Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, April 26, 2012 1:00-4:00 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 coverage, PDL composition, or utilization control recommendations to the OHA.

I. CALL TO ORDER 1:00 pm – 1:05 pm
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)

II. ProDUR 1:05 pm – 1:40 pm
- a. New Drug Evaluation* (10 min) — A. Burns (OSU)
  1. Kalydeco® (ivacaftor)
  2. Public comment
  3. Discussion of clinical recommendations to OHA
- b. 15-day Initial Supplies* (15 min) — R. Citron (OSU)
  1. Proposed List of Medications
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- c. New Drug Evaluation* (10 min) — M. Herink (OSU)
  1. Egrifta® (tesamorelin)
  2. Public Comment
  3. Discussion of clinical recommendations to OHA

III. NEW BUSINESS 1:40 pm – 2:00 pm
- a. Diabetes Medications Class Update* (20 min) — K. Sentena (OSU)
  1. Updated PA Criteria
  2. Tradjenta® (linagliptin)
  3. Bydureon® (exenatide)
  4. Public comment
  5. Discussion of clinical recommendations to OHA

BREAK 2:00 pm – 2:10 pm

III. NEW BUSINESS (continued) 2:10 pm – 3:30 pm
- b. New Drug Evaluation* (15 min) — M. Herink (OSU)
  1. Dificid® (fidaxomicin)
  2. Public comment
  3. Discussion of clinical recommendations to OHA

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

c. Antidepressant New Drug Reviews* (15 min) — A. Wheeler (OSU)
    1. Viibryd® (vilazodone)
    2. Public Comment
    3. Discussion of clinical recommendations to OHA
d. Smoking Cessation Class Update* (15 min) — A. Burns (OSU)
    1. Proposed PDL/Step Therapy
    2. Public comment
    3. Discussion of clinical recommendations to OHA
e. Drug Class Scans* (15 min) — M. Herink (OSU)
    1. Pulmonary Arterial HTN
    2. Oral Hypoglycemics/TZDs
    3. Insulins
    4. Public Comment
    5. Discussion of clinical recommendations to OHA

IV. OLD BUSINESS

a. Hepatitis B* (15 min) — M. Herink (OSU)
    1. Introduction of Ad-Hoc Expert
    2. Proposed PA criteria & PDL Placement
    3. Public Comment
    4. Discussion of clinical recommendations to OHA

V. EXECUTIVE SESSION 3:25 pm

VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

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

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, March 29, 2012 1:00-4:00 PM
Hewlett-Packard Building
4070 27th Ct SE
Salem, OR 97302

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to coverage, PDL composition, or utilization control recommendations to the OHA.

Members Present: Tracy Klein, PhD, FNP; William Origer, MD; Stacy Ramirez, PharmD; Zahia Esber, MD
Members Present by Phone: Andris Antoniskis, MD; Joshua Bishop, PharmD; Phillip Levine, PhD
Staff Present: Roger Citron, RPh; Megan Herink, PharmD, BCPS; Kathy Ketchum, RPh, MPA:HA; Valerie Smith; Richard Holsapple, RPh; Ralph Magrish, MPA; Ann Hamer, PharmD; Bing-Bing Liang, PharmD;
Staff Present by Phone: Brandy Fouts, PharmD
Audience Present: Jim Graves (BMS); Jeff Forshey (Shire); Ben Davidson (Physician); Deron Grothe (Teva); Deborah Crawford (Acorda); Lauren Letzenberger (Janssen Scientific Affairs); Craig Black (Biogen Idec); Jeana Colabianchi (Sunovion); Lyle Laird (Sunovion); Paul Sparks; Kimberly Langmeier (BMS); Lori Howarth (Bayer); Bruce Howard (Acorda); Rosalynde Finch (Biogen Idec); Kathy Kirk (OPMC); Elaine Thomas (Bayer); Don Stetcher (Novartis); John Brokars; Mary Kemhus; Denise Poole; Rob Pearson; Deborah Wafe; Diann Matthews; Angela Hamman; Paul Nielsen; James Matthucci; Amy Tice; Canan Shumann

I. CALL TO ORDER
a. The meeting was called to order at approximately 1:20pm
b. Conflict of interest declarations were reviewed and no new conflicts were reported
c. The February 23, 2012 meeting minutes were reviewed.

ACTION: Approved as is.

II. OLD BUSINESS
a. Hepatitis C criteria were brought back with the addition of steps 5-9 after consulting with a Hepatologist.

***ACTION:** Approved as amended from the last meeting.
b. Dose optimization concept was presented by Mr. Citron.

ACTION: Approved as amended to remove drugs that required titration (e.g. hypertention drugs, lamotrigine, quetiapine). Staff directed to identify drugs to target for this policy based upon past claim data. .

III. NEW BUSINESS
a. Dr. Williams presented on Short Acting Opioids and recommended using the same criteria for Short Acting Opioids as Long Acting Opioids.

***ACTION:** Approved as is after Executive Session. Staff directed to implement with educational component and adequate notice to providers. Also recommended butorphanol NS non-preferred, oxycodone 5mg capsule non-preferred, oxycodone concentrate non-preferred, oxycodone 2.5mg/APAP non preferred, Conzip® non-preferred.

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

b. Dr. Herink presented on Multiple Slerosis drug class including new drug reviews for fingolimod and dalfampridine. It was recommended that finolimod be made non-preferred with a trial of interferon first. Dalfampridine was recommended to be managed with prior authorization criteriaand it was referred to HERC for cost-effectiveness evaluation in comparison to non-pharmacological treatments. Dr. Ben Davidson presented public comment on MS drug class in general. Elaine Thomas from Bayer presented public comment on Betaseron®. Rosalynde Finch from Biogen Idec presented public comment on Avonex®. Mary Kenhus from Novartis presented public comment on Gilenya®. Deborah Crawford from Acorda presented public comment on Ampyra®.

***ACTION:** Approved as presented after Executive Session.

c. Dr. Hamer presented on Antipsychotic drug class recommending education outreach to promote appropriate utilization and minimize inappropriate off-label use and making lurasidone non-preferred. Lyle Laird from Sunvion presented public comment on Latuda®. Written testimony was provided by Dr. Lisa Boy on Latuda®. Mary Kemhus from Novartis presented public comment on Fanapt®.

***ACTION:** Approved as presented after Executive Session. It was also recommended to review class pricing again in three months and to have staff to present a specific educational proposal.

d. Dr. Liang presented the Statin drug class update recommending that quantity limits be implemented on 80mg simvastatin, and making pitavastatin non-preferred.

***ACTION:** Approved as presented after Executive Session and recommended revisiting pricing in three months.

e. Dr. Fouts presented the new drug evaluation and recommended implementing dose limits, age restrictions, and diagnosis documentation on icatibant.

***ACTION:** Committee deferred action and asked staff for more information regarding current utilization of this class and icatibant's place in therapy.

f. Dr. Williams presented the ADHD drug class update recommending not considering extended release forms of clonidine and guanfacine superior to other stimulant and non-stimulant ADHD treatments for PDL placement. John Brokers from Eli Lilly presented public comment on Stratera.

***ACTION:** After Executive Session it was recommended Kapvay®, Daytrana®, generic methamphetamine and Concerta® and its generic equivalent be made non-preferred. It was recommended Intuniv® be listed preferred after successful contract negotiations.

g. Dr. Herink presented drug class scans.
    1. Sedative Hypnotics – recommend no further research or review at this time. Make Silenor® and Edular® non-preferred.
    2. Skeletal Muscle Relaxants – recommend no further research or review at this time.
    3. Triptans – recommend no further research or review at this time.

***ACTION:** After executive session the Sedative Hypnotic recommendations were approved and it was recommended to make all Skeletal Muscle Relaxant agents non-preferred except baclofen, cyclobenzaprine and tizanidine.

IV. EXECUTIVE SESSION

V. RECONVENE for PUBLIC RECOMMENDATIONS*

VI. The meeting adjourned at 4:45pm.

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

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Kalydeco (ivacaftor) –

Indication: Ivacaftor was FDA approved in January 2012 for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation on at least one Cystic Fibrosis Transmembrane Regulator (CFTR) allele.[1,2] If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the G551D mutation.

Limitations of use:

- Ivacaftor is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene.
- Ivacaftor has not been studied in other populations of patients with CF.

Efficacy: FDA approval of ivacaftor was based on two randomized, double blind, placebo-controlled, phase III trials submitted by Vertex pharmaceuticals including ENVISION (unpublished) and STRIVE (published).[2, 3] Both were designed to assess the efficacy and safety of 24 weeks of treatment with ivacaftor 150 mg PO twice daily in patients age 12 years and older (STRIVE) and 6 to 11 years (ENVISION). Placebo-controlled treatment was continued through 48 weeks to confirm response. All eligible patients who completed the prior 48-week randomized, controlled trials including patients previously receiving placebo were rolled over into the open-label extension study (PERSIST) which is currently ongoing.[2] Both trials demonstrated a statistically significant improvement in the primary outcome of FEV1 after 24 weeks with a treatment difference from baseline FEV1 of 10.6% in STRIVE and 12.5% in ENVISION ($p<0.001$).[2,3] The STRIVE trial also showed an increased proportion of patients free from pulmonary exacerbations (67% vs. 41%, HR 0.46, p=0.0012).

While these trials evaluated subjects with specifically a G551D-CFTR mutation, data from the DISCOVER trial evaluated the efficacy of ivacaftor in CF patients who are homozygous for the F508del mutation in the CFTR gene in patients aged 12 years and older.[4] Through 16 weeks, no statistically significant differences from placebo were observed in change from baseline FEV1 (treatment difference 1.7%, p=0.15), risk for pulmonary exacerbation, CF respiratory symptoms, or weight gain.[4]

Safety: The most common adverse reactions in 353 patients with CF were headache (17%), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), dizziness (5%), arthralgia (5%), and bacteria in sputum (5%). No serious adverse events known.

Conclusions: CF affects about 30,000 people in the United States and only about 4 percent of those with CF are believed to have the G551D mutation. Two 48-week, placebo-controlled clinical studies involving 213 patients, one in patients ages 12 years and older and another in patients ages 6 years to 11 years, were used to evaluate the safety and efficacy of ivacaftor in CF patients with the G551D mutation. Both showed significant improvements in the primary outcome of change in FEV1 from baseline through week 24. There remains insufficient evidence to determine the ongoing gains in FEV1 beyond 48 weeks, or its effects on structural lung disease. Data from one study demonstrated ivacaftor to lack efficacy in patients with CF who are homozygous for the F508del mutation in the CFTR gene, which is the most prevalent disease-causing mutation and the drug has not been studied in any other CF patient populations. Until a more detailed evidence-based review is conducted, it is recommended to implement a prior authorization for ivacaftor to limit use to its FDA indication and in patients in which it has been studied for efficacy and safety.

