HCL	METFORMIN HCL	TABLET	Y
MICRONASE	GLYBURIDE	TABLET	Y
RIOMET	METFORMIN HCL	SOLUTION	N
GLIPIZIDE ER	GLIPIZIDE	TAB ER 24	N
GLIPIZIDE XL	GLIPIZIDE	TAB ER 24	N
GLUCOTROL XL	GLIPIZIDE	TAB ER 24	N
GLUMETZA	METFORMIN HCL	TABERGR24H	N
CHLORPROPAMIDE	CHLORPROPAMIDE	TABLET	N
GLIPIZIDE-METFORMIN	GLIPIZIDE/METFORMIN HCL	TABLET	N
GLUCOVANCE	GLYBURIDE/METFORMIN HCL	TABLET	N
GLYBURIDE MICRONIZED	GLYBURIDE,MICRONIZED	TABLET	N
GLYBURIDE-METFORMIN HCL	GLYBURIDE/METFORMIN HCL	TABLET	N
GLYNASE	GLYBURIDE,MICRONIZED	TABLET	N
NATEGLINIDE	NATEGLINIDE	TABLET	N
PRANDIMET	REPAGLINIDE/METFORMIN HCL	TABLET	N
PRANDIN	REPAGLINIDE	TABLET	N
REPAGLINIDE	REPAGLINIDE	TABLET	N
STARLIX	NATEGLINIDE	TABLET	N
TOLAZAMIDE	TOLAZAMIDE	TABLET	N
TOLBUTAMIDE	TOLBUTAMIDE	TABLET	N
ACARBOSE	ACARBOSE	TABLET	
GLYSET	MIGLITOL	TABLET	
PRECOSE	ACARBOSE	TABLET	



### Class Update: Disease Modifying Agents for Multiple Sclerosis

**Month/Year of Review:** September 2014

**PDL Classes:** Neurologic– MS Drugs (Disease modifying agents)

**New Drug(s):** Peginterferon beta-1a (Plegridy®)

**Date of Last Review:** September 2013

**Source Document:** OSU College of Pharmacy

#### Current Status of PDL Class:

- **Preferred Agents:** INTERFERON BETA-1A IM (AVONEX®/AVONEX PEN®, AVONEX ®ADMINISTRATION PACK), INTEFERON BETA-1A SUBQ (REBIF®), INTERFERON BETA-1B SUBQ (BETASERON® AND EXTAVIA®), GLATIRAMER ACETATE 20mg/ml (COPAXONE®)
- **Non-Preferred Agents:** NATALIZUMAB IV (TYSABRI®), MITOXANTRONE IV, FINGOLIMOD (GILENYA®), TERIFLUNOMIDE (AUBAGIO®), DIMETHYL FUMARATE (TECFIDERA®), GLATIRAMER ACETATE 40mg/ml (COPAXONE®)

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

#### 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 peginterferon beta- 1a effective and safe for the treatment of MS and/or offer safety or efficacy advantages over currently available therapies for the treatment of MS?
- Are there certain patient subgroups which would benefit from peginterferon beta-1a?

#### Conclusions:

- There is moderate strength of evidence that glatiramer 40mg three times a week (tiw), a recently approved dosage and new formulation, reduced annualized relapses compared to placebo by 34% (mean ARR = 0.331 vs. 0.505; RR 0.66 [95% CI 0.539 to 0.799],  $p < 0.0001$ ) based on one 12-month, good quality study. Limited data suggests similar efficacy to glatiramer 20mg daily, however, no direct comparisons are available.<sup>1</sup>
- There is low-moderate strength of evidence that fingolimod 0.5mg reduced the mean annualized relapse rate by 48% in patients with relapsing-remitting multiple sclerosis (MS) compared to placebo, 0.21 versus 0.40, respectively (rate ratio 0.52, 95% CI 0.40 to 0.66;  $p < 0.001$ ) as demonstrated by one fair quality study.<sup>2</sup>

- There is moderate strength of evidence from one good-quality study that peginterferon beta-1a significantly reduced relapses in patients with relapsing-remitting MS when given every 14 or 29 days compared to placebo.<sup>3</sup> Annualized relapse rates at 48 weeks were 0.397 for placebo, 0.256 for peginterferon beta-1a every 2 weeks and 0.288 for peginterferon beta-1a every 4 weeks. The most common adverse event with active treatment were injection site reactions which were higher in the peginterferon beta-1a groups receiving injections every 2 weeks.<sup>3</sup>

#### **Recommendations:**

- Limited evidence suggests glatiramer 40mg tiw is effective in preventing relapses in patients with RRMS. Evaluate costs in executive session.
- Recommend requiring a prior authorization for peginterferon beta-1a (Appendix 1).
- No changes are recommended to PDL as a result of this review. Evaluate comparative costs in executive session.

#### **Reason for review:**

The class of MS treatments was last reviewed in September of 2013. Annual updates of the class allow for incorporation of new literature and to ensure recommendations are relevant and accurate. Since the last review one new drug and one new formulation has been approved. New primary literature and guidelines will be reviewed and evaluated.

#### **Previous Conclusions and Recommendation:**

- There is low strength of evidence indicating dimethyl fumarate 240 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.<sup>4</sup> Dimethyl fumarate is available by PA to patients who have tried and failed first line agents including beta interferons and/or glatiramer.
- 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).<sup>5</sup> There is conflicting evidence on disease progression outcomes. The committee recommended that all interferons be included on the PDL.

#### **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.<sup>4</sup> 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.<sup>6</sup> 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.<sup>7</sup> The McDonald criterion is a tool used to help in the diagnosis of MS and is based upon number of clinical attacks, lesions, and dissemination in time and space.<sup>8</sup>

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 relapse of neurological symptoms followed by full or partial recovery.<sup>5</sup> Some patients with RRMS will develop secondary progressive MS, which is associated with rapid neurological damage.

Acute exacerbations or relapses of MS can be disabling. Treatment of MS includes corticosteroids for acute relapse, symptom management, and disease modification.<sup>5</sup> 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.<sup>6</sup> Treatment with these agents should not be delayed in patients with a definite

diagnosis of MS with active, relapsing disease. Goals of treatment include decreasing exacerbations, hospitalizations, slowing disease progression, and disability.<sup>6</sup>

There are currently ten DMDs approved by the U.S. Food and Drug Administration (FDA) for use in RRMS.<sup>9</sup> Disease modifying treatments are the preferred choice, however, optimal treatment is dependent upon patient characteristics and response. Interferons (interferon beta-1a and interferon beta-1b) and glatiramer were the first available disease modifying treatments and are often considered first-line options despite the need for injectable administration.<sup>10</sup> Natalizumab, a monoclonal antibody, is also an approved for the treatment of MS, however, its association with progressive multifocal leukoencephalopathy limits its use to patients that have failed other therapies.<sup>10</sup> Three oral agents have been approved for treatment of MS; fingolimod, teriflunomide and dimethyl fumarate.<sup>11</sup> Efficacy and safety data beyond two years and adverse events, such as hepatotoxicity and cardiovascular risks, have resulted in many of the oral therapies being second line treatment options.<sup>10-12</sup>

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.<sup>13</sup> 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).<sup>13,14</sup> 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.<sup>15</sup> Due to treatment length “sustained disease progression” is often used instead of hitting a long-term disease progression milestone.<sup>14</sup> 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.<sup>16</sup> 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 of 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.<sup>9</sup> This is generally studied after one or more years of treatment. However, the frequency of relapses in the general population is highly variable.<sup>17</sup> According to data from the Marshfield Multiple Sclerosis Center in Wisconsin, 1,078 RRMS patients 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.<sup>18</sup>

MS causes demyelination of neuronal axons which form lesions of the central nervous system on a magnetic resonance imaging (MRI).<sup>5</sup> 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.<sup>8</sup> 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.<sup>6</sup> In July 2013, a meta-analysis explored the potential of MRI lesions being used as a surrogate for effect of treatment on relapses.<sup>16</sup> 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 August 2013 and ending July 2014 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.

#### **New Guidelines:**

##### *National Institute for Health and Clinical Excellence*

A NICE technology appraisal on teriflunomide for the treatment of RRMS was released in January of 2014.<sup>19</sup> Recommendations were to consider teriflunomide therapy in adults with active RRMS if there is no evidence of highly active or rapidly evolving severe relapsing-remitting MS. Recommendations were based on three, phase III studies, Study 2001, TEMSO and TOWER. A meta-analysis of placebo controlled comparison of the trials showed a reduction in annualized relapse rate (RR: 0.66, 95% CI 0.59 to 0.75).<sup>19</sup>

#### **New FDA Safety Alerts:**

In April 2014, the FDA added a safety warning to interferon Beta-1a adverse reaction section.<sup>20</sup> The warning included the following: injection site reactions and cases of pseudo-relapses erythema multiforme and Steven-Johnson syndrome, suicide and hepatic injury, reports of thrombotic thrombocytopenic purpura and hemolytic uremia syndrome, retinal vascular disorders and convulsive disorders and systemic lupus erythematosus, autoimmune hepatitis and pancytopenia.

A FDA warning and subsequent label change was issued for fingolimod (Gilenya®) in April 2014 for the risk of posterior reversible encephalopathy syndrome (PRES).<sup>21</sup> Fingolimod should be discontinued if PRES is suspected.

#### **New drugs/formulations/indications:**

A new dosing regimen was approved for glatiramer 40mg tiw in January of 2014 as an alternative option to daily injections.<sup>22</sup> The glatiramer three times weekly dosing regimen was shown to be effective in one good quality study.<sup>1</sup>

Khan, et al studied the use of subcutaneous glatiramer 40mg tiw compared to placebo in a randomized, double-blind study in 2,928 patients with RRMS (GALA). Included patients had a least one relapse within the last year and an EDSS of  $\leq 5.5$ . Patients were ineligible if they had previously used glatiramer and/or were being treated with immunomodulators. Included patients were a mean age of 38 years, majority were female (67.5%) and a mean EDSS score of 2.75. The primary endpoint was the number of confirmed relapses in the 12-month placebo controlled phase. Relapses included changes from baseline in functional

system (FS) and Kurtzke's EDSS assessment in addition to neurologic abnormalities. Secondary endpoints were cumulative GdE T1 lesions at 6 and 12 months, cumulative new or newly enlarging T2 lesions at 6 and 12 months and percentage change in brain volume at 12 months.

There is moderate strength of evidence that glatiramer was shown to reduce annualized relapses compared to placebo by 34% (mean ARR = 0.331 vs. 0.505; RR 0.66 [95% CI 0.539 to 0.799],  $p < 0.0001$ ). Changes assessed by the EDSS score demonstrated similar rates of no progression in those receiving glatiramer (95.5%) and placebo (96.3%). Secondary endpoints were significantly reduced for cumulative GdE T1 lesions in the glatiramer group (0.905) compared to placebo (1.639) and for cumulative new or newly enlarging T2 lesions in patients randomized to glatiramer compared to placebo, 3.650 versus 5.592, respectively. Patients in the glatiramer group showed less reduction in brain volume compared to placebo but not significantly so.

Discontinuations were similar in glatiramer and placebo groups, 8.9% and 6.7%, respectively. The most common adverse event was injection site reactions in the glatiramer group (35%) compared to placebo (5%). Serious adverse events were similar between groups (4.5%) and discontinuations due to adverse events occurred in 3.1% of glatiramer patients and 1.3% of those in the placebo group.

Patients included in GALA were predominately white females with low levels of disability. Extrapolation of results to other populations should be done with caution. Annualized relapse rates were similar to 20mg once daily glatiramer injections which have been shown to have an approximate 30% reduction in relapses.<sup>9</sup> Injection site reactions and systemic immediate post injection reactions were lower, in indirect comparisons, with glatiramer 40mg tiw compared with those reported with glatiramer 20mg daily. An open-label phase of this trial is ongoing.

#### **New Primary Literature:**

##### *Fingolimod*

Calabresi, et al studied the use of fingolimod 0.5mg or 1.25mg compared to placebo in a double-blind, randomized, phase 3 study in 1083 patients with RRMS (FREEDOMS II).<sup>2</sup> The data safety monitoring board recommended that all patients be switched to fingolimod 0.5mg dose on November 12, 2009. This group was still analyzed as the fingolimod 1.25mg group. Patients were a mean age of 40 years (18-55 years) The primary endpoint was annualized relapse rate at month 24. Secondary endpoints were percentage of brain volume change from baseline and time-to-disability-progression at 3 months.

There is low-moderate strength of evidence that fingolimod 0.5mg reduced the mean annualized relapse rate by 48% in patients with RRMS compared to placebo, 0.21 versus 0.40, respectively (rate ratio 0.52, 95% CI 0.40 to 0.66;  $p < 0.001$ ). Percentage of patients free from disability at month 6 was significantly greater in fingolimod 1.25mg and fingolimod 0.5mg groups compared to placebo, NNT of 21 and 25, respectively. Mean percent brain volume change was significantly less in both fingolimod groups compared to placebo,  $p = 0.0002$ . Disability progression was similar between groups.

Common adverse events were upper respiratory tract infections, nasopharyngitis, urinary tract infection and sinus infections. Hypertension, bronchitis, influenza and herpes viral infection were more common in the fingolimod groups. Fingolimod was associated with increased liver function tests compared to placebo (10% with fingolimod 1.25mg, 8% with fingolimod 0.5mg and 2% in placebo group). Serious adverse events included macular edema and lymphopenia. More patients in the fingolimod groups compared to placebo developed basal-cell carcinomas, 2% in the fingolimod 1.25 mg group, 3% in the fingolimod 0.5mg group and 1% in the placebo group. No abnormal findings were found related to valve disease onset or stenosis. Bradycardia following the administration of the first dose was reported in 27 patients, however, most did not require treatment and resolved within 24 hours.

Small sample size and high attrition rates are limitations of this study. Applicability of results to patients naïve to disease-modifying treatment is low since a majority (75%) of study patients had been previously treated with these therapies. Most patients were of limited disability with a mean EDSS score of 2.45.

### **New Drug Evaluation – Peginterferon beta-1a (Plegridy®)**

FDA Indication: Peginterferon beta-1a was approved in August 2014 for the treatment of patients with relapsing forms of multiple sclerosis.<sup>23</sup> Peginterferon beta-1a is a subcutaneous formulation requiring administration once every 14 days in contrast to other forms of interferon beta-1a which require subcutaneous administration three times a week (Rebif®) or intramuscularly once a week (Avonex®).<sup>24, 25</sup>

Clinical Efficacy (see evidence table below):

One good-quality study was used for the approval of peginterferon beta-1a (ADVANCE). ADVANCE was a double-blind, placebo-controlled, parallel group, phase 3, randomized trial of 1516 patients.<sup>3</sup> Patients were randomized to placebo, peginterferon beta-1a every 2 weeks (PG2) or peginterferon beta-1a every 4 weeks (PG4) for 48 weeks. A majority of patients were female with relapsing-remitting MS, mean age of 36 and mean EDSS score of 2.46. The primary endpoint was annualized relapse rate at 48 weeks. Important secondary endpoints were proportion of patients with relapse at 48 weeks and disability progression at 48 weeks ( $\geq 1$  point increase on the EDSS from baseline score of  $\geq 1$  sustained for 12 weeks or at least a 1.5 point increase from baseline score of 0 sustained for 12 weeks).

There is moderate strength of evidence that PG2 and PG4 significantly decreased relapses compared to placebo. The adjusted annualized relapse rate per patient-year was 0.397 for placebo, 0.256 for PG2 and 0.397 for PG4 at week 48 (rate ratio for PG2 vs. placebo: 0.644 [95% CI 0.500 to 0.831,  $p=0.0007$ ] and PG4 vs placebo: 0.725 [95% CI 0.565 to 0.930,  $p=0.0114$ ]).<sup>3</sup> The number of patients with 12 weeks of sustained disability progression at 48 weeks and proportion of patients with a relapse at 48 weeks were both significantly reduced with peginterferon beta-1a compared to placebo, NNT of 25 for both groups and NNT of 10 for PG2 and 14 for PG4, respectively. The number of T1 hypointense and gadolinium-enhancing lesions were less in the peginterferon beta-1a group compared to placebo. This study is ongoing, with the placebo phase ending at 48 weeks with those patients randomized to one of the active treatment groups for an additional year.

Clinical Safety:

The most common adverse reactions associated with peginterferon beta-1a were injection site reactions, influenza-like symptoms, pyrexia, and headache. Injection site reactions were more common in the PG2 group compared to the PG4 group, 62% and 56%, respectively.<sup>3</sup> Serious adverse reactions were relapse, pneumonia and urinary tract infections with relapse being the most common. Discontinuations due to adverse events were higher in both the peginterferon beta-1a groups with influenza-like illness being the most common cause. Hepatic enzyme elevations and reduced hematologic parameters were more common in the peginterferon beta-1a groups compared to placebo but most did not result in treatment discontinuation. Less than 1% of patients in the active treatment groups developed neutralizing antibodies. Results of a 2-year safety extension study suggest similar findings as the ADVANCE trial.

In conclusion, PG2 and PG4 were found to be effective in reducing relapse rates in patients with relapsing-remitting MS. Reductions in relapses were similar to other interferon beta-1a treatments but no head to head comparisons are available. Study limitations include short duration and small number of patients on previous MS therapy limiting applicability of results to those with less severe disease.