Ivacaftor (Kalydeco)

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 client have a diagnosis of cystic fibrosis and is 6 years of age or older?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Does the patient have a documented G551D mutation in the CFTR gene? • If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *G551D* mutation.	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Is the prescription for ivacaftor 150mg twice daily, once daily or twice-a-week?	**Yes:** Approve for one year.	**No:** Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

• Ivacaftor is not effective in patients with Cystic Fibrosis who are homozygous for the *F508del* mutation in the *CFTR* gene.
• Ivacaftor has not been studied in other populations of patients with Cystic Fibrosis.

DUR Board Action:
Revision(s):
Initiated:

References:

1. Kalydeco [package insert]. Vertex Pharmaceuticals Inc., Cambridge, MA; January 2012. http://pi.vrtx.com/files/uspi_ivacaftor.pdf.
2. Kalydeco™" (ivacaftor) for the Management of Cystic Fibrosis. Formulary Submission Dossier. Vertex Pharmaceuticals. February 2012.
3. Ramsey B., Davies J., McElvaney G., et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. N Engl J Med 365;18. November 3, 2011
4. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. Chest. 2012 Mar 1. [Epub ahead of print]

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Proposed Fifteen Day Initial Prescription List

Drugs that have been identified with high side effect profiles, high discontinuation rates, or frequent dose adjustments are proposed to be limited to a 15-day initial supply. The initial prescription supply limit ensures cost effectiveness without waste of unused medications.

ANTIDEPRESSANTS- SELECTED SSRI'S
Aplenzin
Bupropion
Bupropion SR
Cymbalta
Effexor XR
Fluoxetine HCl Tablets (PMDD)
Fluvomaxine Maleate
Lexapro Vesicare
Luvox CR
Maprotiline
Nefazodone
Oleptro
Paroxetine ER
Pexeva
Pristiq
Sarafem
Savella
Venlafaxine
Venlafaxine ER
Viibryd

ANTIPSYCHOTICS-ATYPICALS
Abilify
Fanapt
Geodon
Invega
Latuda
Risperdal
Risperidone
Saphris
Seroquel
Zyprexa

ANTISPASMODICS
Detrol
FlavoxateHCl
Sanctura

ANTISPASMODICS- LONG ACTING
Detrol LA
Enablex
Gelnique
Oxybutynin Chloride ER
Oxytrol
Sanctura XR
Toviaz

CHOLINERGIC
Bethanechol Chloride

STIMULANTS
Desoxyn
Procentra

STIMULANTS-AMPHETAMINES-LONG ACTING
Adderall XR
Dexedrine
Vyvanse

STIMULANTS-AMPHETAMINES-SHORT ACTING
Amphetamine-Dextroamphetamine
Dextroamphetamine Sulfate

STIMULANTS-METHYLPHENIDATE
Focalin
Methylin chew
Methylphenidate HCl solution

STIMULANTS-METHYLPHENIDATE-LONG ACTING
Concerta
Focalin XR
Metadate
Methylphenidate HCl SR
Ritalin LA
Ritalin SR

STIMULANTS-OTHER /LIKE STIMULANTS
Intuniv
Kapvay
Nuvigil
Provigil
Strattera

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Month/Year of Review: April 2012
Generic Name: Tesamorelin
PDL Class: Synthetic growth hormone-releasing factor analog
Dossier received: Yes

End date of literature search: January 31, 2012
Brand Name (Manufacturer): Theratechnologies, Inc.
Comparator Therapies: None

EXECUTIVE SUMMARY:

FDA Approved Indications: Tesamorelin is a growth hormone releasing factor (GRF) analog indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.[1]

Background/Reason for Review: Patients with human immunodeficiency virus (HIV) taking antiretroviral therapy frequently develop increased visceral adiposity, dyslipidemia, and insulin resistance, which may be associated with increased cardiovascular risk. Studies have shown that growth hormone-releasing hormone (GHRH) has shown positive changes in fat distribution in HIV-infected patients.[1, 2] Tesamorelin is a synthetic growth hormone-releasing factor analog that has been approved for the use of HIV infected patients with lipodystrophy. This review will evaluate the available evidence of efficacy, safety, and tolerability to further define its role in therapy and to identify potential parameters for use.

Issues/Key questions:
Is tesamorelin effective and safe for the treatment of excess abdominal fat in HIV-infected patients?
Does treatment with tesamorelin result in improved health outcomes?

Efficacy: There were two, Phase 3, randomized, controlled studies that evaluated the efficacy of tesamorelin compared to placebo; both studies conducted an initial 26-week phase and a 26-week extension phase to evaluate long-term safety.[7-9] Both studies saw a significant change in visceral adipose tissue (VAT) in patients treated with tesamorelin (-15.2% and -10.9%) compared to placebo (+5.0% and -0.6%, $p<0.001$ for both trials). Secondary efficacy endpoints from the extension phases indicate that this decrease in VAT is not maintained after treatment discontinuation. There was limited reduction in body mass index or waist circumference after 26 weeks after treatment with tesamorelin.

Safety: Patients receiving tesamorelin experienced a higher rate of adverse events compared to those in the placebo group.[1] The most common adverse events were headache, arthralgias, injection-site bruising, diarrhea, peripheral edema, myalgia, and limb pain. Contraindications to tesamorelin include those with active malignancy, hypersensitivity to tesamorelin and/or mannitol, pregnancy, and patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, or pituitary tumor/surgery, head irradiation or head trauma. The long term safety and potential long term cardiovascular benefit of tesamorelin is unknown.[1]

Conclusions/Evidence Grade: Strength of evidence is moderate. Clinical trials were generally well designed and show that tesamorelin is associated with a statistically significant decrease in visceral adipose tissue, the clinical significance of which is unclear. There is no evidence to show that a decrease in visceral adipose tissue is associated with improved medication adherence, morbidity or mortality in HIV-infected patients with lipodystrophy. Tesamorelin also requires daily subcutaneous administration and the effect is not maintained following discontinuation.

Recommendations: Require a prior authorization for approved OHP diagnoses only.

BACKGROUND/CURRENT LANDSCAPE:

Highly active antiretroviral therapies (HAART) are considered the standard of care in HIV-infected patients who require treatment. Treatment with HAART has clearly demonstrated significant reductions in HIV-associated morbidity and mortality but is not without adverse effects. Patients receiving treatment with HAART, and especially protease inhibitors, are at high risk for development of HIV-associated lipodystrophy, which is characterized by changes in lipid composition, insulin resistance, diabetes mellitus, and fat redistribution.[3-6] There is no standardized definition for diagnosing HIV-associated lipodystrophy, so estimations of its prevalence range from 5-83% of patients using protease inhibitors. Disease prevalence for patients using nucleoside reverse transcriptase inhibitors is not available.

The long-term implications of lipodystrophy are not known, but there is concern that an increase lipid abnormalities is linked to an increase in the risk of cardiovascular disease. There have been some studies that suggest there is a relationship between the degree of coronary artery disease and the amount of visceral fat deposition, but none of these studies were conducted in HIV-positive patients using HAART, and many of the studies included patients who had additional risk factors for cardiovascular disease (e.x. diabetes, impaired glucose tolerance, hypercholesterolemia). Nonetheless, there is no clear association between lipodystrophy in HIV-infected patients and cardiovascular disease. [1, 3-6]

Until the approval of tesamorelin, there was no FDA-approved treatment for lipodystrophy in HIV-infected patients. Patients who developed intolerable fat distribution may have been switched to an alternative HAART regimen. Hypertriglyceridemia may be treated with a fibrate or peroxisome proliferator-activated receptor (PPAR) agonist. GHRH has lipolytic properties and studies have shown positive changes in fat distribution in HIV-infected patients, however any improvement seen on fat distribution was reversed upon discontinuation of growth hormone. Tesamorelin is a synthetic growth hormone-releasing factor analog that has been approved for the use of HIV infected patients with lipodystrophy.[1]

CLINICAL PHARMACOLOGY:

Tesamorelin acts on pituitary cells in the brain to stimulate the synthesis and release of endogenous growth hormone, causing increases in insulin-like growth factor I and insulin-like growth factor binding protein 3.[1]

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:

1) Mortality

2) Major cardiovascular events

3) Compliance with anti-retroviral therapy measured by the proportion of days covered (PDC) ratio.

4) Rate of treatment related adverse events

Study Endpoints:

1) Primary endpoint: Percent change in the visceral adipose tissue (VAT) from baseline to week 26.
2) Percent change in insulin-like growth factor 1 (IGF-I)
3) Body image – determined by questionnaire in which subjects rate their belly size, belly image distress, and belly profile.
4) Percent change in biochemical indices – Lipid levels [triglycerides, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol], glucose, insulin and free testosterone.

Extension phase:

1) Primary endpoint was safety
2) Secondary efficacy endpoints: 52-week efficacy endpoints (% change in VAT, IGF-I, biochemical indices and body image survey scores).

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH[3]	Quality Rating[4]; Comments
1.Falutz 2007[7,8] RCT, DB, PC, MC	1. Tesamorelin 2mg SQ daily 2. Placebo	HIV+ patients stable on ART for ≥ 8 weeks with evidence of abdominal fat accumulation defined as a waist circumference of ≥ 95 cm and a waist-to-hip ratio of ≥ 0.94 for men and a waist circumference of ≥ 94 cm and a waist-to-hip ratio of ≥0.88 for women. More patients in the tesamorelin group had received non-nucleoside reverse-transcriptase inhibitors (53.7 vs 41.6, p=0.03) **Exclusion Criteria:** Type 1 or 2 diabetes, serum creatinine >1.5, elevated liver enzymes, history of malignancy, untreated hypothyroidism or hypertension	N=412 Randomized 2:1, tesamorelin:placebo (PBO) Tx: n=275 PBO: n=137 Extension Phase (randomized 3:1) T-T: n=154 T-P: n=50	RCT – 26 weeks Extension phase (6 months) – subjects who remained in the trial for the extension phase were re-randomized 3:1 t receive tesamorelin or placebo.	• **% Δ VAT** Tx: -15.2% PBO: 5.0% Diff -32.9%, 95% CI (-40.7 to -25) p<0.001 • **% Δ IGF-I** Tx:81 PBO:-5.0 Diff: 125; 95% CI (105 to 146) p<0.001 • **% Δ Total cholesterol** Tx: -3.3 PBO: -0.7 p=0.02 • **% Δ fasting glucose** Tx: 3.7 PBO: 1.6 p=0.28 EXTENSION PHASE • **% Δ VAT** T-T: 17.5% p<0.001 T-P: 1.3% p=0.432	NA NA NA NA NA NA	% patients experiencing any AE: Tx: 82.8 PBO:75.2 p=0.09 % patients experience treatment-related AE: Tx: 53.8 PBO: 36.5 p=0.001 Withdrawals due to adverse events: Tx: 12.1 PBO: 2.9 p=0.002 EXTENSION PHASE: # withdrawn due to adverse events: T-T: 2 patients T-P: 4 patients	NA ARR: 17.3% NNH: 6 ARR: 9.2% NNH: 11	The study lacked a thorough description of randomization. Rates of adverse events were high in both study groups, but may be attributed to the nature of the disease of patients included in the trial. Treatment groups had significantly different HAART regimens at baseline. Efficacy endpoints for VAT and cholesterol remained significantly superior to placebo after controlling for increased NNRTI use in the treatment group. Antibodies developed in 50% of tesamorelin treated patients, the long-term implications of this are unknown. The primary endpoint is used as a surrogate marker of cardiovascular outcomes, for which there is limited evidence to support. Patients intolerant to tesamorelin likely discontinued treatment prior to re-randomization for the extension phase. This may contribute to the low withdrawal rate seen in the extension phase. LOCF used for subjects who didn't complete the study Initial phase, drop-out rates: 22.7% for tesamorelin 16.1% for placebo

Falutz, et al[9] RCT, DB, PC	1. Tesamorelin 2mg SQ daily 2. Placebo Extension Phase: 1) Tesamorelin 2mg SQ daily (T-T) 2) Placebo (T-P)	HIV+ patients stable on ART for ≥ 8 weeks with evidence of abdominal fat accumulation defined as a waist circumference of ≥ 95 cm and a waist-to-hip ratio of ≥ 0.94 for men and a waist circumference of ≥ 94 cm and a waist-to-hip ratio of ≥0.88 for women. Baseline characteristics similar between groups. Exclusions Criteria: Type 1 or 2 diabetes, serum creatinine >1.5, elevated liver enzymes, history of malignancy, untreated hypothyroidism or hypertension	N=404 Randomized 2:1, tesamorelin:PBO Tx: n=270 PBO: n=126 Extension Phase (randomized 1:1) T-T: n=92 T-P: n=85	RCT – 26 weeks Extension phase (6 months) – subjects who remained in the trial for the extension phase were re-randomized 3:1 to receive tesamorelin or placebo.	• **% Δ VAT** Tx: -10.9% PBO: -0.6% p<0.001 • **% Δ IGF-I** Tx:85.8 PBO:5.6 p<0.001 • **% Δ Total cholesterol** Tx: 2.1 PBO: 3.9 p=0.10 • **% Δ fasting glucose** Tx: 3.2 PBO: 2.7 p=0.15 EXTENSION PHASE • **% Δ VAT** T-T: 17.5% p<0.001 T-P: 1.3% p=0.432	NA	% patients experiencing any AE: Tx: 74.1 PBO:69.8 p=0.398 % patients experience treatment-related AE: Tx: 53 PBO: 37.3 p=0.005 % Withdrawals due to adverse events: Tx: 10 PBO: 8.7 p=0.855 EXTENSION PHASE: % patients experiencing any AE: T-T: 73.9% T-P:57.6% Withdrawals due to adverse events: T-T: 2.2% T-P: 4.7%	NA ARR: 15.7% NNH: 7 NA	Despite the reduction in VAT, glucose levels were not improved. The author suggests this is due to possible disruption of insulin functionality but this is counterbalanced by the improvement in VAT. There was no significant impact on triglyceride levels as seen in previous trials. This could be related to lower baseline TRG levels or variation in diets for patients treated at European centers. There is no evidence to show that improved body image distress correlates with improved adherence. The primary endpoint is used as a surrogate marker of cardiovascular outcomes, for which there is limited evidence to support. Adverse event rates were similar in the extension phase and in the primary phase. Patients intolerant to tesamorelin likely discontinued treatment prior to re-randomization for the extension phase. This may contribute to the low withdrawal rate seen in the extension phase. Initial phase, drop-out rates: 25% for tesamorelin 27% for placebo

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Summary of Findings –

Tesamorelin was studied in two phase 3 trials that were identical in study design. Each randomized, placebo-controlled trial included patients with HIV who were stable on antiretroviral therapy for at least 8 weeks, and randomized them 3:1 to receive tesamorelin 2mg subcutaneously daily or placebo for 26 weeks. After 26 weeks, patients were re-randomized to tesamorelin or placebo for a 26 week extension phase. For both studies, the primary efficacy endpoint was the change in visceral adipose tissue (VAT) from baseline to week 26, measured by computerized tomographic (CT) scan.

A secondary endpoint was the impact on body image perception measured by a questionnaire in which subjects rated their belly size [from thinner (-100) to much bigger (+100)], belly image distress [extremely distressing (0) to extremely encouraging (100)], and belly profile by choosing from 6 silhouettes. Other secondary endpoints included changes in lipid levels and biochemical measures such as Insulin-like growth factor I (IGF-I) and blood glucose. The goal of the extension phase was to assess the long term safety of tesamorelin and evaluated effects on glucose, insulin, and body image.

Both studies saw a statistically significant change in VAT in patients treated with tesamorelin (-15.2% and -10.9%) compared to placebo (+5.0% and -0.6%, $p<0.001$ for both trials). Efficacy endpoints from the extension phases indicate that this decrease in VAT is not maintained after treatment discontinuation and these results were not seen in patients switched to placebo in the extension arm. Both studies also found no significant difference in the change in body mass index (BMI) after 26 weeks when comparing patients treated with tesamorelin versus placebo. In one study (2010), the BMI slightly increased in patients treated with tesamorelin (+0.6%).

The impact of tesamorelin on lipid levels slightly varied between the two studies. In the earlier study, there was a significant difference in the change in triglycerides when comparing tesamorelin to placebo (-7.5% vs +11.6%, $p<0.001$). Additionally, the change in the ratio of total cholesterol to HDL cholesterol was -4.7% in the tesamorelin group compared to +6.1 in the placebo group, $p<0.001$). In the second study, the change in triglycerides was not significant when compared to placebo (+2.8% vs +7.6%, $p=0.10$), and patients in the tesamorelin group actually saw a slight increase in triglyceride levels. There was also no difference in the change in ratio of total cholesterol to HDL cholesterol (+1.5% in the tesamorelin group vs +5.0% in the placebo group, $p=0.10$).

Despite a very small change in waist circumference in either study (-2.2cm and -2.6cm), as well as no difference in questionnaire scores for "belly size" after 26 weeks, there was a significant change in patient scores for "belly image distress." Biochemical measures showed that patients treated with tesamorelin saw an increase in IGF-I (+81% and +85.8%) but had little impact on fasting glucose levels (+3.7% and +3.2%).

Overall, rates of adverse events and any serious adverse events were high, but similar between the two treatment groups, which may be due to the nature of the disease in this patient population. In the earlier study, 53.8% of patients treated with tesamorelin experienced treatment-related side effects compared to 36.5% treated with placebo, and 12.1% of tesamorelin-treated patients discontinued the study. The most common adverse

events were headache, arthralgias, injection-site bruising, diarrhea, peripheral edema, myalgia, and limb pain. These results were consistent with safety results seen in the second study, with the exception being that there was no significant difference in the percent of patients who discontinue the study due to adverse events (10% tesamorelin vs 8.7% placebo, p=0.855).

After 26 weeks of treatment, the mean HbA1c was higher among patients treated with tesamorelin compared to placebo; the mean treatment difference for patients receiving tesamorelin was +0.12% (p=0.0004) while the HbA1c of patients in the placebo group did not change from baseline. Patients in the tesamorelin group had an increased risk of developing diabetes compared to placebo [4.5% vs 1.3%, HR 3.3 (1.4,9.6)].

In the first extension phase, there were 154 patients who were treated with tesamorelin for the entire 52 weeks. Rates of adverse events were lower than those seen in the initial efficacy phase at the end of 26 weeks. Overall, 57.8% of patients experienced any adverse event, 14.3% experienced treatment-related adverse events, and 2.6% discontinued the study. These are similar to the results seen in the extension phase of the second study. In this study, 92 patients were treated with tesamorelin for the entire 52 weeks, and 73.9% experienced an adverse event, 37% experienced an adverse event related to the study treatment, but only 2.2% resulted in study discontinuation. These are slightly lower than the rates seen in the initial efficacy phase of the trial (2010).

DRUG SAFETY:

Contraindications[1,2]:

- patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, or pituitary tumor/surgery, head irradiation or head trauma
- active malignancy
- known hypersensitivity to tesamorelin and/or mannitol
- pregnancy

Warnings and precautions[1,2]:

Neoplasms: Patients with a history of non-malignant neoplasms should only begin tesamorelin treatment after careful evaluation of the potential benefit of treatment. The decision to start treatment with tesamorelin should be considered carefully based on the increased background risk of malignancies in HIV-positive patients.

Elevated IGF-1: The impact of elevated IGF-1 levels on the development of malignancies is unknown. Careful consideration should be given to discontinuing tesamorelin in patients with persistent elevations in IGF-1 levels.

Fluid retention: Fluid retention may result in a variety of adverse reactions which are either transient or will resolve with discontinuation of treatment.

Glucose intolerance: Tesamorelin treatment may result in glucose intolerance. An increased risk of developing diabetes with tesamorelin relative to placebo was observed in clinical trials [HR 3.3 (1.4,9.6)]. Therefore, glucose status should be carefully evaluated prior to initiating tesamorelin treatment. Patients should be monitored periodically for changes in glucose metabolism to diagnose those who develop impaired glucose tolerance or diabetes.

Hypersensitivity reactions: Hypersensitivity reactions included pruritus, erythema, flushing, urticaria, and other rash. In cases of suspected hypersensitivity reactions, patients should be advised to seek prompt medical attention and treatment should be discontinued immediately.

Injection site reactions: Reactions include injection site erythema, pruritus, pain, irritation, and bruising. In order to the incidence of injection site reactions, it is recommended to rotate the site of injection to different areas of the abdomen.

Acute critical illness: Increased mortality was see in patients with acute critical illness due to complications following open heart surgery, abdominal surgery, or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of growth hormone. Tesamorelin has not been studied in patients with acute critical illness.

Tolerability: During the initial treatment phase of clinical trials, discontinuations as a result of adverse reactions occurred in 9.6% of patients receiving tesamorelin and 6.8% of patients receiving placebo. The most common reasons for discontinuation of tesamorelin treatment were adverse reactions due to the effects of growth hormone (4.2%) and local injection site reactions (4.6%). Dueing the 26-week extension phases, discontinuations as a result of adverse events occurred in 2.4% of patients in the T-T group and 5.2% of patients in the T-P group.

Pregnancy/Lactation rating: Pregnancy category X. Visceral adipose tissue increases during pregnancy and modifying this offers no known benefit and may result in fetal harm. Administration to rats during organogenesis and lactation produced hydrocephaly in offspring at a dose 2-4x higher than the clinical dose.

Unanswered safety questions:
IGF-1 is a growth factor and the effect of prolonged elevations in IGF-1 levels on the development or progression of malignancies is unknown. Additionally, since tesamorelin increases IGF-1, patients with diabetes who are receiving ongoing treatment with tesamorelin should be monitored at regular intervals for potential development of worsening of retinopathy.