### **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) Annualized relapse rate
- 2) Percent change in brain volume/ number of brain lesions
- 3) Relapse free / free of disability progression

Ref./Study Design <sup>a</sup>	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
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<p>GALA trial Khan, et al<sup>1</sup></p> <p>Phase III, RCT, DB, PC</p> <p>142 sites and 17 countries</p>	<p>1. Glatiramer 40mg/mL tiw (GL)</p>	<p>Mean age: 38 Age range: 18-55 yrs. Mean EDSS: 2.75 Females: 68% White: 98%</p>	<p>1. n= 1524</p>	<p><u>Annualized relapse rate at 12 months</u> GL: 0.331 P: 0.505 RR: 0.656 (95% CI 0.539 to 0.799), P&lt;0.0001</p>	<p>N/A</p>	<p><u>Serious adverse events</u> GL: 42 (4.5%) P: 21 (4.6%)</p>	<p>N/A</p>	<p>Quality rating: Good Internal validity: <u>Selection:</u> Constrained blocks stratified by center was used for randomization. Baseline characteristics were similar. <u>Performance:</u> Placebo and active treatment identical. All providers involved in patient management were blinded to treatment assignment. <u>Detection:</u> data management was blinded to treatment. <u>Attrition:</u> Overall attrition was 13% in both groups. A modified ITT was used that included all patients randomized.</p> <p>External validity: <u>Setting:</u> From 142 sites in 17 countries. <u>Patient characteristics:</u> Age range representative of general population. Primarily white patients (98%). Mean EDSS score suggests minimal disability. <u>Outcomes:</u> Clinically relevant efficacy and safety endpoints.</p>
	<p>2. Placebo</p> <p>Duration: 12 months</p>	<p><u>Inclusion Criteria:</u> age 18- 55 years, confirmed diagnosis of RRMS, baseline EDSS ≤5.5, relapse free for ≥30 days at least 1 relapse within the 12 months prior to screening, ≥2 relapses within 24 months prior to screening, or one relapse between 12 and 24 months prior to screening with at least 1 T1 Gd enhancing lesions within previous 12 months.</p>	<p>2. n= 943</p>	<p><u>Relapse-Free at 12 months</u> GL: 726 (77%) P: 306 (66.5%) OR: 1.9 (95% CI 1.5 to 2.5), p&lt;0.0001</p>	<p>ARR: 11.5% NNT: 9</p>	<p><u>Discontinuations due to adverse event</u> GL: 29 (3.1%) P: 6 (1.3%)</p>	<p>N/A</p>	
		<p><u>Exclusion Criteria:</u> progressive relapsing MS, previous glatiramer treatment, treatment with immunomodulators within previous 2 months immunosuppressive agents, cytotoxic agents, chronic corticosteroid treatment within previous 6 months, monoclonal antibody treatment within 2 years of screening, Gd or mannito sensitivity or not able to undergo MRI scanning.</p>		<p><u>Cumulative GdE T1 lesions at 6 and 12 months</u> GL: 0.905 P: 1.639 RR: 0.55 (95% CI 1.300 to 2.066), p&lt;0.0001</p>	<p>N/A</p>			
				<p><u>Cumulative new or newly enlarging T2 lesions at 6 and 12 months</u> GL: 3.650 P: 5.592 RR: 0.653 (95% CI 0.546 to 0.780), p&lt;0.0001</p>	<p>N/A</p>			



FREEDOMS II <sup>2</sup>  Calabresi P, et al  Phase III, RCT, DB, PC          117 centers	1. Fingolimod 0.5mg daily (F0.5)	Mean age: 40 years Females: 78% Mean EDSS score: 2.45	1. n= 358	<u>Annualized relapse rate at 2 years:</u> F0.5:0.21 F1.25: 0.20 P: 0.40	N/A	<u>Serious adverse events</u> F0.5: 53 (14%) F1.25: 53 (15%) P: 45 (13%)	N/A	Quality rating: Fair Internal validity: <u>Selection:</u> Randomization done via automated system. <u>Performance:</u> Placebo and active treatments identically packaged. <u>Detection:</u> independent data board. <u>Attrition:</u> Overall attrition was high and varied between groups (32% for fingolimod 1.25mg, 24% for fingolimod 0.5mg and 28% for placebo. ITT analysis was used for all randomized patients.  External validity: <u>Recruitment:</u> Not provided. <u>Patient characteristics:</u> Age range representative of general population. Patients with major comorbidities were excluded. Majority (75%) of patients had previously used disease-modifying treatments. <u>Setting:</u> Included 117 centers (101 US sites). Sponsored by Novartis Pharma AG. <u>Outcomes:</u> Clinically relevant efficacy and safety endpoints.
	2. Fingolimod 1.25mg daily (F1.25)  3. Placebo (P)  Duration: 24 months  *Patients in the 1.25mg group were switched to the 0.5mg dose 11/12/09	Inclusion Criteria: patients 18-55 years old with RRMS, EDSS score of 0 -5.5, at least 1 relapse within the 12 months prior to screening (or two or more relapses within the previous 2 years), and no relapse or steroid treatment within 30 days before randomization. Previously treated patients were included if interferon beta or glatiramer was discontinued at least 3 months prior to randomization and natalizumab treatment was stopped at least 6 months before randomization.  Exclusion Criteria: Patients with significant systemic disease, malignancy, diabetes, cardiac, pulmonary, or hepatic disorders and active infection or macular edema.	2. n= 370  3. n= 355	Rate Ratio for F0.5 vs.P: 0.52 (95% CI 0.40 to 0.66) P<0.0001  Rate Ratio for F1.25 vs.P: 0.50 (95% CI 0.39 to 0.65) P<0.0001  <u>Percentage of patients free of disability progression at 6 months</u> F0.5: 309 (86.2%) F1.25:319 (86.9%) P: 291(82.2%)  HR for F0.5 vs. P: 0.72 (95% CI, 0.48 to 1.07) P = 0.101  HR for F1.25 vs P: 0.72 (95% CI 0.48 to 1.08) p= 0.113  <u>Mean Percent Change in Brain Volume from Baseline to month 24:</u> F0.05: -0.858% F1.25: -0.595% P: -1.279%  F0.5 vs P: p=0.0002  F1.25 vs P: p<0.0001	N/A          F0.5 vs.P: ARR: 4% NNT: 25  F1.25 vs. P: ARR: 4.7% NNT: 21    NA	<u>D/c of study drug due to adverse event</u> F0.5: 66 (18%) F1.25: 72 (20%) P: 37 (10%)	N/A	

ADVANCE <sup>3</sup>	1. Peginterferon beta-1a every 2 weeks (PB2)	Mean age: 36 years Females: 71% Mean EDSS score: 2.46	N= 512	<u>Annualized relapse rate at 48 weeks:</u> PB2: 0.256 PB4: 0.288 P: 0.397	NA	<u>Serious adverse events</u> PB2: 55 (11%) PB4: 71 (14%) P: 76 (15%)	NA	Quality rating: Good Internal validity: <u>Selection:</u> Randomization done via interactive voice response or web system. <u>Performance:</u> Placebo and active treatments identically packaged in pre-filled syringe. All study management and site personnel, investigators, and patients were masked to treatment assignment. Separate examining and treating neurologists were at each site. <u>Detection:</u> blinded independent data and safety monitoring board. <u>Attrition:</u> Overall attrition was 9% for the placebo group, 14% for the PB2 group and 12% for the PG4 group. ITT analysis was used for all randomized patients.  External validity: <u>Recruitment:</u> Not provided. <u>Patient characteristics:</u> Age range representative of general population. Patients had moderate disability and only seventeen percent had previously used treatments for MS. <u>Setting:</u> Included 183 centers and 26 countries (approximately 3.5% from North America). Sponsored by Biogen Idec. <u>Outcomes:</u> Clinically relevant efficacy and safety endpoints.
Calabresi, et al	2. Peginterferon beta-1a every 4 weeks (PB4)	Inclusion Criteria: patients 18-65 years old with RRMS, EDSS score of 0 -5.0, at least 2 relapses within the previous 3 years, with at least one having occurred within the past 12 months.  Exclusion Criteria: Patients with progressive forms of MS, pre-specified laboratory abnormalities, and previous treatment with interferon for MS for more than 4 weeks or discontinuation less than 6 months before baseline	N= 500	Rate Ratio for PB2 vs.P: 0.644 (95% CI 0.500 to 0.831) P=0.0007		<u>D/c of study drug due to adverse event</u> PB2: 25 (5%) PB4: 24 (5%) P: 7 (1%)	NA	
PC, DB, PG, Phase 3, RCT	3. Placebo		N= 500	Rate Ratio for PB4 vs.P: 0.725 (95% CI 0.565 to 0.930) P=0.0114  <u>Disability progression at 48 weeks:</u> PB2: 31 (6%) PB4: 31 (6%) P: 50 (10%)  HR for PB2 vs. P: 0.62 (95% CI, 0.40 to 0.97) P = 0.0383  HR for PB4 vs P: 0.62 (95% CI 0.40 to 0.97) p= 0.0380  <u>Proportion of patients with a relapse at 48 weeks:</u> PB2: 90 (18%) PB4: 105 (21%) P: 142 (28%)  HR for PB2 vs P: 0.61 (95% CI 0.47 to 0.80) p= 0.0003  HR for PB4 vs P: 0.74 (95% CI 0.57 to 0.95) p=0.02	For PB2 vs. P and PB4 vs. P: ARR: 4% NNT: 25  PB2 vs P: ARR: 10% NNT: 10  PB4 vs. P: ARR: 7% NNT: 14			
183 sites	* Patients assigned to peginterferon beta-1a groups underwent dose escalation over first 4 weeks  * Duration 48 weeks							
Author: Kathy Sentena, Pharm.D.								
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## Appendix 1: Suggested PA Criteria

### Peginterferon Beta-1a (Plegridy®)

**Goal(s):** Approve therapy for covered diagnoses which are supported by the medical literature.

**Length of Authorization:**  
Up to 12 months

**Requires PA:**  
- Non-preferred drugs

**Covered Alternatives:**  
- Preferred alternatives listed at [www.orpd.org](http://www.orpd.org)

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of relapsing-remitting Multiple Sclerosis?	<b>Yes:</b> Go to #3.	<b>No:</b> Pass to RPH; Deny (medical appropriateness)
3. Will the prescriber consider a change to a Preferred MS product?	<b>Yes:</b> Inform Provider of covered alternatives in the class. Additional information can be found at <a href="http://www.orpd.org">www.orpd.org</a>	<b>No:</b> Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPH; Deny (medical appropriateness).
5. Does the patient have any of the following: - Adherence issues necessitating less frequent administration - dexterity issues limiting ability to administer subcutaneous injections	<b>Yes:</b> Approve for up to one year.	<b>No:</b> Pass to RPH; Deny (medical appropriateness)

*P&T Action: 9/23/14 (KS)*

*Revision(s):*

*Initiated:*

## 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)?	<b>Yes:</b> Go to #3.	<b>No:</b> 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.	<b>Yes:</b> Inform Provider of covered alternatives in class. <a href="http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml">http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml</a> .	<b>No:</b> Go to #4.
4. Has the patient failed or cannot tolerate a full course of interferon beta 1a or interferon beta 1b, and glatiramer?	<b>Yes:</b> Go to #5.	<b>No:</b> Pass to RPH; Deny (medical appropriateness).
5. Is the medication being prescribed by or in consultation with a neurologist?	<b>Yes:</b> Go to #6.	<b>No:</b> 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)?	<b>Yes:</b> Pass to RPH; Deny (medical appropriateness).	<b>No:</b> Go to #7.
7. Is the prescription for teriflunomide?	<b>Yes:</b> Go to #8.	<b>No:</b> Go to #10.

<b>8.</b> Is the patient of childbearing potential?	<b>Yes:</b> Go to #9.	<b>No:</b> Approve for up to one year.
<b>9.</b> Does the patient currently on a documented use of reliable contraception?	<b>Yes:</b> Approve up to one year.	<b>No:</b> Pass to RPH; Deny (medical appropriateness)
<b>10.</b> Is the prescription for fingolimod?	<b>Yes:</b> Go to #11.	<b>No:</b> Go to #14.
<b>11.</b> Does the patient have evidence of macular edema (ICD-9 362.07)?	<b>Yes:</b> Pass to RPH; Deny (medical appropriateness).	<b>No:</b> Go to #12.
<b>12.</b> Does the patient has preexisting cardiac disease, risk factors for bradycardia, or is on antiarrhythmics, beta-blockers, or calcium channel blockers?	<b>Yes:</b> Go to #13.	<b>No:</b> Approve up to one year.
<b>13.</b> Has the patient had a cardiology consultation before initiation?	<b>Yes:</b> Approve up to one year.	<b>No:</b> Pass to RPH; Deny (medical appropriateness).
<b>14.</b> Is the prescription for dimethyl fumarate?	<b>Yes:</b> Approve up to one year.	<b>No:</b> 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 Teriflunomide, 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 Teriflunomide to report symptoms of infections, and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting Teriflunomide, monitor ALT levels at least monthly for 6 months after, consider additional ALT monitoring when Teriflunomide 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.

*P&T Action:* 3-29-2012

*Revision(s):* 5-30-2013 (MH)

*Initiated:* 6/21/2012

## 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)?	<b>Yes:</b> Go to #3.	<b>No:</b> Pass to RPH; Deny (medical appropriateness)
3. Is the medication being prescribed by or in consultation with a neurologist?	<b>Yes:</b> Go to #4.	<b>No:</b> Pass to RPH; Deny (medical appropriateness)
4. Is the request for continuation of therapy? (Patient has completed two month trial)	<b>Yes:</b> Go to "Continuation of Therapy"	<b>No:</b> 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)?	<b>Yes:</b> Pass to RPH; Deny (medical appropriateness)	<b>No:</b> Go to #6
6. Does the patient have moderate to severe renal impairment (CrCl <50 ml/min)?	<b>Yes:</b> Pass to RPH; Deny (medical appropriateness)	<b>No:</b> 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 <ul style="list-style-type: none"> <li>• Is able to complete the baseline timed 25 foot walk between 8 and 45 seconds</li> </ul>	<b>Yes:</b> Approve initial fill for 2 month trial.	<b>No:</b> 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 $\geq 20\%$ improvement in timed 25 foot walk).	<b>Yes:</b> Go to #2	<b>No:</b> Pass to RPH; Deny (medical appropriateness)
2. Is the medication being prescribed by or in consultation with a neurologist?	<b>Yes:</b> Approve for 12 months	<b>No:</b> 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.

P&T Action: 3-29-2012

Revision(s):

Initiated:

### Appendix 3: Drug Information

#### NDE: Peginterferon beta-1a (Plegridy®)

**Pharmacology:** The mechanism in which peginterferon beta-1a exerts its effects in patients with multiple sclerosis is unknown.

**Table 1. Pharmacokinetics**

Parameter	Peginterferon beta-1a	Parameter	Peginterferon beta-1a
<b>Half-Life</b>	78 hours	<b>Renal Dose Adjustment</b>	Monitor for adverse reactions in severe renal impairment due to increased drug exposure.
<b>Elimination</b>	Renal		
<b>Metabolism</b>	Catabolism and excretion	<b>Hepatic Dose Adjustment</b>	No recommendation.



**Contraindications/Warnings:**

- **Contraindications:** Peginterferon beta-1a should not be used in patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon or any other component of the formulation.
- **Warning:** Prescribing peginterferon beta-1a has been associated with hepatic injury (monitoring recommended), seizures, anaphylaxis, other allergic reactions, and injection site reactions. Symptoms of depression or suicide should be reported to provider and consider discontinuing peginterferon beta-1a if appropriate. Monitor patients with congestive heart failure for worsening of symptoms. Consider discontinuing peginterferon beta-1a if a new autoimmune disorder occurs.

**Dose**

The recommended dose of peginterferon beta-1a is 125 micrograms (mcgs) every 14 days. The dose should be titrated, starting with 63 mcgs on day one and 94 mcgs on day 15 and 125 mcgs on day 29. Patients should be consulted on correct technique for self-administering subcutaneous injections using the prefilled pen or syringe. Analgesics and/or antipyretics may be given to help with flu-like symptoms associated with peginterferon beta-1a use.

## Abbreviated Class Update: Antidepressants (First and Second Generation)

**Month/Year of Review:** September 2014

**End date of literature search:** June 1, 2014

### Current Status of Voluntary PDL Class:

- Preferred Agents: BUPROPION HCL TABLET/TABLET ER, CITALOPRAM TABLET/SOLUTION, FLUOXETINE CAPSULE/SOLUTION/TABLET, FLUVOXAMINE, MIRTAZEPINE TAB RAPDIS/TABLET, PAROXETINE TABLET, SERTRALINE ORAL CONC/TABLET, VENLAFAXINE TABLET, VENLAFAXINE ER
- Non Preferred Agents: BUPROPION XL, DESVENLAFAXINE (PRISTIQ ER), DULOXETINE (CYMBALTA®), ESCITALOPRAM, FLUOXETINE DF (PROZAC® WEEKLY), NEFAZODONE, PAROXETINE HCL (PAXIL CR®), SELEGILINE PATCH (ENSAM®), VILAZODONE (VIIBRYD®), OLANZAPINE/FLUOXETINE (SYMBYAX®), VORTIOXETINE (BRINTELLIX®), LEVOMILNACIPRAN (FETZIMA®)

### Research Questions:

- What is the comparative efficacy of first and second generation antidepressants in the treatment of major depressive disorder?
- How do first and second generation antidepressants differ in type and incidence of adverse events?

### Conclusions:

- There is low quality evidence that shows there are minimal differences in efficacy between first and second generation antidepressants. While some meta-analyses show a trend towards greater improvement with TCAs compared to SSRIs, TCAs are no longer favored when only higher quality studies are considered.
- The safety profiles of antidepressants vary by class, and there is no comprehensive analysis that directly compares the rate and type of adverse events between first and second generation antidepressants. There is low quality evidence to show that SSRIs are more tolerable than TCAs, as a larger proportion of patients treated with TCAs withdrew treatment due to adverse events compared to those treated with SSRIs. MAOIs are associated with more drug-drug and food-drug interactions than any other class of antidepressants.

### Recommendations:

- The selection of the appropriate medication for a patient should be chosen based on the properties of an individual drug, as opposed to a drug group.
- In alignment with treatment guidelines, first and second generation antidepressants should be accessible to patients, with the selection of the individual agent dependent on severity of condition, comorbidities, medication history, and tolerability of side effects for the individual patient.
- Recommend including first generation antidepressants to the voluntary PDL and evaluate costs in executive session. Consider a non-preferred status for MAOIs, given the known safety concerns including high risks of drug-drug and drug-food interactions. Also maintain nefazodone as non-preferred due to hepatic safety concerns.

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**Reason for Review:**

To understand where first generation antidepressants fit on the PDL. Currently, all antidepressants are available without restriction and are not subject to prior authorization. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs, such as prior authorization. Thus, the mental health PDL is strictly voluntary. Second generation antidepressants have been reviewed for clinical efficacy and safety and specific agents have been chosen as clinically preferred. The advantage of this is the elimination of a copay. Reviewing the first generation agents and adding clinically appropriate agents to the PDL would reduce the copay burden to the client, while improving access to these medications.

**Previous P&T conclusions and recommendations (May 2014):**

- Comparative efficacy and effectiveness of second-generation antidepressants does not differ substantially for treating patients with major depressive disorder.
- There is moderate quality evidence that vortioxetine is safe and effective for the treatment of major depressive disorder (MDD) based on short-term placebo-controlled trials. There is insufficient evidence to determine the most effective treatment dose.
- There is moderate quality evidence that vortioxetine is not superior to duloxetine 60 mg daily or venlafaxine XR 225 mg daily in efficacy.
- There is low quality evidence that levomilnacipran is safe and effective for the treatment of MDD based on short-term placebo-controlled trials.
- There is insufficient evidence to determine the effectiveness of either vortioxetine or levomilnacipran in the maintenance treatment of MDD, as well as in pediatric patients or patients with severe hepatic impairment.
- Based upon current comparative effectiveness research, no changes are recommended for the second generation antidepressant preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.

**Background:**

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines major depressive disorder (MDD) as having one or more major depressive episodes (MDE) and the lifetime absence of mania and hypomania. An MDE is defined as having five of nine symptoms during a two week period. To qualify as an MDE one of the following symptoms must be present (1) depressed mood or (2) loss of interest or pleasure in usual activities that lasts for  $\geq 2$  weeks. This coincides with other symptoms of MDD which include: significant weight loss when not dieting or weight gain, insomnia or hypersomnia nearly every day, psychomotor agitation or retardation nearly every day, fatigue or loss of energy nearly every day, feelings of worthlessness or excessive or inappropriate guilt nearly every day, diminished ability to think or concentrate or indecisiveness nearly every day, or recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or suicide attempt or a specific plan for committing suicide. These symptoms must cause significant distress or impairment, not be attributable to a substance or medical condition, and cannot be better explained by a psychotic disorder.<sup>1</sup>

Depression is a very common disorder throughout the world with an estimated lifetime prevalence of 12%.<sup>2</sup> The lifetime prevalence in the US is estimated at 17%, which reflects the variation of the disease.<sup>3</sup> The average age of onset for MDD in the United States is 32 years old.<sup>4</sup> Women are 70% more likely to experience depression at some point in their life than men.<sup>4</sup> Before the late 1980s, the pharmacologic treatment of Axis I psychiatric disorders (such as depressive disorder, anxiety disorder, adjustment disorder, and premenstrual disorders) was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).<sup>5</sup> Antidepressant medications are generally broken down into two categories; first-generation and second generation. TCAs and MAOIs are often referred to as traditional or first-generation antidepressants. While these medications often are effective they are associated with more side effects than the second-generations. Common side effects of TCAs include classic anticholinergic effects including dry mouth and eyes, urinary retention, and constipation.