Dose Index (efficacy/toxic): Not applicable

Look-alike / Sound-alike (LA/SA) Error Risk Potential
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for [generic]	temisirolimus				
LA/SA for [brand]					

Incidence of patients (%) with adverse drug reactions		
Adverse Events (1) **(MedDRA System Organ Class and Preferred Term)**	**Tesamorelin**	**Control**
Number of Patients	543	263
Musculoskeletal and connective tissue disorders		
Arthralgia	13.3	11.0
Pain in extremity	6.1	4.6
Myalgia	5.5	1.9
Musculoskeletal pain	1.8	0.8
Musculoskeletal stiffness	1.7	0.4
Joint stiffness	1.5	0.8
Muscle spasms	1.1	0.8
Joint swelling	1.1	0
General disorders and administration site conditions		
Injection site erythema	8.5	2.7
Injection site pruritus	7.6	0.8
Edema peripheral	6.1	2.3
Injection site pain	4.1	3.0
Injection site irritation	2.9	1.1
Pain	1.7	1.1
Injection site hemorrhage	1.7	0.4
Injection site urticaria	1.7	0.4
Injection site swelling	1.5	0.4
Injection site reaction	1.3	0.8
Chest pain	1.1	0.8
Injection site rash	1.1	0.0
Nervous system disorders		
Paresthesia	4.8	2.3
Hypoesthesia	4.2	1.5
Carpal tunnel syndrome	1.5	0
Gastrointestinal disorders		

Nausea	4.4	3.8
Vomiting	2.6	0
Dyspepsia	1.7	0.8
Abdominal pain upper	1.1	0.8
Cardiac disorders		
Palpitations	1.1	0.4
Psychiatric disorders		
Depression	2.0	1.5
Skin and subcutaneous tissue disorders		
Rash	3.7	1.5
Pruritus	2.4	1.1
Night sweats	1.1	0.4
Vascular disorders		
Hypertension	1.3	0.8
Injury, poisoning and procedural complications		
Muscle strain	1.1	0
Investigations		
Blood creatine phosphokinase increased	1.5	0.4

DOSE & AVAILABILITY: [1,2]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
1mg	vial	SQ	2mg once daily	N/A	N/A	Not studied	Not studied	None

PHARMACOKINETICS: [1,2]

Parameter	Result
Bioavailability	4%
Cmax	2822.3 pg/mL
Protein Binding	Not reported
Elimination	Not reported
Half-Life	38 minutes in HIV-infected patients
Metabolism	Not studied in humans

ALLERGIES/INTERACTIONS:[1,2]

Drug-Drug:

Possible interactions with CYP P450 metabolized drugs. Monitor during concurrent use with tesamorelin.

Patients receiving glucocorticoid replacement for hypoadrenalism may require an increase in maintenance or stress doses following initiation of tesamorelin.

Food-Drug: None

Allergy/Cross Reactive Substances: None

Suggested PA

Tesamorelin (Egrifta)

Goal(s):

- Cover for only OHP covered diagnoses.
- Restrict to indications supported by medical literature.

Length of Authorization: 6 months

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Is the diagnosis a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy?	Yes: Go to #3	No: Pass to RPH; Deny (medical appropriateness).
3. Is the diagnosis an OHP covered diagnosis?	Yes: Approve for 6 months	No: Pass to RPH; Deny, (Not covered by the OHP).

REFERENCES:

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2. "FDA Summary Review: Tesamorelin". Center for Drug Evaluation and Research, November 9, 2010.

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Amylin Analog

Initiative: To optimize the correct use of amylin analogs.
Length of Authorization: Up to 1 year

Preferred Alternatives: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA: Pramlintide (Symlin®).

Approval Criteria		
1. Does the patient have a diagnosis of Type1 diabetes and is taking mealtime insulin?	**Yes:** Approve for 1 year	**No:** Go to #2
2. Does the patient have Type 2 diabetes and is taking mealtime insulin?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/main.html	**No:** Go to #4.
4. Has the patient tried and failed metformin **and** sulfonylurea therapy or have contraindications to these treatments? Contraindications include: - Renal disease or renal dysfunction - Know hypersensitivity to metformin - Acute or chronic metabolic acidosis - Patients at increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) Contraindications to sulfonylureas: - Known hypersensitivity	**Yes:** Approve for up to 1 year.	**No:** Pass to RPH; Deny (medical appropriateness). **Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.**

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: *3/17/11(KS), 4/26/12 (KS)*
Revision(s): *1/31/12 (KS)*
Initiated:

Incretin Enhancers

Initiative: Optimize the safety and efficacy of incretin enhancer use.

Length of Authorization: Up to 1 year

Preferred Alternatives: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA: sitagliptin (Januvia®), sitagliptin/metformin (Janumet®), saxagliptin (Onglyza®) and saxagliptin/metformin (Kombiglyze XR®), linagliptin (Tradjenta®), linagliptin/metformin (Jentadueto®).

Approval Criteria		
1. Does the patient have a diagnosis of type 2 diabetes?	**Yes:** Go to #2	**No:** Pass to RPH; Deny (medical appropriateness)
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/main.html	**No:** Go to #3.
3. Has the patient tried and failed metformin **and** sulfonylurea therapy or have contraindications to these treatments? Contraindications to metformin: - Known hypersensitivity - Renal disease or renal dysfunction - Acute or chronic metabolic acidosis - Increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) Contraindications to sulfonylureas: - Known hypersensitivity	**Yes:** Approve for up to 1 year.	**No:** Pass to RPH; Deny (medical appropriateness) **Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.**

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: *3/17/11 (KS), 4/26/12 (KS)*
Revision(s):
Initiated: *10/26/11 (KS)*

Incretin Mimetics

Initiative: To optimize the correct use of insulin mimetics.

Length of Authorization: Up to 1 year

Preferred Alternatives: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA: Exenatide (Byetta®) and Liraglutide (Victoza®), Exenatide Extended-Release (Bydureon®)

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	**No:** Pass to RPH; Deny (medical appropriateness)
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/main.html	**No:** Go to #3.
3. Has the patient tried and failed metformin **and** sulfonylurea therapy or have contraindications to these treatments? Contraindications to metformin: - Known hypersensitivity - Renal disease or renal dysfunction - Acute or chronic metabolic acidosis - Increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) Contraindications to sulfonylureas: - Known hypersensitivity	**Yes:** Go to #**4.**	**No:** Pass to RPH; Deny (medical appropriateness). **Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.**
4. Is the patient currently taking insulin?	**Yes:** Go to #5	**No:** Approve for up to 1 year.
5. Is the patient requesting exentatide (Byetta) and is taking insulin glargine?	**Yes:** Approve for up to 1 year.	**No:** Pass to RPH; Deny (medical appropriateness). The safety and efficacy of other insulin formations and GLP-1 Agonists have not been studied.

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: 3/17/11 (KS), 4/26/12 (KS)
Revision(s): 1/31/12 (KS)
Initiated:

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Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: April 2012
Generic Name: Linagliptin

End date of literature search: February 2012
Brand Name (Manufacturer): Tradjenta (Boehringer Ingelheim)
Dossier received: Yes
Comparator Therapies: Metformin, sulfonylureas, pioglitazone sitagliptin, saxagliptin, exenatide, liraglutide, pramlintide

PDL Class: Incretin Enhancers
Preferred Agents: metformin, glimepiride, glipizide, glyburide, pioglitazone
Non-preferred Agents: sitagliptin, saxagliptin, exenatide, liraglutide, pramlintide

EXECUTIVE SUMMARY:

FDA Approved Indications: Linagliptin is a dipeptidyl peptidase-4 (DPP-4) Inhibitor used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1]

Background: Oral antidiabetic medications are the standard of care, after lifestyle modifications fail, to control glycemic levels in patients with type 2 diabetes. Metformin is widely considered as the first line agent for patients requiring drug therapy. However, within three years of being diagnosed with type 2 diabetes, 50% of patients require combination therapy to control rising glucose levels.[2] American Diabetes Association (ADA) consensus recommendations for tier-1 agents include sulfonylureas and basal insulin. Thiazolidinediones and glucagon-like, peptide-1 (GLP-1) agonists are recommended as tier-2 agents. Because of their glucose lowering ability and cost alpha-glucosidase inhibitors, pramlintide, and dipeptidase-4 (DPP-4) inhibitors are considered third-line therapies.[3] Despite a variety of oral antidiabetic agents, many patients fail to meet HbA1c goals as well as experience troublesome side effects. Linagliptin is the third agent in the DPP-4 class which also includes sitagliptin and saxagliptin. Linagliptin has a modest glucose lowering effect , is generally well tolerated, considered to be weight neutral, needs no adjustment for impaired renal or hepatic disease and has a low incidence of hypoglycemia. Sitagliptin and saxagliptin require adjustments for renal function but do not require changes for reduced hepatic function. Sitagliptin has the least potential for drug interactions out of the three available DPP-4 agents. Studies with linagliptin are of short duration and have no conclusive evidence of improvement in mortality, macrovascular or microvascular outcomes.

Issues:

Key Questions:

1. Is linagliptin more effective than currently available preferred agents for the treatment of type 2 diabetes?
2. Is linagliptin better tolerated than currently available preferred agents?
3. Are there specific populations which linagliptin would be better tolerated or more effective?

Efficacy: Most studies of oral antidiabetic drugs evaluate intermediate outcomes, such as HbA1c and weight. Ideally, health outcomes such as mortality and macrovascular and microvascular events would be included. In the linagliptin studies the primary outcome was the adjusted mean change from baseline HbA1c, captured at 24 weeks.

Seven trials were submitted to the FDA for evaluation of efficacy, two studies comparing linagliptin to placebo and five studies comparing the addition of linagliptin to other antidiabetic therapies.[4, 5, 6, 7, 8] Four phase III, fair quality published studies are available for the evaluation of efficacy of linagliptin.[4, 5, 6, 7] The other three studies were not published and therefore were not peer reviewed and could not be appraised for risk of bias and quality but will be discussed briefly in the clinical efficacy section.

The four, fair quality published trials comparing linagliptin to placebo as monotherapy or as add-on therapy had similar study designs; patients with type 2 diabetes with mean baseline A1Cs between 8.0%-8.6% and a mean age 56-58 years.[4,5,6,7] Linagliptin was studied as monotherapy and found to be superior to placebo with an adjusted mean change from baseline A1C of -0.69 (95% CI -0.73 to -0.50, p<0.0001).[5] In the add-on trials linagliptin was compared to placebo when added to metformin, metformin and a sulfonylurea, or pioglitazone. All studies found add-on linagliptin to be superior to placebo add-on with adjusted mean treatment effect on HbA1c ranging from -0.51% to -0.64% for linagliptin.[4,6,7] Linagliptin decreased post-prandial glucose (PPG) levels more than placebo.[5,6] Linagliptin was weight neutral in all studies with the exception of the study by Gomis, et al., which the combination of pioglitazone and linagliptin resulted in a mean weight gain of 1.1kg over pioglitazone and placebo.[4] Lipid parameters were minimally affected by linagliptin with changes similar or less than placebo.[1]

There is no data on the relative efficacy and safety of linagliptin compared to sitagliptin or saxagliptin. The FDA summary reiterates the observation that HbA1c lowering was greater with metformin and sulfonylureas (glimepiride) than with linagliptin.[8]

Safety: Linagliptin was well tolerated with low levels of discontinuation rates due to adverse effects. Serious adverse events were similar in the linagliptin and placebo groups, 2.8% and 2.7%, respectively.[9] The most common adverse reactions that were greater for linagliptin compared to placebo were nasopharyngitis (5.9% and 5.1%) and cough (1.7% and 1.0%). Rates of hypoglycemia were similar to placebo and <1% in monotherapy studies. Higher rates of hypoglycemia were experienced in add-on studies with the greatest incidence occurring with the combination of linagliptin and a sulfonylurea, 22.7% and 14.8%, respectively.[7] Infection risk was similar or less than placebo. No dosage adjustment is required in renal or hepatic impairment.