The original MAOIs are rarely used due to their potential to produce hypertensive crisis if taken along with certain foods or dietary supplements containing excessive amounts of tyramine.<sup>5</sup> Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs that selectively target neurotransmitters.<sup>5</sup> In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine. Since then several other SSRIs have been introduced: sertraline, paroxetine, citalopram, fluvoxamine, escitalopram, and vilazodone. The SNRIs were first introduced to the market in 1993 and include venlafaxine, duloxetine, and most recently desvenlafaxine.<sup>5</sup> Other agents used for treatment of MDD include bupropion, levomilnacipran, mirtazapine, and nefazodone.

Due to the heterogeneity and unknown definitive cause of depression, determining successful treatment in clinical trials can be difficult. The FDA has accepted primary success as improvement between a baseline score and a post-treatment score using commonly used observer-administered depression rating scores. The most widely used observer-administered depression rating scales are the Hamilton Depression Rating Scale (HAMD), 24-item and 17-item versions (HAMD24 and HAMD17, respectively), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinician Global Impressions-Severity of Illness (CGI-S) scale. The HAMD scores patients on a scale of 0-5 on 24 items associated with major depression. MADRS uses a range of 0-6 on 10 items associated with major depression. The CGI-S measures disease severity on a 7-point scale which scores the clinician's global assessment of the patient rather than individual aspects of the disease state. Clinically meaningful changes on these scales are not well defined, yet these scales are still considered the gold standard in clinical trials for antidepressants.

Defining consensus outcomes has been described in previous papers.<sup>6,7</sup> The term 'response' is used to describe a clinically significant degree of depressive symptom reduction following treatment initiation.<sup>6,7</sup> Those who no longer have depressive symptoms are considered to be in remission.<sup>6</sup> The period of remission may end with either relapse (a return of the index major depressive episode following the onset of remission) or recovery (recognized when the period of remission has been successfully sustained).<sup>6</sup> Trials have used various changes in depression scales to define response and remission, but the most widely accepted cutoffs for response is a  $\geq 50\%$  reduction from baseline (both MADRS and HAMD), and a specific threshold for remission. For the HAMD17 a score of  $\leq 7$  on the HAMD17 is widely accepted, while some argue a score of  $\leq 5$  be used, but there are differing recommendations for remission using MADRS.<sup>7</sup> A HAMD17 score of  $\leq 7$  corresponds to a MADRS score of  $\leq 9$ , but others recommend a MADRS score of  $\leq 5$  to define remission, while most clinical trials use a score of  $\leq 10$ .<sup>7</sup> This variance has led to disagreements in the scientific community but represents the best method for defining pharmacological treatment success.

#### **Methods:**

A Medline literature search ending June 2014 for new systematic reviews and randomized controlled trials (RCT's) comparing first generation antipsychotics to second generation antipsychotics. 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.

#### **1. Systematic Reviews/Meta-analyses:**

The relative efficacy and safety of first and second generation antidepressants for the treatment of major depressive disorder were evaluated in a 2012 meta-analysis. The analysis included studies that were randomized, double-blind, placebo-controlled trials in adults with acute, apparently unipolar, major depressive

episode, based on DSM-III, III-R, or –IV, ICD-9 or -10, or RDC diagnostic criteria, and had at least 20 subjects per arm.<sup>8</sup> Antidepressants must have been studied as a monotherapy. Trials were excluded from the review if they evaluated drugs that were not FDA-approved for the treatment of acute episodes of major depressive disorder. The primary outcome measure was ‘response,’ which was defined as  $\geq 50\%$  reduction in initial depression rating-scale scores. Ratings were typically based on the HAMD or MADRS Depression Rating Scales. When these measures were not available, scores were based on the CGI ratings.<sup>8</sup>

In total, 107 trials met the inclusion criteria with 27,127 total subjects (17,059 randomized to one of 19 different antidepressants, 9,925 randomized to placebo). The antidepressants studied were: imipramine, fluoxetine, venlafaxine, paroxetine, amitriptyline, duloxetine, bupropion, desvenlafaxine, sertraline, R,S-citalopram, S-citalopram, mirtazapine, selegiline, desipramine, clomipramine, nortriptyline, phenelzine, tranylcypromine, and trazodone. The frequency of studies by antidepressant types is as follows: SSRIs [52 trials (36.6%)], TCAs [38 (26.8%)], SNRIs [33 (23.2%)], atypical agents (bupropion, mirtazapine, trazodone) [14 (9.9%)], and MAOIs [5 (3.5%)].<sup>8</sup>

The pooled responder rate ratio (RR) for all agents was 1.42 (CI 1.38-1.48) compared to placebo. Overall, phenelzine ranked the highest in terms of efficacy, and trazodone the lowest. However in addition to tranylcypromine and clomipramine, these four drugs were ranked as outliers among the other antidepressants, as each drug only had one related study included in the meta-analysis. When only drugs with greater than one trial are considered, amitriptyline is ranked highest and bupropion the lowest. All confidence intervals overlap, indicating the need for cautious interpretation of trial data. Authors also compared classes of antidepressants using response rate ratios (RRs), and found TCAs to be the most effective, followed by SNRIs, MAOIs, SSRIs, and atypicals, in order of decreasing efficacy. For the outcome of responder rate differences, the classes were ranked in order of decreasing efficacy: TCAs, SNRIs, SSRIs, MAOIs, atypicals. Adverse events, discontinuation rates, and other safety outcomes were not included in this analysis.<sup>8</sup>

This comprehensive meta-analysis found that the differences between antidepressants and placebo were moderate, yet statistically significant, and that differences in efficacy among the different agents are minimal. These findings are similar to results from previous meta-analyses, but differ in that TCAs demonstrated clear statistical superiority over the other classes of antidepressants. The authors propose that this is a reflection of evolving clinical trial design that has occurred over the last three decades, including increasing size and complexity, greater heterogeneity in diagnostic and clinical assessments, inclusion of patients with less severe depression, and increasing trial length. These factors may have contributed to an increase in placebo-response rate or a decline in antidepressant-response rate, so further research is needed to determine the optimal trial design for evaluating antidepressants.

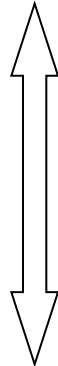
Two different meta-analyses evaluated TCAs and SSRI's for depression, specifically in the primary care setting. Each study included randomized, placebo-controlled trials using TCAs or SSRIs in adults who had a diagnosis of depression and received treatment in the primary care setting, but the studies differed in primary endpoints. In the meta-analysis by Arrol et al., the primary endpoint was the efficacy of TCAs and SSRIs in comparison with placebo, calculated using the weighted mean difference in studies where the same outcome scale was used. Where there were dichotomous outcomes, the relative risk was calculated. Patient-reported adverse events were evaluated as a secondary outcome.<sup>9</sup> In the meta-analysis by MacGillivray et al., the primary endpoint was the relative efficacy of TCAs compared to SSRIs, measured by the mean difference of final mean depression scores and relative risk of response using the CGI score.<sup>10</sup>

Arrol et al. found that both TCAs and SSRIs were statistically superior to placebo, for both continuous and dichotomous outcomes. In total, 12 studies with 2,753 participants (596 using TCAs, 890 using SSRIs, and 1,267 using placebo) were evaluated. The relative risk for improvement was 1.26 (95% CI 1.12-1.42) with TCAs and 1.37 (95% CI 1.21-1.55) with SSRIs. The numbers needed to treat for one improved patient was 3-4 and 6, for TCAs and SSRIs, respectively. Comparative efficacy of TCAs and SSRIs was not evaluated in this analysis. The relative risk for withdrawal due to adverse events was 2.35 (95% CI 1.59-3.46) for TCAs and 2.01

(95% CI 1.1-3.7) for SSRIs with a number needed to harm range of 5-10 and 21-94, respectively. All the studies included were of short duration (6-8 weeks), and all of the SSRI studies had commercial involvement.<sup>9</sup>

The analysis conducted by MacGillivray et al. included 11 studies with 2,954 total participants (1,607 using an SSRI and 1,347 using a TCA). Six studies contributed to the overall efficacy analysis and found that the standardized weighted mean difference on depression rating scales was 0.07 (95% CI -0.02-0.15). Though TCAs and SSRIs were not statistically significantly different, the data trended in favor of TCAs. When evaluators only considered the three studies that were deemed to be higher quality, TCAs are no longer favored, with a standardized mean difference of -0.03 (95% CI -0.2- 0.14). There was also no difference between TCAs and SSRIs for the endpoint of CGI improvement [relative risk 1.11 (95%CI 0.86-1.43)]. Fewer patients treated with SSRIs withdrew treatment due to an adverse event [11.6% (9.9%-13.3%)] compared to those treated with TCAs [17% (14.8%-19.1%)]. The results of this trial indicate that there is no difference in efficacy between TCAs and SSRIs, and that SSRIs may be better tolerated than TCAs. This is consistent with meta-analyses that have conducted similar comparisons of efficacy in patients of all care settings, however data is conflicting on the relative tolerability of the two classes. It appears that SSRIs may be marginally more tolerable, however high quality, long-term trials are needed to confirm this assertion.<sup>10</sup>

**Table 1. Summary of meta-analysis comparing first and second generation antidepressants**

Reference	Population	Primary Endpoint	Results					
Underraga 2012 <sup>8</sup>  Meta-analysis of all FDA-approved antidepressants	Adults with major depression  107 trials  Antidepressants: n=17,059  Placebo: n=9,925	Pooled rate ratios (RRs) of responder rates based on HDRS, MADRS, or CGI rating scales. Response: ≥ 50% reduction in rating-scale scores.	<div>Most effective</div> <div></div> <div>Least effective</div>		Relative response rates for drugs with >1 trial (95% CI, p-value)		Relative response rates for drugs by class (95% CI, p-value)	
						TCAs	1.62 (1.47-1.78), p=0.0001	
				Amitriptyline	1.74 (1.5-2.01), p≤0.001			
				Mirtazapine	1.73 (1.26-2.36), p≤0.001			
				Imipramine	1.58 (1.37-1.83), p≤0.001	SNRIs	1.40 (1.3-1.51), p=0.0001	
				Citalopram	1.48 (1.24-1.76), p≤0.001			
				Desipramine	1.45 (1.07-1.96), p≤0.001			
				Venlafaxine	1.45 (1.35-1.56), p≤0.001	MAOIs	1.39 (1.11-1.48), p=0.0001	
				Paroxetine	1.44( 1.26-1.66), p≤0.001			
				Desvenlafaxine	1.41 (1.16-1.72), p≤0.001			
				Escitalopram	1.33 (1.2-1.48), p≤0.001	SSRIs	1.37 (1.27-1.48), p=0.0001	
				Sertraline	1.33 (1.2-1.47), p≤0.001			
				Selegiline	1.33 (1.07-1.65), p≤0.001			
				Fluoxetine	1.31 (1.07-1.60), p≤0.001	Atypicals	1.25 (1.15-1.35), p=0.0001	
				Duloxetine	1.29 (1.09-1.52), p≤0.001			
				Bupropion	1.23 (1.14-1.33), p≤0.001			
			Pooled	1.42 (1.38-1.48), p<0.0001				
Arroll 2005 <sup>9</sup>  Meta-analysis comparing TCAs and SSRIs to placebo	Adults with major depression, receiving care in the primary care setting  TCAs: n=596 SSRIs: n=890 Placebo: n=1,267	Response, measured by HAMD, MADRS, or CGI rating scales		Events (treatment)	Events (placebo)	Relative risk (95% CI)		
			Efficacy endpoint: Response on depression rating scales (definition of response varied by scale)					
			TCAs vs. Placebo	323/535 (60.4%)	216/460 (47.0%)	1.26 (1.12-1.42)		
			SSRIs vs Placebo	310/552 (56.2%)	231/562 (41.1%)	1.37 (1.21-1.55)		
			Safety endpoint: Adverse events leading to withdrawal					
			TCAs vs. Placebo	81/692 (11.7%)	30/578 (5.2%)	2.35 (1.69-3.46)		
			SSRIs vs Placebo	30/576 (5.2%)	15/573 (2.6%)	2.01 (1.10-3.69)		
MacGillivray 2003 <sup>10</sup>	Adults with major depression, receiving	Standard mean difference of final mean depression scores	Standardized mean difference in final mean depression scores: 0.07 (-0.02, 0.15), in favor of TCAs.					

Meta-analysis comparing TCAs to SSRIs	care in the primary care setting  TCAs: n=1,347 SSRIs: n=1,607		Relative risk of treatment withdrawal due to drug related adverse events: 0.73 (0.60, 0.88), in favor of SSRIs.
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HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scales; CGI: Clinical Global Impression rating scale; HAMD: Hamilton Depression rating scale

## 2. Guidelines – Major Depressive Disorder:

The 3<sup>rd</sup> edition of the Practice Guideline for the Treatment of Patients with Major Depressive Disorder where released in 2010 by the American Psychiatric Association. Recommendations fell into one of three categories:<sup>11</sup>

[I] Recommended with substantial clinical confidence

[II] Recommended with moderate clinical confidence

[III] May be recommended on the basis of individual circumstances

For the acute phase of treatment, clinicians may use pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies to achieve a full return to the patient's baseline level of functioning. The guidelines recommend an antidepressant medication for the initial treatment for patients with mild to moderate major depressive disorder [I] and definitely should be used in severe major depressive disorder unless ECT is planned [I]. The guidelines state that because the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g. half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference [I]. The guideline's preferred agents for most patients are SSRIs, SNRIs, mirtazapine, or bupropion [I]. MAOIs should be restricted to patients who do not respond to other treatments [I], due to the necessity for dietary restrictions and drug-drug interactions. For patients who prefer complementary and alternative therapies, S-adenosyl methionine (SAME) [III] or St. John's wort [III] might be considered although evidence of efficacy is modest at best.<sup>8</sup>

After starting a medication, the rate at which it is titrated to the full therapeutic dose depends on age, the treatment setting, the presence of co-occurring illnesses, concomitant pharmacotherapy, or medication side effects [I]. During the early phase of treatment patients should be closely monitored on the response and to identify side effects [I]. The frequency of patient monitoring should be determined on patient factors including symptom severity, co-occurring disorders, cooperation with treatment, availability of social supports, and the frequency and severity of side effects with the chosen treatment [II]. If side effects do occur, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect [I].<sup>11</sup>

If at least moderate improvement in symptoms is not observed within 4-8 weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed, and the treatment plan adjusted [I]. Therapeutic alliance and treatment adherence should also be addressed [I]. For antidepressant medications the psychiatrist should determine whether pharmacokinetic [I] or pharmacodynamic [III] factors suggest a need to adjust medication doses. For some TCAs a drug blood level can help with dose adjustments [I]. For patients who require a change in treatment plan, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit has not been reached [II]. Particularly for those who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the

antidepressant with a depression-focused psychotherapy [I] or with other agents [II] or changing to another non-MAOI antidepressant [I]. Patients may be changed to something within the same pharmacological class or to one from a different class [II]. Patients who have not responded to trials of SSRIs, a trial of an SNRI may be helpful [II]. Augmentation of antidepressant medications can utilize another non-MAOI antidepressant [II], generally from a different pharmacological class or a non-antidepressant medication such as lithium [II], thyroid hormone [II], or second-generation antipsychotic [II]. In patients capable of adhering to dietary and medication restrictions, an additional option is changing to a non-selective MAOI [III] after allowing sufficient time between medications to avoid deleterious interactions [I]. Transdermal selegiline can also be considered [II].<sup>11</sup>

During the continuation phase patients should have systematic assessment of symptoms, side effects, adherence, and function status [I]. To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for 4-9 months [I]. In general, the dose used in the acute phase should be used in the continuation phase [II]. Patients who respond to an acute course of ECT should receive continuation pharmacotherapy [I], with the best evidence available for the combination of lithium and nortriptyline.<sup>11</sup>

If it is decided to proceed to the maintenance phase of therapy, considerations including whether the patient has additional risk factors for recurrence, such as the presence of residual symptoms, ongoing psychosocial stressors, early age at onset, and family history of mood disorders [II]. Additional considerations that may play a role include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes, the persistence of depressive symptoms after recovery, and the presence of co-occurring disorders [II]. During the maintenance phase, an antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose [II].<sup>11</sup>

When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks to minimize the likelihood of discontinuation symptoms [I]. A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome [II].<sup>11</sup>

A patient's co-occurring medical conditions can contribute to what therapy a patient should receive. In patients with preexisting hypertension or cardiac conditions, treatment with specific antidepressant agents may suggest a need for monitoring of vital signs or cardiac rhythm (e.g., ECG with TCA treatment; heart rate and blood pressure assessment with SNRIs and TCAs) [I]. When using antidepressant medications with anticholinergic side effects, it is important to consider the potential for increases in heart rate in individuals with cardiac disease, worsening cognition in individuals with dementia, development of bladder outlet obstruction in men with prostatic hypertrophy, and precipitation or worsening of narrow angle glaucoma [I]. Some antidepressant drugs reduce the seizure threshold and should be used with caution in individuals with preexisting seizure disorders [II]. Serotonergic agents can worsen Parkinson's disease symptoms [II] and selegiline has antiparkinsonian and antidepressant effects but may interact with L-dopa and with other antidepressant agents [I]. For patients being treated following a stroke, consideration should be given to potential interactions with anticoagulation medications [I]. The side effect of weight gain should be considered when choosing an agent. Patients who have undergone bariatric surgery should reconsider the pharmacokinetics and pharmacodynamics of medications [I]. Drug interactions with HIV medications should be considered [I]. Interferon can exacerbate depressive symptoms, making close monitoring important [I]. Patients receiving tamoxifen who are going to be started on an antidepressive medication, should be treated with an agent that has minimal effect on the P450 2D6 isoenzyme [I]. When depression occurs in the context of chronic pain, SNRIs and TCAs may be preferable to other antidepressive agents [II].<sup>11</sup>



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  34. Venlafaxine Prescribing Information. at <[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/022104s009lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022104s009lbl.pdf)>
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  38. Trazodone Prescribing Information. at <[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/022411lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022411lbl.pdf)>
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  40. Nefazodone Prescribing Information. at <[http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006B1\\_11\\_Serzone-Label.pdf](http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006B1_11_Serzone-Label.pdf)>