Conclusions: There is moderate level of evidence to suggest that linagliptin is superior to placebo for glucose lowering as demonstrated by changes in HbA1c levels. There is moderate level of evidence that linagliptin is well tolerated with a low incidence of hypoglycemia and withdrawals due to adverse effects. There are no published head-to-head trials on comparative efficacy and safety of linagliptin to other antidiabetic medications.

The efficacy and safety evaluation of linagliptin was limited by studies of short term duration. Longer-term studies evaluating direct outcomes such as all-cause mortality, macrovascular and microvascular events would be helpful. Additionally, allocation concealment and randomization details were incomplete suggesting the potential for selection bias.

Linagliptin demonstrated reduced efficacy compared to established oral antidiabetic agents but proves to be an appropriate choice in those whom have contraindications to metformin and/or are concerned with hypoglycemia or weight gain associated with other oral antidiabetic treatments.

Recommendations:
It is recommended to use clinical prior authorization criteria to limit the use of linagliptin to patients that have tried and failed oral antidiabetic treatments that have a proven history of safety and efficacy as outlined in the PA criteria for Incretin Enhancers (appendix).

BACKGROUND/CURRENT LANDSCAPE

Three widely used clinical guidelines are available to guide the medical management of type 2 diabetes. The ADA incorporates study review and clinical judgment, with an emphasis on glucose-lowering ability and cost, into determining whether treatments are well-validated versus less well-validated therapies. In the 2012 ADA Standards of Medical Care in Diabetes Additions and Revisions, levels of evidence were included with recommendations, which used their own grading system ranking evidence A through E. The American Association of Clinical Endocrinologists (AACE)/ American College of Endocrinology (ACE) considers medical literature and the judgment of panel members into their recommendation, with a focus on benefits versus risks of treatments. No specific grading of evidence is included. The American College of Physicians (ACP) guidelines utilize an adaptation of the GRADE (Grading of Recommendations, Assessments, Development and Evaluation) workgroup to determine if the evidence is of high, moderate or low quality.

The ADA consensus panel recommends metformin as step 1 therapy [highest level of evidence grade (A)], followed by either a sulfonylurea or basal insulin for step 2. Less well validated tier 2 therapies include the addition of pioglitazone, a GLP-1 agonist, or pioglitazone and a sulfonylurea to step 1 recommendations. Step 3 recommendations include the addition of intensive insulin to step 1 treatments. The DPP-4 inhibitors are considered third line by the ADA, based on glycemic effectiveness and relative cost.[3] The AACE/ACE consensus panel considers DPP-4 inhibitors preferred agents, after metformin, as monotherapy or add-on therapy.[10] The ACP recommends metformin first line for monotherapy. Pooled results showed moderate strength of evidence that metformin had greater HbA1c lowering than DPP-4 inhibitors (mean difference, -0.37%, 95% CI

-0.54 to -0.20). Metformin was also recommended for combination therapies. The greatest HbA1c lowering was found with metformin + sulfonylurea (mean difference, 1.00%, 95% CI 0.75 to 1.25; high-quality evidence), followed by metformin + DPP-4 inhibitors (mean difference, 0.69%, 95% CI 0.56 to 0.82; moderate-quality of evidence) and lastly with metformin + thiazolidinedione (mean difference, 0.66%, 95% CI 0.45 to 0.86; high-quality of evidence).[11]

The Cochrane Review of DPP-4 inhibitors for type 2 diabetes mellitus reported no advantages of DPP-4 inhibitors over existing therapies (linagliptin not approved at time of review).[12] Data on mortality, diabetic complications as well as long term cardiovascular outcomes and safety data are lacking. Animal models suggest beta-cell preservation with chronic use of DPP-4 inhibitors but additional studies are needed to determine if this can be extrapolated to humans. DPP-4 inhibitors may be an option for patients close to their HbA1c goal and are unable to tolerate other hypoglycemic agents due to adverse effects, including hypoglycemia.

CLINICAL PHARMACOLOGY[1]

Linagliptin blocks the degradation of DPP-4, which is the enzyme responsible for degrading the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Linagliptin increases the available amount of active incretin hormones available which stimulates the release of insulin in a glucose-dependent manner and decreases the levels of glucagon in circulation.[1] It is suggested that linagliptin enhances beta-cell function due to the increases in GLP-1 availability, attenuating loss of glycemic control over time, however long-term studies are needed.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	30%
Protein Binding	70-99% (concentration dependent)
Elimination	80% enterohepatic in feces and 5% urine
Half-Life	12 hours
Metabolism	90% excreted unchanged

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints

All Studies: HbA1C and weight (intermediate outcomes)
Microvascular Disease
Macrovascular Disease
All-cause Mortality

Study Endpoints:

All Studies: A1C, weight

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
Study 15[4]									
Gomis, et al Phase III, PC RCT, DB, PG Multi-centre 7 Countries (No US sites	1. Pioglitazone 30mg + linagliptin 5mg daily 2. Pioglitazone 30mg + placebo * 6 week washout for patients previously on oral diabetic treatment (included 2 week placebo run-in) * 2 week placebo run-in for all patients	Age: 58 yrs Male: 61% Mean baseline A1C: 8.6% Inclusion: Treatment naïve or on one oral diabetic agent, 18-80 yr olds with type 2 DM, BMI $\leq$ 40 kg/m^2, and baseline A1C 7.5% to 11% in pretreated patients and 7% to 10% in treatment-naïve patients. Exclusion: Patients with a history of using a GLP-1 analogue or agonist, insulin or antiobesity drug within 3 months, hepatic, cardiac or cerebral vascular disease.	1. 259 2. 130	24 weeks	Adjusted mean change from baseline A1C: Pio + L (252): -1.06% Pio + P (128): -0.56% Adjusted mean treatment effect: -0.51% 95% CI -0.71 to -0.30 P<0.0001 Adjusted Mean Weight Gain: Pio + L: 2.3kg Pio + P: 1.2Kg Difference: 1.1kg 95% CI 0.2 to 2.0 P=0.014	NA	Hypoglycemia: P io + L: 5 (2%) Pio + P: 0 (0%) Discontinuation due to AE: Pio + L: 4 (1.5%) Pio +P: 6 (4.6%) RR: 0.33 95% CI 0.10 to 1.2		• Fair Quality • Baseline A1c higher at inclusion which could lend for greater A1c lowering effect. Results showed A1C changes were reduced to greatest extent in pt.s with higher baseline A1C values • Potential for assessment bias due to limited information on provider and assessor blinding • Rescue treatment needed in 7.9% of Pio + L and 14.1% in Pio +P • No reports of severe hypoglycemia
Study 16[5]									
Del Prato S, et al	1. Linagliptin 5mg QD	Age: 56 yrs Male: 48% Mean baseline A1C: 8%	1. 336	24 weeks	Adjusted mean change from baseline A1C: L (333): -0.44	NA	Hypoglycemia: L: 1 (0.3 %) P: 1 (0.6%)		• Fair • Allocation concealment details not discussed

Phase III, PC RCT, DB, PG Multi-centre 11 Countries FAS analysis with LOCF	2. Placebo * 6 week washout for patients previously on oral diabetic treatment (included 2 week placebo run-in) * 2 week placebo run-in for all patients	<u>Inclusion:</u> Treatment naïve or on one oral diabetic agent, 18-80 yr olds with type 2 DM, BMI $\leq$ 40 kg/m^2, and baseline A1C 6.5% to 9% in pretreated patients and 7% to 10% in treatment-naïve patients. <u>Exclusion:</u> Patients with a history of using rosiglitazone, pioglitazone, a GLP-1 analogue, insulin or antiobesity drug within 3 months, instability in thyroid dose, steroid use, hepatic, cardiac or cerebral vascular disease.	2. 167		P (163): 0.25 Adjusted mean treatment effect: -0.69% 95% CI -0.85 to -0.53 P<0.0001		RR: 0.50 95% CI 0.30 to 7.8 <u>Discontinuation du</u> <u>to AE</u>: L: 4 (1.2%) P: 4 (2.5%) RR: 0.50 95% CI 0.12 to 1.9		• No severe hypoglycemia events in either group • No significant changes in body weight in either group • Unclear if central adjudicators were blinded
Study 17[6]									
Taskinen M, et al Phase III, RCT, PC 82 Centers 10 Countries FAS analysis with LOCF	1. Metformin >1500mg/day + Linagliptin 5 mg once daily 2. Metformin >1500mg/day + Placebo * 4 week washout for patients previously on oral antidiabetic treatment	Mean Age: 57 yrs Male: 57% (P) and 53% (L) Mean baseline A1C: 8.1% DM for >5 yrs: 55% <u>Inclusion:</u> 18-80 yr olds with type 2 DM, BMI $\leq$ 40 kg/m^2, stable metformin dose of >1500 mg/day or ma tolerated dose and not more than one other oral DM medication and baseline A1C 7-10%.	1. 524 2. 177	24 weeks	<u>Adjusted mean change from baseline A1C</u>: M + L (513): -0.49% M + P (175): 0.15% Adjusted mean treatment effect: -0.64% 95% CI -0.78 to -0.50 P<0.0001	NA	<u>Hypoglycemia:</u> M + L: 3 (0.6%) M + P: 5 (2.8%) RR: 0.20 95% CI 0.05 to 0.84 <u>Discontinuation du</u> <u>to AE</u>: M + L: 8 (1.5%) M + P: 3 (1.7%) RR: 0.90 95% CI 0.24 to 3.4		• Fair • Allocation concealment and randomization details not discussed • Effect was greater in patients previously treated with one oral antidiabetic drug • As expected, A1C changes were reduced to greatest extent in patients with higher baseline A1C values • No significant changes in mean body weight in either group • Rescue medication was indicated for patients in the