## Appendix 1: Specific Drug Information

### CLINICAL PHARMACOLOGY

#### DOSE & AVAILABILITY

MEDICATIONS	USUAL DOSAGE	INDICATIONS
<b>Tricyclic Antidepressants (TCAs)</b>		
Amitriptyline, generic <sup>12</sup>	75-150 mg/day in divided doses	<ul style="list-style-type: none"><li>• Depression</li></ul>
Amoxapine, generic <sup>13</sup>	100-400 mg/day; Doses > 300mg should be divided	<ul style="list-style-type: none"><li>• Depression</li></ul>
Desipramine, generic <sup>14</sup>	100-200 mg/day	<ul style="list-style-type: none"><li>• Depression</li></ul>
Doxepin, generic <sup>15</sup>	25-300 mg/day	<ul style="list-style-type: none"><li>• Depression</li><li>• Insomnia</li></ul>
Imipramine, generic <sup>16</sup>	50-150 mg/day	<ul style="list-style-type: none"><li>• Depression</li><li>• Childhood enuresis</li></ul>
Maprotiline, generic <sup>17</sup>	25-225 mg/day (Max of 150mg in most patients)	<ul style="list-style-type: none"><li>• Depression</li></ul>
Nortriptyline, generic <sup>18</sup>	50-100 mg/day	<ul style="list-style-type: none"><li>• Depression</li></ul>
Protryptiline, generic <sup>19</sup>	15-60 mg/day in divided doses	<ul style="list-style-type: none"><li>• Depression</li></ul>
Trimipramine, generic <sup>20</sup>	50-150 mg/day	<ul style="list-style-type: none"><li>• Depression</li></ul>
<b>Monoamine Oxidase Inhibitors</b>		
Isocarboxazid, generic <sup>21</sup>	20-60 mg/day	<ul style="list-style-type: none"><li>• Depression</li></ul>
Phenelzine, generic <sup>22</sup>	15mg (every other day)-60 mg/day	<ul style="list-style-type: none"><li>• Depression</li></ul>
Selegiline patch, generic <sup>23</sup>	6-12mg/24 hours patches	<ul style="list-style-type: none"><li>• Depression</li></ul>
Tranlycypromine, generic <sup>24</sup>	30-60 mg/day	<ul style="list-style-type: none"><li>• Depression without melancholia</li></ul>
<b>Selective Serotonin Reuptake Inhibitors</b>		

Citalopram, generic <sup>25</sup>	20-40 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> </ul>
Escitalopram, generic <sup>26</sup>	10-20 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> <li>• Generalized anxiety disorder</li> </ul>
Fluoxetine, generic <sup>27</sup>	10-60 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> <li>• Acute and maintenance treatment of obsessive compulsive disorder age 7-17</li> <li>• Treatment of Bulimia Nervosa in adult patients</li> <li>• Acute treatment of Panic Disorder in adult patients</li> </ul>
Paroxetine, generic <sup>28</sup>	20-50 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> <li>• Panic disorder</li> <li>• Obsessive compulsive disorder</li> <li>• Social anxiety disorder</li> <li>• Generalized anxiety disorder</li> <li>• Post-traumatic stress disorder</li> <li>• Premenstrual dysphoric disorder</li> </ul>
Sertraline, generic <sup>29</sup>	50-200 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> <li>• Obsessive compulsive disorder</li> <li>• Panic disorder</li> <li>• Post-traumatic stress disorder</li> <li>• Premenstrual dysphoric disorder</li> <li>• Social anxiety disorder</li> </ul>
Vilazodone (Viibryd) <sup>30</sup>	10-40 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> </ul>
<b>Serotonin-norepinephrine reuptake inhibitors (SNRIs)</b>		
Desvenlafaxine, generic <sup>31</sup>	50 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> </ul>
Duloxetine, generic <sup>32</sup>	40-60 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> <li>• Generalized anxiety disorder</li> <li>• Diabetic peripheral neuropathic pain</li> <li>• Fibromyalgia</li> <li>• Chronic musculoskeletal pain</li> </ul>
Levomilnacipran (Fetzima) <sup>33</sup>	40-120 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> </ul>
Venlafaxine, generic <sup>34</sup>	37.5-225 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> <li>• Social anxiety disorder</li> </ul>

Atypical antidepressants		
Bupropion, generic <sup>35</sup>	IR: 200-450 mg/day in divided doses SR: 150-400 mg/day in divided doses ER: 150-450 mg/day once daily	<ul style="list-style-type: none"> <li>• Depression</li> <li>• Seasonal affective disorder</li> <li>• Adjunct in smoking cessation</li> </ul>
Mirtazapine, generic <sup>36</sup>	15-45 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> </ul>
Nefazodone, generic <sup>37</sup>	200-600 mg/day in two divided doses	<ul style="list-style-type: none"> <li>• Depression</li> </ul>
Trazadone, generic <sup>38</sup>	150-600 mg/day in divided doses  Extended Release: 150mg once daily up to 375 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> </ul>
Vortioxetine (Brintellix) <sup>39</sup>	5-20 mg/day	<ul style="list-style-type: none"> <li>• Depression</li> </ul>

## SAFETY<sup>12-40</sup>

### Black box warnings:

- All antidepressants
  - Suicidality/suicidal thoughts and behaviors – antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adults, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Nefazodone
  - Life threatening liver failure – Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000-300,000 patient-years of treatment. Treatment with nefazodone should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases.

### Contraindications:

- All antidepressants
  - Concomitant use of non-MAOIs with MAOIs
- TCAs: Nortriptyline, trimipramine, protryptiline, maprotiline
  - Acute recovery period after myocardial infarction
- TCAs: Doxepin
  - Urinary retention
  - Narrow-angle glaucoma
- MAOIs (all)
  - With pheochromocytoma
  - Congestive heart failure
  - Severe renal impairment or renal disease
  - History of liver disease or abnormal LFTs
  - With sympathomimetic drugs
  - Foods high in tyramine or dopamine/Food restrictions with high doses of selegiline patch
  - Do not use in combination with dextromethorphan or CNS depressants. Do not use with meperidine. Do not use multiple MAOIs together
  - Do not use in combination with buspirone
  - General anesthesia, spinal anesthesia. MAOIs should be stopped at least 10 days prior to procedure
  - Drug interactions – all medications should be checked before starting an MAOI or adding a new medication
- SSRIs – citalopram, escitalopram, fluoxetine, paroxetine, sertraline
  - Do not use with pimozide
- SSRIs – fluoxetine, paroxetine (sertraline, escitalopram, citalopram – double check PI),
  - Do not use with thioridazine
- SNRIs – duloxetine
  - Use in patients with uncontrolled narrow-angle glaucoma
- Atypicals – bupropion
  - Seizure disorders
  - Current or prior diagnosis of bulimia or anorexia
  - If undergoing abrupt discontinuation of alcohol or sedatives
- Atypicals – nefazodone
  - If previous use has caused liver injury
  - Avoid combining with triazolam in most patients
  - Coadministration of terfenadine, astemizole, cisapride, pimozide, or carbamazepine
  - In the recovery phase of an MI

#### DOSE ADJUSTMENTS

MEDICATIONS	RENAL ADJ	HEPATIC ADJ	Pediatric	Elderly	OTHER DOSING CONSIDERATIONS
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			Dose	Dose	
<b>Tricyclic Antidepressants (TCAs)</b>					
Amitriptyline, generic <sup>12</sup>	None specified	None specified	Not recommended in under 12 years of age	50 mg/day in divided doses	Sedative effect may be apparent before the antidepressant effect is noted, but therapeutic effect may take up to 30 days to develop.
Amoxapine, generic <sup>13</sup>	None specified	None specified	Not discussed	50-300 mg/day	Hospitalized patients refractory to antidepressant therapy may be cautiously titrated to 600 mg/day in divided doses
Desipramine, generic <sup>14</sup>	None specified	None specified	20-100 mg/day	20-100 mg/day	Higher doses should be initiated administered in hospitals
Doxepin, generic <sup>15</sup>	None specified	Use a lower dose and adjust gradually.	Not discussed	10-75 mg/day	A single dose should not exceed 150mg, select patients may respond to 25-50 mg/day.
Imipramine, generic <sup>16</sup>	None specified	None specified	Not to exceed 100 mg/day	Not to exceed 100 mg/day	If hospitalized, max dose is 250-300mg/day
Maprotiline, generic <sup>17</sup>	None specified	None specified	Not discussed	50-75 mg/day	Long half-life so initial doses should be maintained for 2 weeks.
Nortryptiline, generic <sup>18</sup>	None specified	None specified	No data on its use	30-50 mg/day	
Protriptyline, generic <sup>19</sup>	None specified	None specified	Adolescents: 15-20 mg/day	15-20 mg/day	
Trimipramine, generic <sup>20</sup>	None specified	None specified	Not discussed	50-100 mg/day	Hospitalized patients may receive 100 mg/day up to 200 mg/day in a few days up to a maximum of 300 mg/day
<b>Monoamine Oxidase Inhibitors</b>					
Isocarboxazid, generic <sup>21</sup>	Contraindicated in renal dysfunction	Contraindicated in liver disease	Not discussed	See adult dosing	Many drug and food interactions Doses of the selegiline patch <9 mg/24 hours do not have dietary restrictions.
Phenelzine, generic <sup>22</sup>	None specified but use caution	None specified but use caution	Not discussed	Use doses on the lower end	
Selegiline patch, generic <sup>29</sup>	No adjustment	No adjustment	Not discussed	6mg/24 hour patch	
Tranlycypromine,	None specified	None specified	Not discussed	See adult dosing	



generic <sup>24</sup>					
<b>Selective Serotonin Reuptake Inhibitors</b>					
Citalopram, generic <sup>25</sup>	No change for moderate renal impairment; use with caution in severe renal impairment.	Maximum 20 mg/day	10-40 mg/day for obsessive-compulsive disorder	Maximum recommended dose is 20 mg/day.	Doses greater than 40 mg/day are not recommended due to risk of QT prolongation and failure to show additional efficacy.
Escitalopram, generic <sup>26</sup>	Use with caution in severe renal impairment	10 mg/day	Age $\geq$ 12 10-20 mg/day	5-10 mg/day	
Fluoxetine, generic <sup>27</sup>	No adjustment	Lower and less frequent dosage should be used in patients with hepatic impairment	10-20 mg/day	Use adult dosing	
Paroxetine, generic <sup>28</sup>	10-40 mg/day	10-40 mg/day	Not discussed	10-40 mg/day	
Sertraline, generic <sup>29</sup>	No adjustment	Lower dose and less frequent dosing should be used	25-50 mg/day (for OCD)	25-100 mg/day	
Vilazodone (Viibryd) <sup>30</sup>	No adjustment	No adjustment	Not approved for pediatric use	No adjustment	Reduce dose if co-administered with a strong inhibitor of CYP3A4
<b>Serotonin and norepinephrine reuptake inhibitors</b>					
Desvenlafaxine, generic <sup>31</sup>	CrCl 30-50 mL/min – max dose 50 mg/day End-stage renal disease – 50 mg every other day	Max dose 50 mg/day	Safety and effectiveness not established	Increased incidence of orthostatic hypotension	No additional benefit was seen at doses greater than 50 mg/day and increased adverse reactions.
Duloxetine, generic <sup>32</sup>	Not recommended for patients with end-stage renal disease or severe renal impairment (CrCl <30 mL/min)	Avoid use	Efficacy not demonstrated Not studied in age <7	No adjustment	
Levomilnacipran	Do not exceed 80	No adjustment	Not studied	No adjustment	

(Fetzima) <sup>33</sup>	mg/day for moderate impairment. Max 40 mg/day for severe impairment.				
Venlafaxine, generic <sup>34</sup>	Reduce dose by 25-50% Reduce by 50% in hemodialysis	Reduce dose by 50% in mild to moderate impairment.	Not approved for pediatric use	No adjustment	
<b>Other Antidepressants</b>					
Bupropion, generic <sup>35</sup>	Use with caution, elimination is reduced, consider lowering frequency in IR formulations	Use with extreme caution in severe hepatic cirrhosis, low doses only	Not studied for depression	IR: 75-300 mg/day in divided doses	Doses given are for hydrochloride salt formulation. See package insert for dose conversions to hydrobromide salt.
Mirtazepine, generic <sup>36</sup>	Be aware that plasma levels increase in renal impairment	Be aware that plasma levels increase in hepatic impairment	Not studied	Use with caution due to decreased clearance in the elderly.	Due to the long half-life, dose changes should only be done every 1-2 weeks.
Nefazodone, generic <sup>40</sup>	Non provided, however it is partially cleared by the kidney	Contraindicated in patients with hepatic impairment	No information given	Initial dose of 100 mg/day in two divided doses	
Trazadone, generic <sup>38</sup>	None specified	None specified	Age 6-12: Initial 1.5-2 mg/kg/day in divided doses with maximum of 6 mg/kg/day in 3 divided doses	Short acting: 25-150 mg/day ER: Use caution	
Vortioxetine (Brintellix) <sup>39</sup>	None specified	None specified	Not studied	Not addressed	Maximum recommended dose is 10 mg/day for known CYP2D6 poor metabolizers. Reduce dose in half if strong CYP2D6 strong inhibitor is started.

### Abbreviated Class Update: Targeted Immune Modulators (TIMs)

**Month/Year of Review:** September 2014

**New drug(s):** apremilast (Otezla®)  
Vedolizumab (Entyvio®)

**End date of literature search:** August 2013

**Manufacturer:** Celgene  
Takeda Pharmaceuticals

#### Current Status of PDL Class:

Generic Name	Trade Name	PDL Status	Indication
Abatacept	Orencia®	Non-preferred	RA, Juvenile RA, Juvenile idiopathic arthritis
Adalimumab	Humira®	Preferred	RA, Psoriatic arthritis, ankylosing spondylitis, Juvenile idiopathic arthritis, Crohn's disease, Plaque psoriasis, ulcerative colitis
Anakinra	Kineret®	Non-preferred	RA, Neonatal-Onset Multisystem Inflammatory Disease (NOMID)
Certolizumab	Cimzia®	Non-preferred	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis
Etanercept	Enbrel®	Preferred	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis
Golimumab	Simponi®	Preferred	RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
Infliximab*	Remicade®	Non-preferred	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis
Natalizumab*	Tysabri®	Non-preferred	Crohn's disease
Rituximab*	Rituxan®	Non-preferred	RA
Tocilizumab*	Actemra®	Non-preferred	RA, juvenile idiopathic arthritis
Tofacitinib	Xeljanz®	Non-preferred	RA
Ustekinumab	Stelara®	Non-preferred	Plaque psoriasis, Psoriatic arthritis
Vedolizumab	Entyvio	Non-preferred	Ulcerative colitis, Crohn's disease

Abbreviations: RA, rheumatoid arthritis

\* Must be billed via J-code and payment requires trial of preferred self-administered drug first.

#### Research Questions:

- Is there new comparative evidence that Targeted Immune Modulators (TIMs) differ in effectiveness for patients with Rheumatoid Arthritis (RA), Psoriatic arthritis (PsA), Crohn's disease, plaque psoriasis, ulcerative colitis (UC), ankylosing spondylitis, or Juvenile idiopathic arthritis?
- Is there any new evidence that TIMs differ in harms?
- Is apremilast more effective or safer than currently available agents for the treatment of plaque psoriasis?

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**Conclusions:**

- There remains low to insufficient evidence of any difference in efficacy between TIMs in the treatment of RA. The most obvious differences that might be clinically relevant involve dosage and administration (oral, intravenous, subcutaneous).<sup>1</sup>
- There is insufficient comparative evidence for the efficacy of TIMs in the treatment of juvenile idiopathic arthritis, ankylosing spondylitis, UC, and Crohn's disease.<sup>1</sup>
- There is insufficient evidence based on 1 randomized controlled trial of no difference in efficacy between adalimumab, etanercept and infliximab for the treatment of PsA.<sup>1</sup>
- There is insufficient evidence based on indirect comparisons of no difference between etanercept, adalimumab and abatacept in preventing disease flares for the treatment of juvenile idiopathic arthritis.
- For the treatment of Crohn's disease, TNF inhibitors (infliximab, adalimumab and certolizumab) were more effective than placebo in inducing remission (RR 1.8; 95% CI 1.4 to 2.4; moderate SOE). However, infliximab is the only biological consistently favored over placebo for multiple outcomes and at multiple time points for both induction and maintenance of remission.<sup>2</sup>
- There is moderate quality evidence that apremilast 20mg twice daily and apremilast 30 mg twice daily improves signs and symptoms of PsA, as measured by the ACR20 response, compared to placebo (32%, 37%, and 19%, respectively). There appears to be a small advantage of apremilast 30mg twice daily dose; however it has not been proven to be statistically superior to 20mg twice daily.
- There is moderate to high quality evidence that vedolizumab is significantly superior to placebo for induction of clinical remission, clinical improvement and prevention of clinical relapse in patients with moderate to severe UC with similar risk of adverse events.<sup>3</sup>
- There is moderate quality evidence of a significantly superior effect of vedolizumab on clinical remission compared to placebo, although the improvement was modest at best. In patients with failure of previous TNF inhibitor, there is low quality evidence of no difference in clinical remission at week 6 between vedolizumab and placebo.
- There is low quality evidence that vedolizumab is significantly superior to placebo for maintenance of clinical remission at week 52 compared to placebo.

**Recommendations:**

- Modify prior authorization criteria to include new FDA approved indications and new medications.
- Evaluate comparative costs of newly approved agents in executive session.

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**Reason for Review:**

A new Drug Effectiveness Review Project (DERP) report was published, two new drugs were approved, and new FDA approved indications were granted for multiple TIMS. This update will evaluate and summarize this new evidence.

**Previous P&T Conclusions (November 2011<sup>2,3</sup>):**

- There is low quality evidence of no conclusive differences in disease activity (ACR 50) between TIMs for the treatment of RA.
- There is moderate quality evidence of improvements in disease activity from combination therapy of a TIM plus methotrexate compared to monotherapy in the treatment of RA.
- There is insufficient evidence comparing individual TIMs to make conclusions for the treatment of chronic plaque psoriasis.
- There is low strength evidence favoring individual TIMs versus non-biologic agents (methotrexate) in the treatment of plaque psoriasis.
- There is insufficient direct evidence comparing tofacitinib to other proven agents for the treatment of RA.
- There is moderate quality evidence that tofacitinib decreases symptoms compared to placebo, as measured by the ACR20 response and increases physical functioning at 3 months in patients with active RA who had prior inadequate response or intolerance to non-biologic or biologic DMARDs.

**Background:**

Targeted immune modulators (TIMs) are used in the treatment of immunologic and inflammatory diseases, including rheumatoid arthritis (RA), juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis (PsA), plaque psoriasis, Crohn's disease, and ulcerative colitis (UC).<sup>1</sup> They work by selectively blocking mechanisms involved in the inflammatory and immune response and include: Tumor necrosis factor (TNF) inhibitors (adalimumab, certolizumab, golimumab, etanercept and infliximab), interleukin-1 blockers (anakinra), and other monoclonal antibodies (abatacept, alefacept, natalizumab, rituximab, ustekinumab and tocilizumab). Tofacitinib was the first oral Janus kinase (JAK) inhibitor approved.

Apremilast is an oral type 4 phosphodiesterase (PDE4) inhibitor indicated for the treatment of psoriatic arthritis. PDE 4 is a key enzyme in the degradation of cyclic adenosine monophosphate (cAMP), an intracellular second messenger that plays an important role in controlling a network of pro-inflammatory and anti-inflammatory mediators.<sup>1</sup> By inhibiting PDE4, the production of TNF-alpha is reduced.

RA is an autoimmune disease that involves inflammation of the synovium with progressive erosion to bone leading in most cases to misalignment of the joint, loss of function, and disability. Treatment goals are to control pain and inflammation, and ultimately, remission or at least low disease activity.<sup>1</sup> Therapies for RA include corticosteroids, oral disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs. Methotrexate is the most commonly used DMARD because of its proven efficacy and well understood long-term effects. In patients with persistent disease despite aggressive management with oral agents, biologic agents, often in combination with methotrexate are considered the standard of care. Juvenile idiopathic arthritis occurs in children under the age of 16. NSAIDs are first line therapy, followed by oral DMARDs, and biologic agents. Abatacept, adalimumab etanercept, and tocilizumab are approved for the treatment of juvenile idiopathic arthritis.

Primary endpoints used in the clinical trials are the American College of Rheumatology (ACR) response, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the Disease Activity Score 28 (DAS-28). The ACR response is a composite endpoint with seven components used to calculate the proportion of patients achieving a target percentage of improvement from baseline and is considered a measure of efficacy and overall disease activity. Patients are said to

meet ACR 20 criteria when they have at least 20% reductions in tender and swollen joint counts and in at least 3 of the domains. ACR 50 and ACR 70 criteria are similar, but with improvement of at least 50% and 70% in individual measures.<sup>4</sup> The FDA accepts ACR 20 response as an acceptable demonstration of efficacy supporting a clinical response claim, and ACR 70 response lasting for 6 months as supportive of a claim of a major clinical response.<sup>3</sup> ACR 50 and ACR 70 are considered more clinically significant than ACR 20. The HAQ-DI is a widely used self-report measure of functional capacity. Scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.<sup>4</sup> According to the FDA, the minimal clinically important difference is 0.25 units for a given patient or 0.22 units based on group means. The DAS is another index of disease activity (similar to the ACR response). A DAS-28 score >5.1 corresponds to high disease activity and <3.2 of low disease activity. A score of 2.6 is considered to correspond to remission. The van der Heijde modified Total Sharp Score (mTSS) is a radiographic scoring system for RA joint damage and a change in joint damage of 5.0 is considered minimally clinically important.<sup>4,5</sup>

Ankylosing spondylitis is a chronic inflammatory arthritis with primary involvement of the axial skeleton and prominent involvement of the spine and sacroiliac joints. Biologic agents targeted TNF are recommended as standard treatment along with DMARDs.

Plaque psoriasis is a chronic autoimmune skin disease which utilizes TIMs for the management of disease. Localized disease may be managed with topical agents, while patients with more widespread disease often require systemic treatment. The American Academy of Dermatology guidelines recommends the use of either biologic or nonbiologic systemic agents or phototherapy in patients with widespread disease, with no clear guidelines for selecting first-line therapy.<sup>6</sup> Methotrexate is the most commonly prescribed nonbiologic systemic treatment for psoriasis worldwide.

Psoriatic arthritis is an inflammatory arthritis closely associated with psoriasis. The goal of treatment is to suppress joint, tendon and enthesal inflammation, and to manage the skin manifestations. Current treatment involves early use of DMARDs and TNF inhibitors in active and progressive disease. These agents are recommended when the person has peripheral arthritis with 3 or more tender joints and 3 or more swollen joints, and the PsA has not responded to adequate trials of at least 2 standard DMARDs, given on their own or together.<sup>7</sup>

Crohn's disease is a type of inflammatory bowel disease. Biologic agents approved for treatment include infliximab, natalizumab, adalimumab, certolizumab, and most recently vedolizumab. Goal of treatment is to induce and then maintain remission. Controversies in the treatment exist and it is unclear if it is better to take immunomodulators and biologics early (top-down therapy) as opposed to taking them after prolonged steroid use (step-up therapy).

UC is a chronic disease with mucosal inflammation within the colon, historically treated with 5-aminosalicylic acid, corticosteroids and oral immunosuppressants with goals of achieving clinical or mucosal remission. When these are ineffective, TNF inhibitors are another option. Infliximab and adalimumab are most commonly used for UC. Recently the U.S. Food and Drug Administration (FDA) expanded the approved use of adalimumab and golimumab to include treatment of moderate-to-severe ulcerative colitis (UC) in adults, and approved the new agent vedolizumab. Previously, infliximab was the only TIM approved for this indication. The treatment goals in UC are to reduce and maintain remission of symptoms and inflammation and prevent complications.<sup>1</sup> Distal disease may be treated with topical agents and mild disease can be controlled with oral and/or topical 5-aminosalicylate drugs. The American College of Gastroenterologists recommends treatment with infliximab for moderate to severe UC for patients who are steroid refractory or steroid dependent. The Mayo Score is a disease activity index that includes endoscopy and one of the most widely used of the indices in clinical trials.<sup>8</sup> It takes into account sum of stool frequency, rectal bleeding, mucosal appearance, and physician's global assessment. The FDA has recognized a definition of remission as a Mayo Clinic Score  $\leq 2.7$ . This definition is

considered less stringent than other endpoints used in clinical trials.<sup>9</sup> Vedolizumab is a new monoclonal antibody FDA approved for the treatment of UC and Crohn's disease. It affects  $\alpha 4\beta 7$  integrin and inhibits leukocyte adhesion to its counter receptors.

### **Methods:**

The DERP report searched Ovid MEDLINE through November 2013 for head to head evidence, including randomized controlled trials (RCTs) comparing any of the TIMs. An additional search through August 2014 was done. 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

### **Systematic Reviews:**

1. The DERP drug class review systematically compared the efficacy, effectiveness, and harms of the TIMS through a literature search through November 2013.<sup>1</sup> Only data from head-to-head trials and systematic reviews with direct comparisons were included in the analysis, which included 15 head-to-head RCTs and 22 head-to-head observational studies. Overall, the authors found low or insufficient evidence for most comparisons about the efficacy, effectiveness, and harms of TIMs. The most obvious differences that might be clinically relevant involve dosage and administration (oral, IV, or SubQ). Results were divided by disease state.

#### *Rheumatoid Arthritis:*

- Single head to head trial evidence shows that efficacy outcomes are similar between abatacept and adalimumab, adalimumab and etanercept, adalimumab and tofacitinib, and etanercept and tocilizumab (low to insufficient strength of evidence [SOE]). The evidence is mixed regarding differences in efficacy between adalimumab and tofacitinib.
- There was one double-blind, head to head trial demonstrating no differences in efficacy between patients treated with abatacept or infliximab after 6 months (low SOE).
- Low SOE, based on 1 open-label RCT, of no difference in efficacy between abatacept and adalimumab.
- Low SOE, based on 1 RCT, of similar efficacy between adalimumab and tofacitinib.
- The majority of trials enrolled patients who had failed at least 1 DMARD and some enrolled those who had also failed an TNF inhibitor.

#### *Juvenile Idiopathic Arthritis:*

- Insufficient comparative evidence.

#### *Ankylosing Spondylitis*

- Insufficient comparative evidence.

#### *Psoriatic Arthritis*

- Insufficient evidence based on 1 RCT of no difference in efficacy between adalimumab, etanercept and infliximab.

### *Crohn's disease*

- Insufficient evidence, based on 1 RCT, that switching from infliximab to adalimumab had higher treatment discontinuation and termination rates compared with maintaining infliximab.
- Insufficient comparative evidence for other medications.

### *Ulcerative Colitis*

- Insufficient comparative evidence.

### *Plaque Psoriasis*

- Low SOE, based on 1 head to head RCT, that ustekinumab is more efficacious than etanercept.

The most comparative evidence on harms was available for the tumor necrosis factor inhibitors adalimumab, etanercept, and infliximab. Infliximab had a higher risk of patients discontinuing treatment due to adverse events compared with adalimumab and etanercept (moderate strength of evidence) and more serious adverse events than abatacept (low strength of evidence). Injection site reactions were less frequent for patients receiving abatacept compared with adalimumab and infliximab (low strength of evidence). There was moderate SOE that infliximab has a higher risk of serious infections compared with abatacept, adalimumab and etanercept.

2. A systematic review and network meta-analysis of TNF-alpha inhibitors, including adalimumab, etanercept, golimumab and infliximab, for the management of active PsA was published in 2014.<sup>10</sup> The quality of the including RCTs were assessed according to the NICE guidelines. Twelve RCTs met inclusion criteria and were included in the systematic review, but only 7 were homogenous enough to be included in a meta-analysis. The fixed-effect meta-analysis demonstrated all 4 agents to be significantly better than placebo in response measured by the Psoriatic Arthritis Response Criteria (PsARC). Etanercept and infliximab were significantly more effective than placebo in improving change in Health Assessment Questionnaire (HAQ), while golimumab was not significantly better than placebo. Golimumab was also not significantly better than placebo in improving HAQ scores in patients who had achieved a PsARC response (WMD -0.06; 95% CI -0.18 to 0.06). An incremental analysis based on clinical efficacy and cost-effectiveness was also done. Based on this, golimumab was dominated by etanercept, as etanercept costs less and is more effective; adalimumab was dominated by etanercept; and etanercept was found to be cost-effective intervention. Infliximab was not cost-effective compared with etanercept.
3. A high-quality systematic review using indirect comparisons evaluated the efficacy of biological agents in juvenile idiopathic arthritis.<sup>11</sup> All RCTs with biological agents were included, irrespective of trial design. Overall, 11 different trials were included in the analysis. Indirect comparisons found no significant difference between etanercept and adalimumab in disease flare (RR 0.92; 95% CI 0.39 to 2.18). In addition, indirect comparisons found no significant difference between anakinra, tocilizumab and canakinumab in achievement of a ACR30 response. There were no trials that directly compared biological agents to each other.
4. The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review for pharmacologic therapies for the management of Crohn's Disease.<sup>2</sup> Overall, there were a number of medications that were proven to be effective in inducing and maintaining remission in Crohn's disease,



but no single medication or class of medications was proven to be the most effective. TNF inhibitors (infliximab, adalimumab and certolizumab) were more effective than placebo in inducing remission (RR 1.8; 95% CI 1.4 to 2.4; moderate SOE). Infliximab was found to have the greatest consistency on disease activity compared to placebo and had high SOE for fistula healing. There was also low SOE that the combination of infliximab and methotrexate was favored over infliximab alone for disease activity. Infliximab also had the most evidence for maintenance of remission and adalimumab was also favored over placebo. There was low to insufficient evidence for all safety-related outcomes. Older patients and non-whites were underrepresented in clinical trials and outcomes were limited to scales not used in clinical practice. There was insufficient evidence to compare step-up versus top-down treatment and to evaluate treatment in newly diagnosed patient.

5. A systematic review of the effectiveness of newer biological therapy (vedolizumab, abatacept, visilizumab, golimumab) for active moderate to severe UC. Was published in January 2014.<sup>12</sup> Eight RCTs met inclusion criteria; all with moderate methodological quality. Two studies showed improved clinical response in the induction phase for vedolizumab compared to placebo (RR 1.82; 95% CI 1.43 to 2.31), as well as improved clinical remission (RR 2.66; 95% CI 1.63 to 4.34). Two studies also demonstrated superior clinical response with golimumab compared with placebo in the induction phase (RR 1.69; 95% CI 1.41 to 2.03), but not a statistically significant improvement in clinical remission compared to placebo (RR 1.95; 95% CI 0.81 to 4.68). Abatacept appeared to be less effective than placebo in the induction phase.
6. A high quality meta-analysis evaluating TNF inhibitors as treatment for UC intolerant or refractory to conventional medical therapy was published in January 2014.<sup>13</sup> A literature search through July 2013 identified RCTs comparing TNF inhibitors with placebo or other intervention. The primary outcome was clinical remission. Eight trials were included in the meta-analysis; all evaluating adalimumab and/or infliximab to placebo, corticosteroids, or cyclosporine. A pooled analysis of 3 trials demonstrated that TNF inhibitors (adalimumab and infliximab) were significantly superior to placebo for maintenance of clinical remission (RR 2.29; 95% CI 1.73 to 3.03). There was no significant difference in clinical remission rates between the anti-TNF agents and glucocorticoid treatment (RR 1.01; 95% CI 0.73 to 1.42).

#### **New Guidelines:**

##### NICE

NICE updated guidelines on the management of ulcerative guidelines in June 2013.<sup>14</sup> For the most part, topical and/or oral aminosalicylates are recommended as first step therapy to induce remission in patients with mild to moderate UC. For more severe disease, IV corticosteroids and IV ciclosporin or surgery are recommended. Infliximab is recommended but the guidance is included in a separate appraisal guidance and has been reviewed previously. No other biological treatments are included in the guideline.

##### American Gastroenterological Association Institute

Guidelines on the use of thiopurines, methotrexate, and anti-TNF alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease were published at the end of 2013.<sup>15</sup> Recommendations including any of the TIMs are included:

- Anti-TNF alpha drugs are recommended to induce remission in patients with moderately severe Crohn's Disease (Strong Recommendation, Moderate quality of evidence)
  - At the time, only infliximab and adalimumab were considered. Certolizumab has not been found to be more effective than placebo in inducing remission in patients.

- Recommend using TNF alpha inhibitor monotherapy over thiopurine monotherapy to induce remission in patients who have moderately severe Crohn's Disease (Strong recommendation, Moderate quality evidence).
- Recommend using TNF alpha inhibitors over no TNF inhibitors to maintain corticosteroid- or TNF inhibitor-induced remission in patients with Crohn's Disease (Strong Recommendation, High quality evidence).

#### **New FDA Safety Alerts:**

None

#### **NEW indications/formulations:**

1. In May, 2013, golimumab was FDA approved to treat adults with moderate to severe UC.<sup>16,17</sup> This new indication was based on two published phase III RCT's; both included in the systematic review described above, which found that golimumab resulted in a superior clinical response than placebo (RR 1.69; 95% CI 1.41 to 2.03), but not a statistically significant improvement in clinical remission compared to placebo (RR 1.95; 95% CI 0.81 to 4.68) in the induction phase.<sup>12</sup> The PURSUIT-SC was an induction trial<sup>17</sup> and PURSUIT was a maintenance study through week 54.<sup>16</sup>
2. In September 2013, certolizumab was FDA approved for the treatment of PsA in adults based on a good quality 24-week, double-blind, placebo-controlled study comparing certolizumab with placebo (RAPID-PsA).<sup>18-20</sup> In June 2014, NICE published an evidence summary of certolizumab for the treatment of PsA.<sup>7</sup> Effectiveness was demonstrated in RAPID-PsA, a phase II study with an initial double-blind, randomized, placebo-controlled phase to week 24, a dose-blind phase without a placebo group to week 48, and an open label phase to week 216. Participants had to have active joint disease and previous failure with at least 1 DMARD. At week 12, compared with placebo, statistically significantly more people in the groups receiving certolizumab 200mg every 2 weeks, and 400mg every 4 weeks achieved an ACR20 response (58%, 51.9%, and 24.3%, respectively;  $p < 0.001$  for both dosage groups compared with placebo). Statistically significant differences were also observed between the certolizumab groups and placebo for ACR50 and ACR70 response at week 12, and continued to week 24. The most common adverse effects were diarrhea and headache. The most common infectious adverse events were nasopharyngitis and upper respiratory tract infection. Discontinuations due to adverse events were low overall. The study was not powered to detect differences in the group. Long term efficacy and safety of certolizumab in PsA remains unknown. The panel concluded that certolizumab may provide an additional treatment option to the currently available agents for PsA. The evidence compared with that for other TNF inhibitors, in addition to individual patient factors and cost should be considered. There are no head-to-head trials comparing certolizumab with other TIMS for treating PsA.
3. In October 2013, certolizumab was also FDA approved for adults with active ankylosing spondylitis based on a fair quality 24-week double-blind RCT (RAPID-axSpA).<sup>21</sup> Eligible patients must have previously had an inadequate response, or been intolerant to at least one NSAID. It was placebo-controlled and double blinded to week 24, dose-blinded to week 48 and is ongoing and open-label through week 204. At week 12, a statistically significant higher proportion of patients in the certolizumab 200mg every 2 weeks and 400mg every 4 week groups achieved a clinical response compared with placebo (57.7%, 63.6%, and 38.3%, respectively;  $p = 0.004$  and  $p < 0.001$ ).
4. In September 2013, ustekinumab received FDA approval for adult patients with PsA. Approval was based on the PSUMMIT 1 trial; a phase 3, double-blind, RCT in adults with active psoriatic arthritis, and the PSUMMIT 2 trial.<sup>22,23</sup>

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NICE published guidance on ustekinumab for treating active psoriatic arthritis in May 2014.<sup>24</sup> The following guidance is provided:

- Ustekinumab is not recommended for treating PsA, alone or in combination with methotrexate in adults when the response to previous non-biological DMARD therapy has been inadequate.
  - The committee concluded that ustekinumab appeared to be less effective than TNF alpha inhibitors for Psoriasis Area and Severity Index (PASI) 75, and Psoriatic Arthritis Response Criteria (PsARC) response rates, particularly for the joint outcome. The committee concluded that ustekinumab could not be recommended as a cost-effective use of resources.
  - In people who have not previously received TNF inhibitors, ustekinumab was dominated (more expensive and less effective than) adalimumab.
  - Evidence from 2 RCTs demonstrates that ustekinumab is clinically effective compared with conventional management, in both TNF inhibitor-naïve and TNF inhibitor-experienced patients, but there remains some uncertainty about the long term effects of ustekinumab.

#### **Apremilast New Drug Evaluation:**

Apremilast is an inhibitor of PDE4, indicated for the treatment of adult patients with active psoriatic arthritis (PsA).<sup>25</sup>

*Potential off-label use:* Apremilast has been studied in the treatment of ankylosing spondylitis in a small pilot study with only 38 subjects.<sup>26</sup> A small phase II dose ranging study evaluated apremilast for the treatment of plaque psoriasis, also an off-label indication.<sup>27</sup> Longer-term and larger studies are needed to fully assess the efficacy and safety of apremilast for these indications. It has also been studied for use in inflammatory rosacea<sup>28</sup> and atopic dermatitis.<sup>29</sup>

#### Clinical Efficacy:

Approval of apremilast for PsA came primarily from 3 phase III studies, with nearly identical study designs (PALACE). Only one of these phase III studies has been published and is included in the evidence table below.<sup>30</sup> The 24 week studies enrolled subjects with active PsA who had an inadequate clinical response to DMARDs and/or biologic therapy and were randomized to apremilast 20mg twice daily, apremilast 30 mg twice daily or placebo<sup>31</sup>. Patients with clinically significant cardiac, endocrine, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, pregnancy, and therapeutic failure of more than 3 agents for PsA, or more than one TNF blocker were excluded. The primary outcome was the proportion of patients meeting 20% improvement in modified ACR response criteria (ACR20) at week 16. At week 16, all subjects who had not improved by 20% or more were required to enter early escape and placebo-treated subjects were re-randomized to receive apremilast 20 or 30 mg. This limits the validity of the secondary outcomes at week 24, as the majority of patients had discontinued their originally assigned treatment group after week 16. Earlier phase II studies demonstrated that treatment with both 20 mg twice per day or 40 mg once a day demonstrated efficacy compared to placebo.<sup>32,33</sup>

PALACE 1 is a published fair quality trial that included patients with active PsA despite prior DMARDs and/or biologics.<sup>30</sup> Biologic-naïve patients generally showed a higher ACR20 response rate compared to biologic-experienced patients and patients with a history of biologic failure achieved the lowest response rates. Secondary measures included the Disability Index of the Health assessment Questionnaire (HAQ-DI). However, this is a less commonly used measure and there is little data defining what a clinically significant improvement is.<sup>34</sup> The study authors define a minimal clinically important difference (MCID) of  $\geq 0.13$  and  $\geq 0.30$  on the HAQ-DI compared to placebo. Patients in the apremilast 30mg twice daily group had a clinically significant change in HAQ-DI significantly more than placebo (39.8% vs. 27.3%; RR 1.5; 95% CI 1.1-2.0; NNT 7), but there was no significant difference between the 20mg twice daily group and placebo (33.7%

vs. 27.3%). Overall, patients in both the 20mg and 30mg BID groups had a significantly greater proportion of patients achieving response, as measured by the ACR20, ACR50, and ACR70 versus placebo.