	* 2 week placebo run-in for both groups	Exclusion Criteria: Patients with a history of using rosiglitazone, pioglitazone, a GLP-1 analogue, insulin or antiobesity drug within 3 months, instability in thyroid dose, steroid use, renal or cardiac disease, abnormal LFTs.							placebo group more often than linagliptin (19% vs. 8%) • No episodes of severe hypoglycemia • Unclear if central adjudicators were blinded • Both groups received dietary counseling which limits external validity.
Study 18[7]									
Owens, et al Phase III, DB, PG, PC, RCT Multi-centre 11 Countries FAS analysis with LOCF	1. Metformin ≥1500mg (or max tolerated dose) + sulfonylurea (max tolerated dose) + linagliptin 5mg once daily 2. Metformin ≥1500mg (or max tolerated dose) + sulfonylurea (max tolerated dose) + placebo * 2 week placebo run-in for both groups * Regimen of sulfonylurea and metformin	Mean Age: 58 yrs. Male: 47% Mean baseline A1C : 8% DM for >5 yrs: 73% Inclusion: Inclusion: 18-80 yr olds with type 2 DM, BMI $\leq$ 40 kg/m^2, metformin dose of >1500 mg/day or max tolerated dose and max tolerated dose of sulfonylurea, and baseline A1C 7-10%. Exclusion: Patients with a history of using rosiglitazone, pioglitazone, a GLP-1 analogue, insulin or antiobesity drug within 3 months, renal or cardiac disease.	1. 793 2. 265	24 weeks	Adjusted mean change from baseline A1C: M + S + L (778): -0.72 M + S + P (262): -0.10 Adjusted mean treatment effect: -0.62% 95% CI -0.73 to -0.50 P<0.0001	NA	Hypoglycemia: M + S + L: 180 (22.7%) M + S + P: 39 (14.8%) RR: 1.6 95% CI 1.1 to 2.1 Discontinuation du to AE: M + S + L: 23 (2.9%) M + S + P: 5 (1.9%) RR: 1.5 95% CI 0.60 to 4.0		• Fair • Allocation concealment and randomization details not discussed • As expected, A1C changes were reduced to greatest extent in pt.s with higher baseline A1C values • No meaningful changes in body weight occurred in either group • Severe hypoglycemia was greater in placebo group (4.8%) vs. linagliptin (2.7%) • Unclear if central adjudicators were blinded • Both groups received dietary counseling which limits external validity. • Details on sulfonylureas used and doses not provided. • Rescue treatment was more common in the placebo group compared to linagliptin (13% vs. 5.4%)

	were unchanged >10 weeks prior to enrolment								

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, FAS = full analysis set data, LOCF= last observation carried forward.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: A1C = hemoglobin A1c, Pio= pioglitazone

CLINICAL EFFICACY-

FDA efficacy approval of linagliptin was based on seven studies, 4 published and 3 unpublished. All published studies were phase III, PC, DB, PG, RCTs in over 2,600 patients with type 2 diabetes.[4,5,6,7] The studies were similar in respect to mean age of the patient populations (56-58 years) and mean baseline HbA1cs (8.0%-8.1%) in three studies, with the study by Gomis, et al, having a slight higher baseline value (8.6%). Studies required a 2 week placebo run-in for all groups. Three of the four studies employed a 4 week washout for patients on prior oral antidiabetic treatments, the forth study continued patients on their previous regimens of metformin and a sulfonylurea; therefore this did not necessitate a washout period. The primary outcome was an intermediate measure, adjusted mean change from baseline HbA1c for all studies. Secondary outcomes included fasting plasma glucose, postprandial glucose, weight and beta-cell function. Health outcomes such as all-cause mortality and macrovascular and microvascular disease were not studied. FDA requirements for cardiovascular outcome analysis is ongoing.[8]

Linagliptin 5mg once daily was studied as monotherapy in a fair quality study by Del Prato, et al.[5] The study population included patients treated previously with oral antidiabetic agents (mean baseline A1C 6.5%-9.0%) and treatment naïve patients (mean baseline A1C 7.0%-10.0%). There was moderate strength of evidence that linagliptin was superior to placebo in lowering A1C (adjusted mean treatment effect -0.69%, 95% CI -0.85 to -0.53, p<0.0001). There was moderate-strength of evidence that rates of hypoglycemia were similar between linagliptin and placebo and both groups were weight neutral. There was moderate strength of evidence to suggest that discontinuation rates due to adverse effects were low and similar for linagliptin and placebo, 2.4% and 1.2%, respectively.

In a fair quality study by Gomis, et al, linagliptin 5mg daily was studied in combination with pioglitazone 30mg daily compared to pioglitazone 30mg daily and placebo.[4] The mean baseline HbA1c was 8.6%, which has been shown in other studies to produce greater glucose lowering compared to lower mean baseline levels. There was moderate strength of evidence that the addition of linagliptin to pioglitazone was superior to the addition of placebo to pioglitazone (adjusted mean treatment effect -0.51%, 95% CI -0.71 to -0.30, p<0.0001). There was moderate strength of evidence that there was statistically significant weight gain in the pioglitazone + linagliptin group compared to pioglitazone + placebo group (1.1kg, 95% CI 0.2 to 2.0, p=0.014). There was moderate strength of evidence that rates of hypoglycemia were similar between groups.

Linagliptin 5mg daily was studied with metformin (>1500mg/day or max tolerated dose) compared to placebo and metformin in a fair quality study by Taskinen, et al.[6] Inclusion criteria required that participants not be on more than one other oral antidiabetic medication besides metformin. There was moderate strength of evidence that linagliptin and metformin were superior to placebo and metformin with a mean treatment effect of -.64%, 95% CI -0.78 to -0.50, p<0.0001. There was moderate strength of evidence that hypoglycemia events were higher for the placebo and metformin group (2.8%) compared to linagliptin and metformin (0.6%), with no episodes of severe hypoglycemia in either group.

A fair quality study was conducted by Owens, et al, which included linagliptin 5mg daily with a sulfonylurea (specific drug and dose not provided) and metformin (1500mg/day or max tolerated dose) compared to placebo and a sulfonylurea (specific drug and dose not provided) and metformin (1500mg/day or max tolerated dose).[7] This study enrolled 73% of patients whom had had type 2 diabetes for greater than 5 years. There was

moderate strength of evidence that linagliptin + sulfonylurea + metformin was superior to placebo + sulfonylurea + metformin (adjusted mean treatment effect -0.62%, 95% CI -0.73 to -0.50, p<0.0001). There was moderate strength of evidence that hypoglycemia rates were higher in the group containing linagliptin (22.7%) compared to the placebo containing group (14.8%). Both groups had an increased incidence compared to other studies that did not contain a sulfonylurea. Severe hypoglycemia events were higher in the placebo + sulfonylurea + metformin group compared to the linagliptin + sulfonylurea + metformin group, 4.8% vs. 2.7%, respectively. Discontinuation rates due to adverse effects remained low with moderate strength of evidence to suggest that rates were similar between the groups (2.9% for linagliptin + sulfonylurea + metformin vs. 1.9% for placebo + sulfonylurea + metformin).

All of the above studies are limited by the abbreviated descriptions of allocation concealment and blinding methodology given to their double-blind design designation. Studies by Taskinen and Owens also failed to describe randomization details. This can produce assessment, performance and selection bias favoring linagliptin. All of the studies were 24 weeks in length providing only short term results, however, glucose lowering by linagliptin was maximized by weeks 6-8 and sustained throughout the duration of the study. These results suggest that linagliptin would provide continued efficacy beyond 24 weeks but long term studies are needed. The effect of linagliptin on direct health outcomes such as mortality and macrovascular and microvascular disease are unknown. Published studies are limited to placebo controlled comparisons. There is insufficient comparative efficacy and safety evidence comparing linagliptin to other antidiabetic agents.

Similar results were found in the unpublished studies used for FDA approval, as in the previously discussed studies.[8] A comparison of linagliptin 5mg daily to placebo demonstrated linagliptin being superior to placebo (-0.57, 95% CI -0.89 to -0.26). Linagliptin was studied as add-on therapy to a sulfonylurea compared to placebo add-on in patients with inadequate glycemic control. Linagliptin 5mg daily was found to be superior to placebo (-0.47, 95% CI -0.71 to -0.22). A non-inferiority, head-to-head comparison study of linagliptin 5mg was compared to glimepiride (initiated at 1mg and titrated up to a max of 4mg) in patients previously on other antidiabetic treatment(s) and maintained on metformin. Linagliptin was found to be non-inferior to glimepiride at an interim analysis of 52 weeks (0.20%, 97.5% CI 0.11 to 0.30).

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): Do not use linagliptin in patients with history of hypersensitivity to linagliptin.

Cautions: If linagliptin is used with an insulin secretagogue (e.g., sulfonylureas) it is recommended that the dose of the insulin secretagogue be lowered to avoid hypoglycemia. Linagliptin should not be used in patients with type 1 diabetes or for treating diabetic ketoacidosis. Linagliptin has not been studied with insulin.

Hypoglycemia: Linagliptin was associated with similar rates of hypoglycemia as placebo when not combined with a sulfonylurea. Highest rates of hypoglycemia were seen when linagliptin was used with a sulfonylurea background treatment, ranging from 4.8% to 23.7%.[8]

Pancreatitis: Linagliptin was associated with higher rates of pancreatitis than placebo, 8 vs. 0, respectively. When correcting for imbalances in group allocation, overall risk suggests an incidence of 1 per 538 patient-years.[8]

Adverse Effects: The most common adverse reaction reported in studies with linagliptin was nasopharyngitis, 5.8% vs. 5.5% for placebo. Adverse effects reported in ≥2% of patients in studies with linagliptin in combination with metformin, pioglitazone or a sulfonylurea include nasopharyngitis, hyperlipidemia, cough, hypertriglyceridemia and increased weight. In a 52 week study comparing linagliptin to glimepiride, with patients also on metformin therapy, adverse effects that occurred in ≥5% of patients in the linagliptin group were arthralgia, back pain and headache.

Tolerability (Drop-out rates, management strategies): Linagliptin was well tolerated in studies. Drop-out rates from adverse effects were low, ranging from 1.5% to 2.9%, not significantly different from placebo.

Pregnancy/Lactation rating: Linagliptin is rated as *Pregnancy Category* B. There are no well-controlled studies on using linagliptin in pregnant individuals. Use in pregnant women only if clearly needed. Caution is advised if used during nursing.

Unanswered safety questions: Efficacy in using linagliptin in patients under 18 years of age has not been studied. Cardiovascular (CV) outcome analysis by FDA was not able to conclude a protective or detrimental effect of linagliptin due to few events and therefore a postmarketing CV outcomes trial will be required. The safety and efficacy of using linagliptin with insulin has not been fully studied, however, ongoing studies using this combination are underway.

Lab Tests: Linagliptin resulted in increases in uric acid levels (1.3% in the placebo group versus 2.7% in the linagliptin).

Dose Index (efficacy/toxic): No dose adjustments are needed in patients with renal or hepatic impairment. Doses up to 100-fold in excess of linagliptin 5mg have been well tolerated.[7]

Look-alike / Sound-alike (LA/SA) Error Risk Potential: LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name (*Va monograph*)	**Lexi-Comp**	**USP Online**	**First DataBank**	**ISMP**	**Clinical Judgment**
LA/SA for linagliptin (generic)	None	None	None	None	Sitagliptin liraglutide
LA/SA for Tradjenta (brand)	None	None	None	None	Treanda Truvada

DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Linagliptin 5mg	Tablets	Oral	Once Daily	No adjustment needed	No adjustment needed	NA	NA	May be taken with or without food.

ALLERGIES/INTERACTIONS[1]

Drug-Drug:

Linagliptin efficacy may be reduced by concomitant administration of P-glycoprotein (P-gp) and CYP3A4 inducers (e.g. rifampin). Recommend using a different agent. Linagliptin is a weak to moderate inhibitor of CYP3A4. Linagliptin is a P-gp substrate and blocks P-gp mediated transport of digoxin at high concentrations. When linagliptin was administered with metformin, glyburide, pioglitazone, digoxin, warfarin and simvastatin no meaningful change in concentrations were observed.[8] In vivo studies suggest that linagliptin has a low propensity to cause drug interactions.