The two other phase III studies are unpublished and cannot be assessed for validity and/or risk of bias. They both demonstrated a statistically significant greater proportion of patients achieving ACR20 response compared to placebo and a greater change in HAQ-DI from baseline.<sup>31</sup> In general, a dose-related effect was observed with higher response rates in those on apremilast 30 mg BID compared to 20 mg BID, although statistical comparison was not conducted and we cannot conclude that the 30mg dose is superior to 20mg twice daily. Overall, greater than 80% of patients had a history of treatment with methotrexate and approximately 20% had been treated with a TNF inhibitor.

#### Clinical Safety:

Most common adverse events included diarrhea, nausea, headache and upper respiratory tract infection. A titration schedule is recommended to avoid gastrointestinal symptoms. Serious adverse events were similar among groups and clinically meaningful laboratory abnormalities were infrequent and comparable between apremilast and placebo. Both doses of apremilast had similar adverse event profiles. A treatment-dependent decrease in body weight was observed with a greater proportion of apremilast subjects experiencing a 5% or greater weight loss compared to placebo-treated subjects.

#### **COMPARATIVE CLINICAL EFFICACY**

##### **Relevant Endpoints:**

- 1) Disease Activity
- 2) Physical Functioning
- 3) Quality of Life
- 4) Withdrawals due to Adverse Events

##### **Primary Study Endpoint:**

- 1) Disease Activity (ACR 20)

Ref./Study Design <sup>a</sup>	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
PALACE 1 <sup>30</sup> RCT, PC, DB	1. apremilast 20mg BID	Demographics: Avg age 50 y/o, 90% white, 50% female, duration of PsA 7.4 yrs  Inclusion Criteria: Active PsA despite prior treatment with DMARDs and/or biologics.  Exclusion Criteria: Significant cardiac, endocrine, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, abnormal ECT, pregnant, chronic infection, malignancy, other autoimmune disease therapeutic failure of more than 3 agents for PsA, or more than 1 biologic TNF inhibitor.	168	<u>ACR20 at week 16:</u> 1. 51 (30.4%) 2. 64 (38.1%) 3. 32 (19.4%) 1 vs. 3 p=0.0166; RR 1.59 (1.06-2.4)	ARR 11% /NNT 9	<u>D/C due to adverse events:</u> 1. 10 (6%) 2. 12 (7.1%) 3. 8 (4.8%)	NS	<b>Quality Rating:</b> Fair  <b>Internal Validity: RoB</b> <u>Selection:</u> Was a randomized trial, but no details on sequence generation and unknown allocation concealment. Patients similar at baseline. More biologic failures in placebo group. <u>Performance:</u> Double blinded; doses provided in a blister card containing identical appearing tablets. <u>Detection:</u> Unclear if outcome assessors blinded <u>Attrition:</u> Total attrition at 12% and similar between groups. Intent to treat Analysis Done  <b>External Validity:</b> <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Significant exclusion criteria limit generalizability. Overall, patients had long-standing active disease and were treatment experienced. <u>Setting:</u> Multinational. Majority from centers in North America and Europe. <u>Outcomes:</u> Common outcomes used. ACR 50 and ACR 70 are considered more clinically significant than ACR 20 and are both provided. Did not assess quality of life.
	2. apremilast 30 mg BID		168					
	3. placebo		168	2 vs. 3 p=0.0001 RR 2.0 (1.3-2.9)	ARR 19%/ NNT 5	<u>Serious AEs:</u> 1. 8 (4.8%) 2. 9 (5.4%) 3. 7 (4.2%)	NS	
				<u>HAQ-DI ≥0.30 (clinically meaningful difference)</u> 1. 33.7% 2. 39.8% 3. 27.3% 1 vs. 3 p=NS	NS			
				2 vs. 3 p=0.0149 RR 1.46 (1.05-2.02)	ARR 13%/ NNT 7			
				<u>ACR50 at week 24:</u> 1. 24 (14.7%) 2. 32 (19.9%) 3. 7 (4.2%) 1 vs. 3 p=0.0013	ARR 10.5%/NNT 9			
				2 vs. 3 p=<0.0001	ARR 16%/ NNT 6			
				<u>ACR70 at week 24:</u> 1. 9 (5.5%) 2. 17 (10.6%) 3. 1 (0.6%) 1 vs. 3 p=0.0102	ARR 5%/ NNT 20			
				2 vs. 3 p=<0.0001	RR 10%/ NNT 10			

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## Vedolizumab:

Vedolizumab is an integrin receptor antagonist indicated for:

- Adults with moderately to severe active UC who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids<sup>35</sup>:
  - Inducing and maintaining clinical response
  - Inducing and maintaining clinical remission
  - Improving endoscopic appearance of the mucosa
  - Achieving corticosteroid-free remission
- Adults with moderately to severely active Crohn's Disease who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids:
  - Achieving clinical response
  - Achieving clinical remission
  - Achieving corticosteroid-free remission

A 2014 Cochrane systematic review evaluated vedolizumab for induction and maintenance of remission in UC.<sup>3</sup> RCTs comparing vedolizumab to placebo or control therapy were included in the review. Four studies, all with a low risk of bias, were identified (n=606). Pooled results demonstrated that vedolizumab was significantly superior to placebo for induction of remission, clinical response, and endoscopic remission and prevention of relapse. The authors concluded that there is moderate to high quality data from 4 studies showing that vedolizumab is superior to placebo for induction of clinical remission (77% of vedolizumab patients failed to enter clinical remission vs. 92% of placebo patients; RR 0.86; 95% CI 0.80 to 0.91) and response (48% of vedolizumab patients failed to have a clinical response compared to 72% of placebo; RR 0.68; 95% CI 0.59 to 0.78) in patients with moderate to severely active UC and prevention of relapse (RR 0.67; 95% CI 0.59 to 0.77) in patients with quiescent UC.<sup>3</sup> Moderate quality data suggests that it is also superior for prevention of relapse and adverse events appear to be similar to placebo (79% vs. 80%; RR 0.99; 95% CI 0.93 to 1.07). More studies are needed to assess the long term efficacy and safety of vedolizumab as well as comparative trials with currently approved therapies. Results from 2 studies showed that fewer vedolizumab patients withdrew due to adverse events compared to placebo (6% vs. 11%; RR 0.55; 95% CI 0.35 to 0.87). There was also no significant difference in serious adverse events between vedolizumab patients (12%) and placebo patients (12%) (RR 1.02; 95% CI 0.73 to 1.42). The most commonly reported adverse events were headache, worsening UC, nausea, frequent bowel movements, fatigue, nasopharyngitis and abdominal pain.<sup>3</sup>

Approval for Crohn's disease was based on two studies that evaluated vedolizumab 300 mg in patients who have failed previous conventional therapy.<sup>36</sup> Induction was evaluated in both trials<sup>37,38</sup>; however, evaluation of maintenance was evaluated in only one trial.<sup>38</sup> Patients were required to have had an inadequate response to, loss of response to, or intolerance of at least a immunomodulator or TIM.

Study C13007 was a study with separate induction and maintenance trials. In the induction trial, patients were randomly assigned to receive blinded vedolizumab or placebo (cohort 1) at weeks 0 and 2 (n=368).<sup>38</sup> An additional 747 patients (cohort 2) were assigned open-label vedolizumab to be eligible for the

randomization into the maintenance study. In the maintenance trial, patients who had a response to vedolizumab (cohorts 1 and 2) were randomized to placebo or vedolizumab every 4 or 8 weeks until week 52. Approximately 50% of patients had previously received therapy with a TIM. There was a significant difference in clinical remission at week 6 between vedolizumab and placebo (14.5% vs. 6.8%;  $p=0.02$ ; NNT 12), but no significant difference in clinical response (31.4% vs. 25.7%;  $p=0.02$ ). The effect on clinical remission at week 6 was modest at best. After 52 weeks of therapy, significantly more patients on vedolizumab every 8 weeks and every 4 weeks were in clinical remission than those on placebo (39%, 36.4%, 21.6%, respectively;  $p<0.001$  and  $p=0.004$  for the comparisons).

Study 13011 is a phase III placebo-controlled, double blind RCT evaluating vedolizumab versus placebo in induction therapy in patients with Crohn's disease who had failed previous therapy.<sup>37</sup> The primary efficacy analysis was only evaluated in patients with prior TNF antagonist failure and the primary outcome was clinical remission at week 6. There was no significant difference in clinical remission at week 6 between those on vedolizumab and those on placebo (15.2% vs. 12.1%; RR 1.2, 95% CI 0.7-2.2). By week 10, this subpopulation that had failed conventional therapy had achieved an improvement in remission and improved clinical remission, suggesting that it takes longer to achieve a treatment effect. In the overall population, there was a significant difference in clinical remission between vedolizumab and placebo (19.1% vs. 12.1%; RR 1.6, 95% CI 1.0-2.5). However, because the primary outcome was not statistically significant, formal hypothesis testing was not done on secondary outcomes.

Most common adverse events included infections, nausea, vomiting, headache, upper respiratory tract infection, arthralgia, nasopharyngitis, and abdominal pain, with similar rates of serious adverse events between placebo and vedolizumab. The most commonly reported serious adverse events seemed largely related to the underlying disease process. According to the FDA analysis, a hepatotoxicity signal was observed in clinical trials and several cases of acute hepatocellular injury during the clinical development program.<sup>36</sup> Vedolizumab has a similar pharmacological mechanism as natalizumab, which also has been associated with acute hepatotoxicity. The FDA was also concerned about its potential impact on Progressive multifocal leukoencephalopathy (PML) risk.

## COMPARATIVE CLINICAL EFFICACY

### Relevant Endpoints:

- 1) Disease Activity
- 2) Physical Functioning
- 3) Quality of Life
- 4) Withdrawals due to Adverse Events

### Primary Study Endpoint:

- 2) Clinical remission (CDAI score of  $\leq 150$  points)
- 3) Clinical Response ( $\geq 100$  point increase in CDAI score)
- 4) Maintenance of Clinical remission

Ref./Study Design <sup>a</sup>	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
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Study C13007 <sup>38</sup> RCT, DB, PC	Induction: Vd 300 mg	Demographics: Mean age 36.1, 46.6% male, 89.2% white, duration of disease 9 years	967 (220 blinded and 747 open-label for maintenance study)	<b>Induction Study:</b> <u>Clinical remission at week 6:</u> Vd: 32 (14.5%) Pl: 10 (6.8%) P=0.02	ARR 8%/ NNT 12	<b>Induction Study:</b> <u>D/C due to adverse events:</u> Vd: 9 (4.1%) Pla: 7 (4.7%)	NS	<b>Quality Rating:</b> Fair  <b>Internal Validity: RoB</b> <u>Selection:</u> Computer generated randomization at a central location. Groups similar at baseline. <u>Performance:</u> Double Blinded <u>Detection:</u> Unclear <u>Attrition:</u> Low attrition in induction study, but high attrition in maintenance study (approximately 50%)  <b>External Validity:</b> <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Significant exclusion criteria reduces generalizability of results <u>Setting:</u> Multinational. <u>Outcomes:</u> Common Clinical outcomes evaluated
	Placebo	Inclusion Criteria: Adults with CDAI score of 220-450 points. Previous lack of response or side effects from steroids, immunosuppressives, or TNF inhibitors. Previous TNF inhibitor limited to 50% of total study population	148	<u>Clinical response at week 6</u> Vd: 69 (31.4%) Pla: 38 (25.7%) P=0.23	NS	<b>Maintenance Study:</b> <u>D/C due to adverse events:</u> Vd: 9 (4.1%) Pla: 7 (4.7%)		
	Maintenance: Vd 300 mg Q4W	Inclusion criteria: previous treatment with natalizumab, rituximab, efalizumab. Patients with a stoma, short-bowel syndrome, abdominal abscess, active or latent TB, cancer, any unstable major medical disorder, substance abuse, active psychiatric problems, SCr > 2 x ULN, alk phos > 3 x ULN, Hg<8g/dl, WBC <3	660	<b>Maintenance Study:</b> <u>Clinical remission at week 52:</u> VdQ8W: 60 (39.0%) VdQ4W: 56 (36.4%) Pla: 33 (21.6%) P<0.001 VdQ8 vs. Pla	ARR 17%/ NNT 5	<u>Serious AEs:</u> VdQ8w: 12 (7.8%) VdQ4w: 80 (14%) Pla: 15 (9.8%)		
	Vd300 mg Q8W placebo	platelet count <100 x 10 <sup>9</sup> /L	154 301	P=0.004 VdQ4 vs. Pla	ARR 15%/ NNT 6			



Study 13011 RCT, DB, PC <sup>37</sup>	<i>Prior TNF failure:</i>  Vd 300mg Placebo	Demographics: Mean age 34.8, 57% female, median disease duration 8 years, prior TIM failure 76%	158 157	<u>Clinical Remission at week 6 (TNF failure):</u> Vd: 15.2% Pla: 12.1% P=0.433 RR 1.2; 95% CI 0.7-2.2  *Official hypothesis testing not done on secondary endpoints since primary outcome was not statistically significant	NS	<u>D/C due to adverse events:</u> Vd: 4 (2%) Pla: 8 (4%)  <u>Serious adverse events:</u> Vd: 13 (6%) Pla: 16 (8%)	NS  NS	<b>Quality Rating:</b> Fair  <b>Internal Validity: RoB</b> <u>Selection:</u> Randomized using a interactive voice response system and computer-generated randomization sequence. <u>Performance:</u> Double Blinded using sale bag covers and labels. <u>Detection:</u> Unclear blinding of outcome assessors. <u>Attrition:</u> Low attrition (4%) but short term study. Similar between groups. Intent to treat analysis done for primary outcome.  <b>External Validity:</b> <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Significant exclusion criteria reduces generalizability of results <u>Setting:</u> Multinational. <u>Outcomes:</u> Common Clinical outcomes evaluated. Only evaluating induction therapy unknown long term maintenance of remission in patients.  Efficacy analysis conducted in subgroup of patients.
	<i>TNF naïve:</i>  Vd 300mg Placebo	Inclusions Criteria: Adults with Crohn’s disease with an inadequate response, loss of response, or intolerance to TNF antagonists, immunosuppressives, or corticosteroids.  Exclusion criteria: Unstable or uncontrolled medical condition, neurologic disorder, malignancy, drug or alcohol dependence, psychiatric disease.	51 50					
CDAI: Crohn’s Disease Activity Index								

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## Appendix 1: Suggested PA Criteria

### Targeted Immune Modulators (TIMS)

#### Goal(s):

- Cover TIMs according to OHP list guidelines.
- Promote use that is consistent with National Guidelines and medical evidence.
- Promote use of high value products.

**Requires PA:** Non-preferred products

Preferred Products: Adalimumab (Humira®), Etanercept (Enbrel®), golimumab (Simponi®)

**Length of Authorization: 12 months**

Generic Name	Trade Name	Indication
Abatacept	Orencia	RA, Juvenile RA, Juvenile idiopathic arthritis
Adalimumab	Humira	RA, Psoriatic arthritis, ankylosing spondylitis, Juvenile idiopathic arthritis, Crohn's disease, Plaque psoriasis, ulcerative colitis
Anakinra	Kineret	RA
Certolizumab	Cimzia	RA, Crohn's disease, <u>psoriatic arthritis, ankylosing spondylitis</u>
Etanercept	Enbrel	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis
Golimumab	Simponi	RA, psoriatic arthritis, ankylosing spondylitis, <u>ulcerative colitis</u>
Infliximab*	Remicade	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis
Natalizumab*	Tysabri	Crohn's disease
Rituximab*	Rituxan	RA
Tocilizumab*	Actemra	RA, juvenile idiopathic arthritis
<u>Tofacitinib</u>	<u>Xeljanz</u>	<u>RA</u>
Ustekinumab	Stelara	Plaque psoriasis, <u>Psoriatic arthritis</u>
<u>Vedolizumab</u>	<u>Entyvio</u>	<u>Ulcerative colitis, Crohn's disease</u>

Abbreviations: RA, rheumatoid arthritis

\* Must be billed via J-code and payment requires trial of preferred self-administered drug first.

#### Approval Criteria : Targeted Immune Modulators

1. What is the diagnosis?

Record ICD-9 code

<b>2.</b> Is the diagnosis covered by OHP?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPH; Deny (medical appropriateness)
<b>3.</b> Will the provider change to a preferred product?	<b>Yes:</b> Inform provider of covered alternatives in class.	<b>No:</b> Go to #4
<b>4.</b> Is the diagnosis psoriasis (ICD-9: 696.1-696.2, 696.8) and the product requested FDA approved for psoriasis (see table above)?  * Moderate/Severe psoriasis treatments are covered on the OHP.	<b>Yes:</b> Refer to anti-psoriatics PA criteria at <a href="http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/OR%20Medical%20PA%20Criteria/PA%200711.pdf">http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/OR%20Medical%20PA%20Criteria/PA%200711.pdf</a>	<b>No:</b> Go to #5
<b>5.</b> Is the diagnosis ankylosing spondylitis (ICD-9 720) and the product requested is FDA approved for ankylosing spondylitis?	<b>Yes:</b> Approve treatment for up to 1 year	<b>No:</b> Go to #6
<b>6.</b> Is the diagnosis rheumatoid arthritis (ICD-9 714.xx) or psoriatic arthropathy (ICD-9 696.0) and the product requested FDA approved for rheumatoid arthritis (see table above)?	<b>Yes:</b> Go to #7	<b>No:</b> Go to #8
<b>7.</b> Has the patient had a trial and inadequate response to methotrexate or other first line DMARDs (leflunomide, sulfasalazine, hydroxychloroquine, penicillamine) and a disease duration of ≥6 months? Or, An intolerance or contraindication to oral DMARDs?	<b>Yes:</b> Approve treatment for up to 1 year	<b>No:</b> Pass to RPH; Deny (medical appropriateness)
<b>8.</b> Is the diagnosis Crohn's disease (ICD-9 555) and the product requested FDA approved for Crohn's (see table above)?	<b>Yes:</b> Go to #9	<b>No:</b> Pass to RPH; Deny (medical appropriateness)
<b>9.</b> Has the patient had a trial and inadequate response to conventional therapy including immunosuppressive therapy (mercaptopurine, azathioprine) and/or corticosteroid treatments? Or, Has intolerance or contraindications to conventional therapy?	<b>Yes:</b> Approve treatment for up to 1 year	<b>No:</b> Pass to RPH; Deny (medical appropriateness)

*P&T Action: 8-30-12 (MH)*

*Revision(s):*

*Initiated:*



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### **Abbreviated Class Update: Topical Antifungal Agents**

**Month/Year of Review:** September 2014

**End date of literature search:** July 2014

**PDL Class:** Dermatologic – Topical antifungal

**New drugs:** efinaconazole (JUBLIA®)  
tavaborole (KERYDIN®)

**Date of Last Review:** March 2014

**Source Document:** OSU College of Pharmacy

**Manufacturer:** Valeant Pharmaceuticals  
Anacor Pharmaceuticals

**Current PDL Status:** Only miconazole cream, nystatin cream and nystatin ointment are preferred (Appendix 1).

**Background:** The Oregon Health Plan list of prioritized services does not fund treatment for CANDIDIASIS OF MOUTH, SKIN AND NAILS or DERMATOPHYTOSIS OF NAIL, GROIN, AND FOOT AND OTHER DERMATOMYCOSIS in immune-competent hosts. Topical antifungal agents are solely indicated for these and other related non-funded conditions (Appendix 1).

**Prior Authorization (PA) criteria:** Required for non-preferred agents covering only for a funded diagnosis and trial of generic formulation (Appendix 2).

#### **Research Questions:**

- Is there any new evidence for differences in efficacy or safety in topical antifungal drugs that would indicate changes are needed to the current PDL?
- Is efinaconazole or tavaborole more effective and/or safer than currently available agents?
- Are there subgroups of patients where efinaconazole or tavaborole may be more effective or safer than currently available agents?

#### **Conclusions**

- There was no new evidence supporting a difference in efficacy/effectiveness or harms between topical antifungals.
- There is moderate level evidence from two placebo-controlled trials that daily application of efinaconazole 10% solution cures onychomycosis in immune competent patients better than the vehicle alone (study 1: 17.8% vs 3.3%, study 2: 15.2% vs 5.5%,  $P < 0.001$ ) and there were no serious adverse events reported.
- There were no published trials identified evaluating tavaborole.

#### **Recommendations:**

- Evaluate comparative costs in executive session.

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### Previous Conclusions and Recommendations

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- There is low quality evidence based on one published fair quality study that luliconazole is effective and safe for the treatment of tinea cruris and is significantly better than placebo in achieving a complete response (21.2% vs. 4.4%;  $p < 0.001$ ).<sup>1</sup> There are no comparative data between luliconazole and other topical antifungal agents. Maintain luliconazole a non-preferred topical antifungal medication on the PDL due to lack of long term clinical outcomes data and direct comparative data to suggest better tolerability or efficacy than currently available agents.

### Reason for Review:

Efinaconazole 10% solution (JUBLIA®)<sup>2</sup> and tavaborole 5% solution (KERYDIN®)<sup>3</sup> were approved by the FDA for the for treatment of onychomycosis of the toenails caused by the organisms *Trichophyton rubrum* and *Trichophyton mentagrophytes* since the last review of this class in March 2014. This update will examine their place in therapy and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

### Methods:

A Medline (Ovid) literature search was conducted for new systematic reviews, meta-analyses, randomized controlled trials (RCT's) and controlled clinical trials comparing antifungal agents head-to-head in the treatment of topical fungal infections and limits for humans, English language with the following search terms: antifungal agents, efinaconazole, tavaborol, tinea, tinea unguium, tinea capitis, tinea corporis, tinea cruris, tinea pedis, pityriasis versicolor, Candidiasis, Onychomycosis. 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

### Systematic Reviews:

Clinical Evidence published a review (October 2013)<sup>4</sup> of treatments for toe onychomycosis which included: topical amorolfine, butenafine, ciclopirox, fluconazole, ketoconazole, terbinafine, tioconazole as well as oral itraconazole, terbinafine and fluconazole. While evidence supported increased cure rates for oral itraconazole and terbinafine, there was no evidence found for topical agents except ciclopirox which modestly improved symptoms over placebo.

### New Guidelines:

No new or updated guidelines were identified.

### New Safety Alerts, Indications:

No new safety alerts or indications were found.

August 7, 2014



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**New Drug Evaluation:** efinaconazole 10% solution

*FDA approved indications:* Topical treatment of onychomycosis of the toenails caused by the organisms *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

*Potential Off-label Use:* Other fungal infections of the skin or nails.

*Clinical Efficacy Data:* Efficacy was established in two (study 1: N = 870, study 2: N = 785) good quality multi-center, double-blinded, randomized vehicle controlled trials.<sup>5</sup> Patients were immune-competent adults with 20-50% fungal involvement of a great toe without dermatophytomas or lunula involvement with positive culture of dermatophyte with or without *Candida* less than or equal to 42 days before baseline. Patients were randomized (3:1) to efinaconazole or vehicle, once daily for 48 weeks, with a 4-week follow-up. The primary outcome was complete cure at 52 weeks and was greater for efinaconazole (study 1: 17.8% vs 3.3%, study 2: 15.2% vs 5.5%, P <0.001).

*Clinical Safety:* Application site dermatitis was the most common adverse reaction leading to discontinuation. The rate of discontinuations for adverse events was low overall (efinaconazole vs vehicle: study 1: 3.2% vs 0.5%, study 2: 1.9% vs 0%).<sup>5</sup> Other adverse events reported did not significantly differ between efinaconazole and the vehicle.

**New Drug Evaluation:** tavaborole 5% solution

*FDA approved indications:* Topical treatment of onychomycosis of the toenails caused by the organisms *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

*Potential Off-label Use:* Other fungal infections of the skin or nails.

*Clinical Efficacy Data:* No published trials were identified.

*Clinical Safety:*

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**References:**

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**Appendix 1 – PDL Status and FDA Indications**

Generic	Brand	Form	Tinea versicolor	tinea pedis	tinea corporis	tinea cruris	onycho-mycosis	seborrheic dermatitis of the scalp	cutaneous candidiasis
<i>Preferred</i>									
MICONAZOLE NITRATE	MICATIN	CREAM (G)		X	X	X			
NYSTATIN	NYSTATIN	CREAM (G)							X
NYSTATIN	NYSTATIN	OINT. (G)							X
<i>Non-Preferred</i>									
BUTENAFINE HCL	LOTRIMIN ULTRA	CREAM (G)	X	X	X	X			
BUTENAFINE HCL	MENTAX	CREAM (G)	X	X	X	X			
CICLOPIROX	CICLODAN, PENLAC	SOLUTION		X	X				
CICLOPIROX	CICLOPIROX	GEL (GRAM)		X	X				
CICLOPIROX	LOPROX	SHAMPOO						X	
CICLOPIROX/NAIL LACQ/FT DEOD#4	PEDIPIROX-4	KIT					X		
CICLOPIROX/NAIL LACQUER REMOVR	CNL 8	KIT					X		
CLOTRIMAZOLE	LOTRIMIN AF, DESENEX	CREAM (G)	X			X			X
CLOTRIMAZOLE	CLOTRIMAZOLE	SOLUTION	X						X
ECONAZOLE NITRATE	ECOZA	CREAM (G)	X	X	X	X			X
KETOCONAZOLE	KETOCONAZOLE	CREAM (G)	X	X	X	X		X	X
KETOCONAZOLE	NIZORAL	SHAMPOO	X					X	
KETOCONAZOLE	XOLEGEL	GEL (GRAM)						X	
KETOCONAZOLE	EXTINA	FOAM						X	
KETOCONAZOLE	KETODAN	FOAM						X	
LULICONAZOLE	LUZU	CREAM (G)		X	X	X			
MICONAZOLE NITRATE	DESENEX; LOTRIMIN AF	AERO POWD		X	X	X			
MICONAZOLE NITRATE	DESENEX; LOTRIMIN AF	POWDER		X	X	X			
MICONAZOLE NITRATE	FUNGOID TINCTURE	TINCTURE		X	X	X			
MICONAZOLE NITRATE	FUNGOID TINCTURE	KIT		X	X	X			
MICONAZOLE NITRATE	MICATIN	OINT. (G)		X	X	X			
MICONAZOLE NITRATE	DESENEX; LOTRIMIN AF	SPRAY		X	X	X			
NAFTIFINE HCL	NAFTIN	CREAM (G)		X	X	X			
NAFTIFINE HCL	NAFTIN	GEL (GRAM)		X	X	X			

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NYSTATIN	NYSTATIN	POWDER							X
NYSTATIN/EMOLLIENT COMBO NO.54	PEDIADERM AF	CREAM (G)							X
NYSTATIN/TRIAMCIN	NYSTATIN- TRIAMCINOLONE	CREAM (G)							
NYSTATIN/TRIAMCIN	NYSTATIN- TRIAMCINOLONE	OINT. (G)							
OXICONAZOLE NITRATE	OXISTAT	CREAM (G)	X	X	X	X			
OXICONAZOLE NITRATE	OXISTAT	LOTION	X	X	X	X			
SERTACONAZOLE NITRATE	ERTACZO	CREAM (G)		X					
SULCONAZOLE NITRATE	EXELDERM	CREAM (G)		X	X	X			
SULCONAZOLE NITRATE	EXELDERM	SOLUTION		X	X	X			
TERBINAFINE HCL	LAMISIL AT	CREAM (G)		X	X	X			
TERBINAFINE HCL	LAMISIL AT	GEL (GRAM)		X	X	X			
TERBINAFINE HCL	LAMISIL	SPRAY		X	X	X			
TOLNAFTATE	TINACTIN	AERO POWD		X	X	X			
TOLNAFTATE	TINACTIN	CREAM (G)		X	X	X			
TOLNAFTATE	(various)	SOLUTION		X	X	X			
TOLNAFTATE	TINACTIN	SPRAY		X	X	X			
UNDECYLENIC ACID	ANTI-FUNGAL	SOLUTION		X		X			

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## Appendix 2

### Antifungals

#### Goal(s):

- Approve use of antifungals only for ~~covered~~funded diagnoses. Minor fungal infections of skin, such as dermatophytosis of nail and skin are only covered when complicated by an immunocompromised host.

#### Length of Authorization:

See criteria

#### Requires PA:

- Non-preferred drugs

#### Covered Alternatives:

Preferred alternatives listed at [www.orpdl.org](http://www.orpdl.org)

**Table 1 – Examples of ~~FUNDED~~COVERED indications (41/1/1406)**

ICD-9	Description
112.1	Candidiasis of vulva and vagina
112.2	Candidiasis of other urogenital sites
112.4	Candidiasis of the lung
112.5	Disseminated Candidiasis
112.81	Candidal Endocarditis
112.82-112.89	Candidal Otitis Externa - Other Candidiasis site
114.0-114.9	Coccidiomycosis various sites
115.00-115.99	Histoplasmosis
116.0-116.2	Blastomycosis
117 & subsets	Rhinosporidiosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycotis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiaceous Fungal Infection, Mycoses Nec and Nos
118	Mycosis, Opportunistic
518.6	Bronchopulmonary Aspergillus, Allergic
616 & subsets	Inflammatory disease of cervix vagina and vulva
681 & subsets	Cellulitis and abscess of finger and toe
771.7	Neonatal Candida infection

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**Table 2 – Examples of NON-~~COVERED FUNDED~~ indications (~~41/1/1406~~)**

ICD-9	Description
<del>110.1</del>	<del>Dermatophytosis of nail (onychomycosis)</del>
111.0	Pityriasis versicolor
111.2	Tinea blanca
111.3	Black piedra
111.8	Dermatomycoses nec
111.9	Dermatomycosis nos
112.3	Cutaneous candidiasis
112.9	Candidiasis site nos
690 & subsets	Erythematous squamous dermatosis
691	Atopic dermatitis and related conditions
691.0	Diaper or napkin rash
691.8	Other atopic dermatitis and related conditions
692 & subsets	Contact dermatitis and other eczema
695.2-695.4	Erythema nodosum, rosacea, lupus erythematosus
695.8-695.9	Other specified erythematous conditions, erythematous cond nec, unspecified erythematous condition
697 & subsets	Lichen
706 & subsets	Diseases of sebaceous glands
782.1	Nonspecif skin erupt nec

**Table 3 – Criteria driven diagnoses (~~41/1/1406~~)**

ICD-9	Description
<del>110.</del>	<del>Dermatophytosis</del>
110.0	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)
<del>110.1</del>	<del>Dermatophytosis of nail (onychomycosis)</del>
110.2	Dermatophytosis of hand (tinea manuum)
110.3	Dermatophytosis of groin and perianal area (tinea cruris)
110.4	Dermatophytosis of foot (tinea pedis)
110.5	Dermatophytosis of body (tinea corporis / tinea imbricate)

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110.6	Deep seated dermatophytosis
110.8	Dermatophytosis of other specified sites
110.9	Dermatophytosis site of unspecified site
111.1	Tinea nigra
112.0	Candidosis of mouth

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP covered diagnosis? See Table 1, Examples of <del>COVERED FUNDED</del> indications ( <del>4/1/141/1/06</del> )?	Yes: Go to #3.	No: Go to #4.
3. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> <li>Preferred products do not require PA.</li> <li>Preferred products are evidence-based reviewed for comparative effectiveness &amp; safety by the <del>Pharmacy &amp; Therapeutics Committee</del> <del>Health Resources Commission (HRC)</del>.</li> </ul>	Yes: Inform provider of covered alternatives in class.	No: Approve for 3 months or course of treatment.
4. Is the diagnosis in Table 2? See Examples of NOT- <del>FUNDED</del> <del>COVERED</del> indications ( <del>4/1/141/1/06</del> )	Yes: Pass to RPH: Deny, (Not Covered by the OHP).	No: Got to #5.
5. Is the diagnosis in Table 3, Criteria driven diagnoses ( <del>4/1/141/1/06</del> )?	Yes: Go to #6.	No: Go to #8.

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## Approval Criteria

6. Is the client immunocompromised?

- Does the client have a current (not history of) diagnosis of cancer **AND** is currently undergoing Chemotherapy or Radiation? Document therapy and length of treatment. **OR**
- Does the client have a diagnosis of HIV/AIDS? **OR**
- Does client have diagnosis of diabetes that requires anti-diabetic medications e.g. Insulin, metformin, glyburide, or any drug in the therapeutic class of Diabetic Therapy? Document medication(s). **OR**
- Does client have sickle cell anemia?

Yes: Record ICD-9 code.

Approve as follows:

(Immunocompromised client)

### ORAL

- Toenails = 12 weeks. Max 1 course per year.
- Fingernails = 6 weeks. Max 1 course every 6 months.

### ORAL & TOPICAL

- All other diagnosis = course of treatment only with PRN renewals.
- If length of therapy is unknown, approve for 3 months.

No: Go to #7.

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## Approval Criteria

7. Is client currently taking an immunosuppressive drug?  
Document drug. **Pass to RPH for evaluation if drug not in list.**

Immunosuppressive drugs include but are not limited to:

Generic	Brand
azathioprine	Imuran
basiliximab	Simulect
cyclosporine	Sandimmune, Neoral
sirolimus	Rapamune
tacrolimus	Prograf
methotrexate (Mtx)	Rheumatrex
hydroxychloriquin	Plaquenil
etanercept	Enbrel
leflunomide	Arava

Yes: Approve as follows:  
(Immunocompromised client)

### ORAL

- Toenails = 12 weeks. Max 1 course per year.
- Fingernails = 6 weeks. Max 1 course every 6 months.

### ORAL & TOPICAL

- All other diagnosis = course of treatment only with PRN renewals.
- If length of therapy is unknown, approve for 3 months.

No: Pass to RPH; Deny, (Not Covered by the OHP)

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## Approval Criteria

8. RPH only: All other indications need to be evaluated to see if they are above or below the line diagnosis:

- If above the line fungal code, then it may be approved for treatment course with prn renewals. If length of therapy is unknown, approve for 3 months intervals only.
- If below the line: Deny, (Not Covered by the OHP).
  - Deny Non-fungal diagnosis (Medical Appropriateness)
  - Deny Fungal ICD-9 codes that do not appear on the OHP list pending a more specific diagnosis code (Not Covered by the OHP).
  - Forward any fungal ICD-9 codes not found in the Tables 1, 2, or 3 to the Lead Pharmacist. These codes will be forwarded to DMAP to be added to the Tables for future requests.

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*P&T / DUR Action:* 09/23/2014 (KK); 03/27/2014 (BL); 09/16/10 (KS/DO); 2/23/06; 11/10/0; 9/15/05; 5/12/05  
*Revision(s):* 1/1/11; 7/1/06; 11/1/0; 9/1/0  
*Initiated:*

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## Appendix 3: Specific Drug Information

### EFINACONAZOLE 10% SOLUTION<sup>2</sup>

#### CLINICAL PHARMACOLOGY

Efinaconazole is an azole antifungal. It inhibits fungal lanosterol 14 alpha-demethylase which is necessary for the biosynthesis of ergosterol, a component of fungal cell membranes.

#### PHARMACOKINETICS

Systemic absorption was studied in 18 adults with onychomycosis. After 28 days of daily application the C<sub>max</sub> was 0.67 ng/mL. In a separate study of healthy volunteers, the plasma half-life was determined to be 29.9 hours.

#### DOSE & AVAILABILITY

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10%	solution	topical	daily x 48 weeks with the integrated flow-through brush applicator	NA	NA	The safety and effectiveness in pediatric patients have not been established.	No dose adjustment is necessary for the elderly.	Ensure the toe nail, the toe nail folds, toe nail bed, hyponychium, and the undersurface of the toe nail plate, are completely covered.

#### DRUG SAFETY

*Serious (REMS, Black Box Warnings, Contraindications):* There are no Serious Drug Safety concerns or contradictions for Efinaconazole at this time.

*Warnings and Precautions:* None.

*Pregnancy Category:* C.

*Adverse Reactions:* application site vesicles, ingrown toenail, application site pain, and application site dermatitis were the most common adverse reactions occurring  $\geq 1\%$ .

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## **TAVABOROLE 5% SOLUTION<sup>3</sup>**

### **CLINICAL PHARMACOLOGY**

Tavaborole is an oxaborole antifungal gal. It inhibits fungal protein synthesis.

### **PHARMACOKINETICS**

Systemic absorption was studied in 24 adults with onychomycosis. After 2 weeks of daily topical dosing, the mean C<sub>max</sub> was 5.17 ± 3.47 ng/mL.