Food-Drug:

No food-drug interactions have been reported.

Allergy/Cross Reactive Substances:

Hypersensitivity reactions have been reported with linagliptin. Higher rates were demonstrated with linagliptin (0.7%) versus comparators (0.5%).

APPENDIX:

Incretin Enhancers (DPP-4 Inhibitors)

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

Length of Authorization: Up to 1 year

Preferred Alternatives: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA: sitagliptin (Januvia®), sitagliptin/metformin (Janumet®), saxagliptin (Onglyza®), saxagliptin/metformin (Kombiglyze XR®), linagliptin (Tradjenta®), linagliptin/metformin (Jentadueto®).

Approval Criteria		
1. Does the patient have a diagnosis of type 2 diabetes?	Yes: Go to #2	**No:** Pass to RPH; Deny (medical appropriateness)
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/main.html	**No:** Go to #3.
3. Has the patient tried and failed metformin **and** sulfonylurea therapy or have contraindications to these treatments? Contraindications to metformin: - Known hypersensitivity - Renal disease or renal dysfunction - Acute or chronic metabolic acidosis - Increased risk of lactic acidosis (CHF,	**Yes:** Approve for up to 1 year.	**No:** Pass to RPH; Deny (medical appropriateness). Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

advanced age, impaired hepatic function) Contraindications to sulfonylureas: - Known hypersensitivity	

Initiating Metformin

1. Begin with l	850 mg once per day.
2. After 5	wice per day (medication to be taken
bef	
3.	later time.
4.	twice per day bu iveness has been observed

day. Gas nal side effects ma dose that ca

yperglycemia in Type A Consensus Algorithm iation and Adjustment of

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New Dosage Formulation

Month/Year of Review: April 2012
Generic Name: Exenatide extended–release injection (EQW)
PDL Class: Incretin Mimetics
Preferred Agents: Metformin, glimepiride, glipizide, glyburide, pioglitazone
Non-preferred Agents: Sitagliptin, saxagliptin, exenatide, liraglutide, pramlintide

End date of literature search: February 2012
Brand Name (Manufacturer): Bydureon (Amylin Pharmaceuticals)
Dossier Received: Pending
Comparator Therapies: Metformin, sulfonylureas, pioglitazone sitagliptin, saxagliptin, exenatide, liraglutide, pramlintide

FDA Approved Indications: Exenatide extended–release, once weekly injection (EQW) is a glucagon-like peptide-1 (GLP-1) agonist approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. EQW is an extended release formulation of the twice daily injectable product exenatide (Byetta) which was FDA approved in 2005. The dose of EQW is a 2mg subcutaneous (SQ) injection once weekly at any time of day without regard to meals.[1]

Background: The GLP-1 analogues, which include EQW, twice daily exenatide and liraglutide, stimulate GLP-1 receptors to increase insulin production in response to glucose, which decreases postprandial glucagon release and slows gastric emptying. Exenatide immediate release was evaluated in the 2011 systematic review on newer drugs for the treatment of diabetes mellitus from the Oregon Drug Effectiveness Review Project (DERP).[2] There were no studies that examined the impact of exenatide therapy on long term health outcomes and four trials found moderate strength evidence that there is no significant difference between exenatide and insulin in reduction in HbA1c (range for exenatide -1.0% to -1.4%; range for insulin -0.9% to -1.4%). As labeling suggests, the GLP-1 analogues are not recommended as first line agents but in the appropriate patients they can be a useful option for optimizing glycemic control while promoting weight loss. The American Diabetes Association (ADA) considers the GLP-1 analogues tier-2 agents; helpful for those patients experiencing hypoglycemia or in which weight loss is important. Additionally, they suggest that GLP-1 analogues be used in conjunction with lifestyle modifications and metformin.[3] The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommends GLP-1 analogues as one of their preferred agents, after metformin, because of effectiveness and low risk of hypoglycemia, used alone or in a multi-drug treatment regimen. The AACE/ACE preference the GLP-1 analogues over the dipeptidyl peptidase-4 (DPP-4) inhibitors due to better postprandial glucose reductions and weight loss.[4] The American

College of Physicians (ACP) guidelines found low or insufficient evidence for efficacy of GLP-1 agonists without specific recommendations for use.[5] Animal studies suggest beta cell preservation and stimulation of beta cell proliferation, however, it is unknown if this can be expected in humans.[6]

Clinical Efficacy: EQW was studied as monotherapy and in combination therapy in two double-blind (DURATION-2 and DURATION-4) and three open-label studies (DURATION-1, DURATION-3, DURATION-5).[7,8,9,10,11] Studies included patients with type 2 diabetes and mean baseline HbA1c values of 8.3- 8.5%. Patients naïve to drug therapy and those on one or more anitdiabetic agents were included. The study durations ranged from 24 to 30 weeks. EQW was compared to twice daily exenatide, metformin, pioglitazone and sitagliptin. The primary outcome was change in HbA1c from baseline. No long-term data is available. No all-cause mortality, microvascular or macrovasular outcomes have been evaluated.

The two double-blind, double-dummy, placebo controlled, RCTs with EQW found similar results, with exception of the pioglitazone comparison arm. In DURATION-4 Patients were randomized to subcutaneous (SQ) EQW once weekly + oral placebo daily, metformin 2000mg/day + SQ placebo once weekly, pioglitazone 45mg/day + SQ placebo once weekly or sitagliptin 100mg/day + SQ placebo once weekly.[9] EQW was found to be noninferior to metformin, inferior to pioglitazone and superior to sitagliptin (Table1). EQW significantly decreased weight more than pioglitazone (-2.0kg for EQW vs. +1.5kg with pioglitazone, p<0.001) and sitagliptin (-2.0kg for EQW vs. -0.8kg for sitagliptin, p<0.001). In DURATION-2 EQW 2mg SQ + oral placebo once daily (n= 160) was compared to 100mg oral sitagliptin + placebo injection weekly (n=166) and 45mg pioglitazone + placebo injection weekly (n=165), with all groups on background metformin therapy.[7] Treatment with EQW resulted in greater HbA1c reductions compared to either sitagliptin or pioglitazone groups. Treatment differences for EQW compared to sitagliptin were -0.6% (95% CI -0.9 to -0.4, p<0.0001) and -0.3% (95% CI -0.6 to -0.1, p=0.0165) for EQW compared to pioglitazone (Table 2). Weight loss was greater with EQW than with sitagliptin or pioglitazone.

Table 1. Primary Outcome Results for DURATION-4[9]

Comparator Treatment	Mean reductions in HbA1c	Actual Treatment Difference EQW vs. Comparator	98.3% Confidence Intervals	P-value
EQW	-1.53%	----	-----	----
Metformin	-1.48%	-0.05%	-0.26 to 0.17	0.62
Pioglitazone	-1.63%	0.10%	-0.15 to 0.35	0.33
Sitagliptin	-1.15%	-0.38%	-0.62 to -0.13	<0.001

Table 2. Primary Outcome Results for DURATION-2[7]

Comparator Treatment	Mean reductions in HbA1c	Actual Treatment Difference EQW vs. Comparator	95%Confidence Intervals	P-value
EQW	-1.5%	----	----	----
Pioglitazone	-1.2%	-0.3%	-0.6 to -0.1	0.0165
Sitagliptin	-0.9%	-0.6%	-0.9 to -0.4	<0.0001

Safety: Studies found the most common adverse reactions (≥5%) to be nausea, diarrhea, headache, vomiting, constipation, injection site pruritus, injection site nodules and dyspepsia. EQW use was associated with a 4.9% (n=45) incidence of withdrawals due to adverse events compared to 4.9% (n=13) with exenatide twice daily and 2.0% (n=23) for comparator therapies.[1] Overall incidence of minor hypoglycemia associated with EQW (monotherapy and combination therapy) ranged from 1.3% to 3.7%, excluding studies with sulfonylureas. In trials with concomitant sulfonylurea therapy minor hypoglycemia rates ranged from 12.5-20%. No major hypoglycemia was reported in any study.[1]

EQW is not recommended for use with insulin. EQW may increase international normalized ratios (INR) in patients taking warfarin. It is recommended to monitor INR frequently if warfarin and EQW are to be administered concomitantly. EQW has a black box warning due to the potential for causing thyroid C-cell tumors in rats and for being contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Postmarketing reports have shown fatal and non-fatal hemorrhagic or necrotizing pancreatitis and renal impairment sometimes requiring hemodialysis and kidney transplant. EQW is not recommended to be used in patients with a history of pancreatitis, renal impairment (CrCl <30 mL/min), severe gastrointestinal disease or hypersensitivity reactions. Caution is advised when using in moderate renal impairment (CrCl 30-50 mL/min). Hypoglycemia risk increases when EQW is used in combination with sulfonylureas and dosage reduction is recommended.[1]

Conclusion: EQW has demonstrated efficacy of as a once weekly formulation of exenatide. Other than the obvious convenience of a once weekly preparation, EQW differs from twice daily exenatide by having a black box warning, due to thyroid C-cell tumor risk, and the ability to administer the weekly dose without regard to meals. Similar side effects are experienced by both formulations with the exception of injection site pruritus and injection site nodules associated with EQW and a higher incidence of nausea associated with twice daily exenatide (30% vs. 14%). Evidence suggests that EQW is similar in efficacy and safety to other currently available GLP-1 agonists, which are recommended as tier 2 agents. EQW is a treatment option for those patients whom hypoglycemia and weight gain are of concern and are unable to tolerate or experience treatment failure with tier 1 agents.

Recommendation: It is recommended to use clinical prior authorization criteria to limit the use of EQW to patients that have tried and failed antidiabetic treatments that have a proven history of safety and efficacy as outlined in the PA criteria for Incretin Mimetics (appendix).

APPENDIX:

Incretin Mimetics

Initiative: To optimize the correct use of insulin mimetics.

Length of Authorization: Up to 1 year

Preferred Alternatives: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA: Exenatide (Byetta®) and Liraglutide (Victoza®), Exenatide Extended-Release (Bydureon®)

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. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/main.html	**No:** Go to #3.
3. Has the patient tried and failed metformin **and** sulfonylurea therapy or have contraindications to these treatments? Contraindications to metformin: - Known hypersensitivity - Renal disease or renal dysfunction - Acute or chronic metabolic acidosis - Increased risk of lactic acidosis (CHF,	**Yes:** Go to #4.	**No: Deny. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.**

advanced age, impaired hepatic function) Contraindications to sulfonylureas: - Known hypersensitivity		
4. Is the patient currently taking insulin?	**Yes:** Go to #5	**No:** Approve for up to 1 year.
5. Is the patient requesting exentatide (Byetta) and is taking insulin glargine?	**Yes:** Approve for up to 1 year.	**No:** Deny. The safety and efficacy of other insulin formations and GLP-1 Agonists have not been studied.