### **DOSE & AVAILABILITY**

<b>STRENGTH</b>	<b>FORM</b>	<b>ROUTE</b>	<b>FREQUENCY</b>	<b>RENAL ADJ</b>	<b>HEPATIC ADJ</b>	<b>Pediatric Dose</b>	<b>Elderly Dose</b>	<b>OTHER DOSING CONSIDERATIONS</b>
5%	solution	topical	daily x 48 weeks with the integrated flow-through brush applicator	NA	NA	The safety and effectiveness in pediatric patients have not been established.	No dose adjustment is necessary for the elderly.	Should be applied to the entire toenail surface and under the tip of each toenail being treated

### **DRUG SAFETY**

*Serious (REMS, Black Box Warnings, Contraindications):* There are no Serious Drug Safety concerns or contradictions for tavaborole at this time.

*Warnings and Precautions:* None.

*Pregnancy Category:* C.

*Adverse Reactions:* application site exfoliation, ingrown toenail, application site erythema, and application site dermatitis were the most common adverse reactions occurring ≥ 1%.

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### **Abbreviated Class Review: Vitamins and Electrolytes (Potassium, Magnesium, and Phosphate Supplementation)**

**Month/Year of Review:** September 2014

**End date of literature search:** August 2014

**PDL Class:** None

#### **Research Questions:**

- Is there evidence to support and cover the use of specific products with good value?
- Are certain reformulations of vitamins more effective than safer than individual components or other formulations?
- Are there subpopulations that certain vitamins are more effective or safer than others?
- Is there evidence that supplementation improves clinical outcomes?

#### **Conclusions:**

- There is moderate to high quality evidence that increased potassium intake reduces blood pressure in adults and low quality evidence for reduced risk of stroke.<sup>1</sup> It is recommended to get potassium intake from dietary sources. There is additional evidence that potassium supplementation with oral potassium supplements has no significant effect on blood pressure.<sup>2</sup>
- Patients with drug-related hypokalemia (therapy with a diuretic) should receive potassium supplementation. Potassium chloride is the most effective for replacing acute potassium loss and is effective for the most common causes of potassium depletion.<sup>10</sup> All potassium formulations (liquid and tablets) are readily absorbed. Potassium phosphate is most commonly used to replace phosphate losses and potassium bicarbonate is recommended in the setting of metabolic acidosis.
- There is insufficient and conflicting evidence on the relationship of magnesium supplementation and blood pressure. There is insufficient evidence for any other benefit in magnesium supplementation, other than in nutritional deficiency.
- Mild to moderate hypophosphatemia in ambulatory patients can be treated with oral phosphate replacement therapy. There is no evidence of improved outcomes for routine supplementation in patients without hypophosphatemia

#### **Recommendations:**

- Evaluate comparative costs in executive session to list specific agents as preferred and non-preferred.
- Include a formulation of the different potassium salt supplements due to different clinical considerations.

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**Reason for Review:**

In March, 2014, the multivitamins and antioxidant multivitamins were reviewed for clinical efficacy/effectiveness and safety. Prior authorization was proposed for multivitamins and antioxidant multivitamin supplements to approve for documented nutritional deficiency or diagnosis associated with nutritional deficiency. For mono vitamin supplements, including calcium, vitamin D, folic acid, vitamin B, and the ferrous salt formulations, specific agents were listed as preferred and non-preferred based on cost comparisons when no clinical advantage was identified. The additional minerals, electrolytes, and vitamins will be reviewed similarly.

**Background:**

Complementary and alternative medicine refers to preventive and therapeutic modalities not considered to be part of conventional medicine.<sup>3</sup> This includes dietary supplements and has increased dramatically in North America recently in general populations, as well as CVD populations. Evidence of both benefits and harms of adding supplements to medical treatments has been reported, and there remains debate concerning the efficacy and safety of dietary supplements.<sup>4</sup> Safety concerns include the potential adverse effects, contamination of preparations, and mislabeling. Dietary supplements are regulated with much less rigor than prescription medications.<sup>5</sup> While randomized controlled trials are the gold standard for evidence based medicine, data on the efficacy and safety of dietary supplements is lacking, insufficient, or inconsistent. There is also a paucity of standardized guidelines for the use of these products. Even if there is guidance and/or evidence that a particular vitamin or dietary supplement may benefit patients, the question of which manufacturer or product to recommend is also raised. There are quality assessment programs available to ensure the quality of these products. This includes consumerlab.com, NSF International, and US pharmacopeia. Currently there are no specific vitamin policies under the Oregon Health Plan. A multivitamin with folic acid is included in the prevention table for pregnant patients.

Nutrient deficiencies are a public health concern in many countries in the world. RCTs in children in developing nations have shown that vitamin A supplementation decreases morbidity and all-cause mortality. However, the benefit of these supplements in nonpregnant adults in the US and other Western nations is less clear.<sup>6</sup> Malnutrition is both a cause and effect of poor health.<sup>7</sup> Factors contributing to disease related malnutrition include impaired intake (confusion, medication, poor appetite), impaired digestion and/or absorption (medical and surgical problems effecting the stomach, intestine, pancreas, and liver), altered requirements (increased metabolic demands), excess losses (vomiting, diarrhea, fistulae, stomas, burns). The National Institute for Health and Clinical Excellence recommends that all patients who have malnutrition due to one of the above reasons, in addition to sufficient calories, protein, and fluids, receive adequate electrolytes, minerals, micronutrients, and fiber if appropriate.<sup>7</sup> However, their evidence review found no data to support the routine use of vitamin and mineral supplements in either acute hospitalized patients or older residents in nursing homes. They recommend that if there is a concern about adequate micronutrient intake, a complete oral multivitamin and mineral supplement providing the reference nutrient intake should be considered by healthcare professionals.

It is well known that electrolyte disorders are common in hospitalized patients and are associated with increased morbidity and mortality.<sup>8</sup> However, chronic and mild electrolyte disorders also occur in the general population and can be associated with adverse outcomes. A recent epidemiological study in subjects 55 years of age or older found that the most common electrolyte disorders were hyponatremia and hypernatremia, and there were significant interactions between increasing age and prevalence. Overall, 15% of subjects had at least 1 electrolyte disorder. Overall, major risk factors for electrolyte disorders were diabetes for hyponatremia (OR 1.98; 95% CI 1.47 to 2.68) and hypomagnesaemia (OR 3.32; 95% CI 2.0-5.50), and diuretics for hypokalemia (OR 7.68; 95% CI 4.92 to 11.98). The authors concluded that an interventional study comparing correction with supplements vs. no correction is needed to prove that this is beneficial. Low potassium intake has been associated with hypertension, cardiovascular disease (CVD), chronic kidney stones, and low bone-mineral density.<sup>9</sup>

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**Methods:**

A Medline literature search ending June 2013 for new systematic reviews, clinical guidelines, and randomized controlled trials (RCTs) for the following dietary and vitamin groups was conducted: potassium, phosphate, and magnesium formulations. 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. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

**Potassium:** Increasing dietary potassium may be sufficient for asymptomatic patients with hypokalemia without underlying cardiac disease and serum potassium levels above 3 mEq/L. Otherwise, potassium replacement is recommended. Potassium salts include potassium chloride, potassium phosphate, and potassium bicarbonate. Potassium chloride is the most effective for replacing acute potassium loss and is effective for the most common causes of potassium depletion.<sup>10</sup> All potassium formulations (liquid and tablets) are readily absorbed. Potassium phosphate is most commonly used to replace phosphate losses and potassium bicarbonate is recommended in the setting of metabolic acidosis.

**Systematic Reviews:**

1. A high quality systematic review was done to evaluate potassium intake and cardiovascular (CV) risk factors and disease.<sup>1</sup> RCTs and cohort studies studying the effects of potassium intake on blood pressure, renal function, blood lipids, mortality, CV disease, stroke, and coronary heart disease (CHD) were included. The review was conducted according to the Cochrane methodology. Twenty one RCTs showed that increased potassium intake reduced systolic blood pressure (SBP) by 5.93 (95% CI 1.70 to 10.15) mm Hg and diastolic blood pressure (DBP) by 3.78 (1.43 to 6.13) mm Hg. Heterogeneity was significant for both analyses (I<sup>2</sup>=96% and I<sup>2</sup>=93%). When removing studies to reduce the heterogeneity (65% and 55%), increased potassium intake was shown to reduce SBP by 3.49 (1.82 to 5.15) mm Hg and DBP by 1.96 (0.86 to 3.06 mm Hg). Nine cohort studies demonstrated a protective effect of high potassium intake on risk of stroke (RR 0.76; 95% CI 0.66 to 0.89). There was a non-significant relation with CV disease and CHD. There was insufficient evidence to evaluate effects on all-cause mortality. Subgroup analysis demonstrated that a decrease in SBP was seen when potassium was increased through a supplement or through dietary advice and changes. There were no adverse effects seen on blood lipid concentrations, catecholamine concentrations, or renal function.

Based on this evidence review, the World Health Organization (WHO) recommends an increase in potassium intake from food to reduce blood pressure and risk of CVD, stroke, and CHD in adults (Strong recommendation).<sup>9</sup> WHO suggests potassium intake of at least 90 mmol/day. WHO suggests an increase in potassium intake from food to control blood pressure in children as well, but this is a conditional recommendation not based on strong evidence. Although the evidence comes from studies evaluating supplements and dietary sources, WHO recommends replacement of potassium through food consumption, as there have been reports of acute toxicity from extremely high potassium intake in supplement form, but not from consumption in food. WHO attempted to detect differences in the effect of increased potassium according to type of intervention (supplements or food) and type of potassium supplement (potassium citrate, potassium chloride, etc.). The analysis of 19 studies using potassium supplements showed high quality evidence of a decrease in SBP of 3.31 mmHg (95% CI 1.55 to 5.07) and the three studies using dietary changes showed a decrease in 4.19 mmHg (95% CI 1.92 to 6.46).

2. In contrast, a Cochrane Collaboration Systematic review found that potassium supplementation has no significant effect on blood pressure.<sup>2</sup> Only RCTs including oral potassium supplements were included in the review; dietary changes were not evaluated. A total of 6 RCTs (n=483) met inclusion criteria, most being of poor quality. Five were able to be combined in a meta-analysis that showed potassium supplementation resulted in a large but not statistically significant reduction in SBP (mean difference -11.2; 95% CI -25.2 to 2.7) and DBP (mean difference -5.0; 95% CI -12.5 to 2.4). There was significant heterogeneity between trials (I<sup>2</sup>=98%) that could not be accounted for by potassium dose, trial quality or baseline blood pressure. The significant heterogeneity along with the short duration of follow-up and small number of participants makes it difficult to draw conclusions based on this evidence. The authors concluded that further high quality RCTs are required to clarify results. No trials reported death or CV events. An older systematic review and meta-analysis of RCTs from 1995 found that potassium supplementation was associated with a significant reduction in mean SBP and DBP of -3.11 mm Hg (95% CI -1.91 to -4.31) and -1.97 mm Hg (-0.52 to -3.42), respectively.<sup>11</sup>
3. The National Council on Potassium in Clinical Practice provided guidelines for potassium replacement therapy.<sup>10</sup> However, the quality of the guidelines is low as they are not evidenced based and do not provide detail of the methodology or how they came to such conclusions. Main conclusions regarding potassium replacement are as following:
  - Potassium replacement is recommended for individuals who are sensitive to sodium or who are unable or unwilling to reduce salt intake for the benefit in blood pressure reduction
  - Potassium replacement is recommended for individuals who are subject to nausea, vomiting, diarrhea, bulimia, or diuretic/laxative abuse. Potassium chloride has been shown to be the most effective.
  - Potassium supplements are best administered orally in a moderate dosage over a period of days.
  - Potassium supplementation regimens should be as uncomplicated as possible to help optimize long-term compliance.
  - A dosage of 20 mmol/day is generally sufficient for the prevention of hypokalemia, and 40 to 100 mmol/day sufficient for its treatment.
  - Patients with drug-related hypokalemia (therapy with a diuretic) should receive potassium supplementation.
  - In patients with asymptomatic hypertension, an effort should be made to achieve and maintain normal serum potassium levels.
  - Potassium replacement should be routinely considered in patient with congestive heart failure (CHF).

#### Randomized Controlled Trials:

1. A 12-week double-blind, placebo-controlled RCT was done to determine the effects of potassium supplementation on endothelial function, CV risk factors, and bone turnover and to compare potassium chloride with potassium bicarbonate.<sup>12</sup> Adults with no previous treatment for elevated blood pressure with SBP of 140 to 170 mmHg or DBP of 90 to 105 mmHg, and who were already on a relatively low-salt and high-potassium diet were included in the study. Patients were randomized to placebo, potassium chloride, or potassium bicarbonate (n= 46). Compared with placebo, there was no significant difference in BP with either potassium chloride or potassium bicarbonate. Paired comparison showed that SBP was slightly lower with potassium chloride compared to potassium bicarbonate. Both potassium chloride and bicarbonate significantly improved endothelial function. Authors concluded that the 2 potassium salts appear to have similar effects on most of the CV parameters with small differences in effects on calcium and bone metabolism and urinary albumin excretion.
2. A double-blind, placebo-controlled 8 week RCT evaluated the effects of potassium chloride and potassium citrate in young healthy normotensive on change in mean arterial pressure (n=114).<sup>13</sup> Mean blood pressure was not significantly different among the three groups at baseline and throughout the duration of



the study. At the end of 6 weeks, mean blood pressure decreased significantly from baseline in both potassium groups, while no change was observed in the placebo group. No significant differences were found between the two potassium treatments, but the difference was statistically significant between placebo and the two potassium groups.

### **Magnesium:**

Studies have shown that magnesium is effective in eclampsia and preeclampsia (intravenous), arrhythmia (intravenous), severe asthma (intravenous, and migraine (oral). Other uses have been explored, including lowering the risk of metabolic syndrome, improving glucose and insulin metabolism, relieving symptoms of dysmenorrhea, and alleviating leg cramps in women who are pregnant. Although limited evidence to support its use, magnesium is often used for constipation.<sup>14</sup> This review will focus on the evidence of efficacy and safety of oral supplementation of magnesium. Magnesium supplements are available in a variety of forms, including magnesium oxide, citrate, and chloride. All have poor bioavailability and sustained release preparations are more slowly absorbed and minimize renal excretion. Low magnesium intake or excessive losses due to certain health conditions, chronic alcoholism, and/or the use of certain medications can lead to magnesium deficiency. Magnesium deficiency is most common in those with gastrointestinal diseases, alcohol dependence, type 2 diabetes and older adults. There is insufficient evidence that magnesium supplementation is effective in preventing migraines.<sup>18</sup>

Patients with symptomatic hypomagnesaemia should receive intravenous magnesium with cardiac monitoring. Asymptomatic outpatients can be given oral replacement.

### Systematic Reviews:

1. A comparative effectiveness review by AHRQ evaluated the evidence of benefits and harms of adding a dietary supplement to cardiovascular drugs routinely prescribed in outpatient settings.<sup>3</sup> A total of 69 studies contributed to the meta-analysis; no systematic reviews were identified. Most of the evidence was graded as insufficient and most had low statistical power due to short-term efficacy design. Strict inclusion criteria excluded patients with uncontrolled comorbidities and acute ischemic events, limiting the generalizability of the results. The authors concluded that the many limitations of the evidence made it difficult to make meaningful conclusions for most supplement-drug combinations. Low-strength evidence suggests benefits of omega-3 fatty acids (incremental improvement of triglyceridemia), vitamin K, (stabilization of INR with warfarin therapy) and garlic administration (improved HDL) only on those specific intermediate outcomes. Evidence on harms was inconclusive. No evidence on clinical effectiveness outcomes was found for Echinacea, garlic, ginseng, niacin, red yeast, vitamin A, or vitamin D supplementation coadministered with a CV drug. No evidence on intermediate outcomes was identified for effects of vitamin A or vitamin D supplementation in combination with CV drugs. No study analyzed statistical interactions between a supplement and a CV drug in terms of clinical outcomes. Additional specific conclusions based on supplement type are as followed:

*Magnesium:* There was insufficient evidence of no difference in myocardial infarction between oral magnesium + beta-blockers compared to beta-blockers alone. Three RCTs evaluated intermediate outcomes with magnesium in combination with hydrochlorothiazide or beta-blockers in participants with hypertension. In two trials, systolic blood pressure (SBP) and diastolic blood pressure (DBP) did not differ significantly between the magnesium hydrochlorothiazide combinations versus hydrochlorothiazide-alone groups (insufficient evidence). There was also no significant difference with the combination of magnesium plus beta-blockers versus beta-blockers alone (insufficient evidence).

2. A Cochrane Collaboration systematic review evaluated magnesium supplementation for the management of essential hypertension in adults.<sup>15</sup> A total of 12 RCTs were included and overall those receiving magnesium supplements compared to control did not significantly reduce SBP (mean difference -1.3 mmHg; 95% CI -4.0 to 1.5,  $I^2=67\%$ ), but did statistically significantly reduce DBP (mean difference -2.2 mm Hg, 95% CI -3.4 to -0.9;  $I^2=47\%$ ). There was significant heterogeneity between trials and subgroup analysis could not explain it by magnesium dose, baseline blood pressure or proportion of males. Studies were also of poor quality. The author concluded that any association seen between magnesium supplementation and blood pressure reduction is weak and probably due to bias as the quality of the studies was poor. The trials were too short and small to show any effect on CV outcomes such as death, heart attack or stroke.
3. A more recent meta-analysis also evaluated the effect of magnesium supplementation on blood pressure.<sup>16</sup> A literature search through July 2010 identified 22 trials to be included in the analysis. Again, the quality of many of the trials was poor and can overestimate the effect of treatment. Meta-analysis showed an overall effect of 0.36 and 0.32 for DBP and SBP, respectively (95% CI 0.27-0.44 for DBP and 0.23-0.41 for SBP) and this increased with increasing dose. This analysis resulted in a very small decrease in blood pressure, with a high risk of bias included in the trials.
4. The combination of calcium, magnesium and potassium supplementation was evaluated in the management of primary hypertension in adults by the Cochrane Collaboration.<sup>17</sup> Only 3 RCTs were included, evaluating 3 combinations of minerals (potassium-magnesium, calcium-magnesium, and calcium-potassium). The potassium-magnesium combination compared to control resulted in non-significant reductions in both SBP (mean difference -4.6 mmHg; 95% CI -9.9 to 0.7) and DBP (mean difference -3.8 mm Hg; 95% CI -9.5 to 1.8), with significant heterogeneity. The authors concluded that there is not robust evidence that supplements with any combination of potassium, magnesium or calcium reduces mortality, morbidity, or BP in adults.

**Phosphates:**

Patients most affected by hypophosphatemia are hospitalized patients with malnutrition, alcoholism, sepsis, and diabetic ketoacidosis. Certain medications may also predispose patients to hypophosphatemia, including insulin, diuretics, sucralfate, and antacids.<sup>19</sup> Mild to moderate hypophosphatemia in ambulatory patients can be treated with oral phosphate replacement therapy (1000-2000 mg/day). There is no evidence of improved outcomes for routine supplementation in patients without hypophosphatemia. No systematic reviews or high quality clinical guidelines on supplementation were found. Oral phosphate supplements contain varying ratios of sodium and potassium phosphate. An oral phosphate supplement should be selected with consideration of its potassium and sodium content and dosed according to millimoles of phosphate. Phosphates can also be used clinically to treat hypercalcemia and calcium based kidney stones. No high quality systematic reviews or clinical guidelines were identified evaluating phosphates on clinical outcomes.

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