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: 3/17/11 (KS), 4/26/12 (KS)
Revision(s): 1/31/12 (KS)
Initiated:

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Month/Year of Review: April 2012
Generic Name: Fidaxomicin
Dossier received: Yes

End date of literature search: February 2012
Brand Name (Manufacturer): Dificid® (Optimer Pharmaceuticals)
Comparator Therapies: Vancomycin, Metronidazole

Executive Summary:

FDA Approved Indications: Fidaxomicin is a macrolide antibacterial drug indicated for treatment of *Clostridium difficile* associated diarrhea (CDAD) in adults ≥ 18 years of age.[1]

Summary: *Clostridium difficile* infection (CDI) is a growing health care problem and a serious healthcare-associated infection that has continued to emerge over the past three decades. Current epidemic rates of CDI in the United States, Canada, and Europe have been associated with a hyper-virulent strain (BI/NAP1/027). This strain is associated with increased toxin production and increased mortality and morbidity.[2] Previously thought to be a disease of hospitalized patients, community-associated CDI is increasingly being recognized in children and adults with similar risk factors. The evidence used for many of the current guidelines is weak due to small studies often with a high risk of bias and frequently excluding patients with severe disease. The relative burden of CDI in nonhospital health-care settings remains unknown. In May, 2011, the FDA approved fidaxomicin for the treatment of CDAD. In December 2011, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review (CER) on the effectiveness of early diagnosis, prevention, and treatment of CDI that was updated to include one of the approval studies of fidaxomicin that was published at the time as well as the increasing amount of published treatment studies coinciding with the increased incidence and severity of CDI.[3] Fidaxomicin is a new antibacterial drug indicated primary for treatment of *Clostridium difficile*.

The authors of the AHRQ CER concluded that no antimicrobial is clearly superior for the initial cure of CDI. There was moderate-strength evidence that fidaxomicin and vancomycin did not differ for the outcome of initial cure but that recurrence was less frequent with fidaxomicin based on one high-quality study.[3] There was also moderate-strength evidence that outcomes did not differ between metronidazole and vancomycin in nonsevere disease and insufficient evidence to evaluate a difference in severe CDI. There was insufficient evidence to compare the risks of any particular antimicrobial with another one. Although guidelines recommend vancomycin as first line in severe disease, there is insufficient evidence to support that it is generally superior to metronidazole. However, there also appears to be clinical consensus to treat mild to moderate CDI with metronidazole, in part because of the concern that overuse of vancomycin may contribute to increasing pathogen resistance and cost considerations.[3]

Efficacy: Two phase III randomized, controlled, double-blind, identically designed clinical trials compared the efficacy of fidaxomicin 200 mg twice daily versus oral vancomycin 125 mg four times daily for 10 days in adult patients with a diagnosis of CDAD and history of ≤ 1 recurrence.[4, 5] The primary endpoint in both trials was the clinical response rate at the end of therapy. One trial was conducted in North America[4] and the second trial in North America and Europe.[5] Both trials demonstrated that fidaxomicin was noninferior to vancomycin in clinical cure rate with 88.2% of patients on fidaxomicin achieving clinical cure compared to 85.8% on vancomycin in one trial (RR 0.97 95% CI 0.91 to 1.04)[4] and 88% of fidaxomicin versus 87% vancomycin patients in the second trial (p=0.074).[5] Both trials also demonstrated a statistically significant difference in recurrence rates between the two groups. Recurrence rates were 15.4% for fidaxomicin versus 25.3% for vancomycin (p=0.005) in one trial and 12.7% for fidaxomicin versus 27% for vancomycin (p<0.001) in the second trial. However, in patients with the hyper-virulent strain, (approximately 40% of all isolates) there was no significant difference in recurrence rate between the two groups in either study.[4, 5] In a subgroup analysis, recurrence rates were significantly lower in fidaxomicin-treated patients who were >65 years old, had no prior episodes of CDAD, were not receiving concomitant antibiotics, and had a non-BI/NAP1/027 strain.

Safety: Rates of adverse and serious adverse events were similar in the fidaxomicin and vancomycin groups and both also had similar rates of discontinuations due to adverse events (5.9% in fidaxomicin compared to 6.9% for vancomycin group).[4,5] The most common adverse reactions associated with fidaxomicin treatment in clinical trials are nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%), and neutropenia (2%).[1] Both the AHRQ review and a recent systematic review from the Cochrane Collaboration found that although harms were often not reported with sufficient detail to compare risks associated with the antibiotics, adverse events were infrequent and transient and were generally not serious.[3,6] The safety and effectiveness of fidaxomicin has not been studied in patients younger than 18 years.[1]

Conclusions:

There is moderate strength evidence that there is no difference in clinical cure rate between fidaxomicin, vancomycin, and metronidazole. There is moderate strength evidence that recurrence occurs less frequently with fidaxomicin versus vancomycin. Current guidelines recommend metronidazole and vancomycin as the standard treatment options for *Clostridium difficile* infection.[7] However, a recent Cochrane review of clinical trials showed that there is no strong evidence to support current recommendations made by the guidelines.[6] Further head-to-head studies are needed in severe disease and to compare directly fidaxomicin to metronidazole. Therapy with fidaxomicin may provide value to patients at high risk of rehospitalization due to recurrence or other serious complications. It is still unknown how to best identify this patient population.

Recommendations:

- Recommend making fidaxomicin a non-preferred antimicrobial for CDI and requiring a documented trial of appropriate therapy of vancomycin (125mg oral four times daily) or metronidazole (500mg orally three times daily) for first recurrence or contraindication to therapy and excluding use of fidaxomicin in patients with severe, complicated CDAD (life-threatening or fulminant infection or toxic megacolon).
- Recommend adding oral metronidazole and oral vancomycin as preferred agents on the PDL for the treatment of CDI.
- Further evaluate comparative costs of therapy.

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BACKGROUND/CURRENT LANDSCAPE/SUMMARY

The incidence, mortality, and medical care costs of CDIs have reached historic highs. From 2000 to 2009, the number of hospitalized patients with any CDI discharge diagnoses more than doubled, from approximately 139,000 to 336,000.[2] Strategies for prevention should be initiated to reduce the incidence of CDI as many of these infections can be prevented.[2] *C. difficile* generally occurs after exposure to broad-spectrum antibiotics, but any antibiotic that disrupts the normal flora of the gut can increase susceptibility.[7] A recent drug safety communication was released by the FDA, notifying the public that the use of stomach acid drugs such as proton pump inhibitors may also be associated with an increased risk of C. difficile associated diarrhea (CDAD).[8] They are also reviewing the risk of CDAD associated with histamine H2 receptor blockers.[8] Recurrence of CDI occurs in approximately 20% of patients. After two recurrences, the risk that additional episodes will occur increases to 65%.[7] The treatment goals for CDI include resolution of diarrhea and other signs and symptoms, lack of disease recurrence, avoidance of colectomy, and no other serious sequelae of disease.

Oral metronidazole and vancomycin are the antibiotics most often used to treat CDI. Guidelines from the Society for Healthcare Epidemiology of America (SHEA) and The Infectious Diseases Society of America (IDSA) were updated in 2010 (prior to fidoxamicin's FDA approval for CDAD) and recommend metronidazole for initial episodes of mild to moderate diseases and oral vancomycin as the drug of choice for severe disease, using changing creatinine values and an abnormally high white blood cell count to define severity.[7] The usual duration of therapy is 10 to 14 days, although no well-performed studies have established the potential advantage of shortening or lengthening the course. Comparative clinical trials demonstrated equivalent rates of clinical cure for the two agents, but metronidazole is preferred for initial disease due to concerns regarding the emergence of vancomycin resistance and costs.[3] Overall, previous systematic reviews have concluded there is insufficient or low-strength evidence for any outcomes evaluating efficacy in severe CDI as many studies excluded these patients, although consensus guidelines recommend vancomycin as first line in severe disease. The only comparative evidence for vancomycin versus metronidazole in severe disease comes from a per-protocol subgroup analysis of 69 patients in a single trial. Although there was a statistically significant difference favoring vancomycin in the per-protocol and modified intention-to-treat analysis, there was no significant difference using a strict intention-to-treat analysis.[3]

A recent Cochrane systemic review from the Cochrane Collaboration aimed to evaluate the efficacy of antibiotic therapy for CDAD.[7] Out of the 15 studies included, 12 were rated as having a high risk of bias. In 3 studies (n=335), no statistically significant difference was found between vancomycin and metronidazole for symptomatic cure of CDAD. Symptomatic cure was achieved in 79% of patients in vancomycin group compared to 71% in metronidazole group (RR 0.91; 95% CI: 0.81-1.03).[7] The authors concluded that due to small number of patients, poor methodological quality studies, and exclusion of severe disease, a recommendation to achieve overall goals could not be made. Also, there was no statistical difference in bacteriologic cure between metronidazole and vancomycin in one study with 62 patients.

Clinical pharmacology

Fidaxomicin is a bactericidal macrolide antibiotic, primarily active against *Clostridium difficile*. The drug works by inhibiting bacterial RNA polymerase which stops RNA synthesis during transcription phase of protein synthesis. [1]

Pharmacokinetics:

Fidaxomicin has poor permeability and solubility; therefore it is minimally absorbed from the gastrointestinal tract. The drug is metabolized via hydrolysis to an active metabolite OP-1118. No CYP enzymes were found to play significant role in the metabolism of fidaxomicin or formation of OP-1118. The drug is primarily excreted in feces. Fidaxomicin fecal concentrations are detected up to 5 days after treatment.[12] The drug dosing does not need to be adjusted for decreased renal function, as there is <1% renal elimination. The impact of hepatic impairment on pharmacokinetics of fidaxomicin has not been evaluated because hepatic metabolism is not significant.[1] Table 1 in Appendix 1 compares pharmacokinetic parameters of fidaxomicin with other treatments for CDI including metronidazole and oral vancomycin.

COMPERATIVE CLINICAL EFFICACY

Relevant Endpoints

Initial Cure
Recurrence
Mortality

Study Endpoints:

Primary: Clinical Cure (resolution of symptoms and no need for further treatment)
Secondary: Recurrence (diarrhea and a positive result on a stool toxin test within 4 weeks after treatment)
Global Cure (cure with no recurrence)

Evidence table

Ref./ Study Design	Drug Regimens	Patient Population	N[5]	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results[2] (CI, p-values)	ARR / NNH	Quality Rating[4]; Comments
Louie et al., Phase III, DB, RCT[4] Study 003	F:Fidaxomycin 200mg PO BID V:Vancomicin 125mg PO QID	Adults with acute symptoms of CDI and a positive result on a stool toxin test in Canada and the USA. Mean age: 61.6 Female 55.9%, Inpatient 59.4%, Mean number of unformed stools/day: 8.2 **Inclusion: criteria:** • ≥16 y.o, *C.difficile* diagnosis (> 3 unformed stools in 24 h prior randomization, presence of toxin A, or both in stool within 48 h of randomization). **Exclusion criteria:** • Life-threatening *C.dificile* infection, Toxic megacolon, History of UC, Crohn's disease, >1 *C.difficile* infection within 3 months, Use of drugs to control diarrhea or those that affect paristalsis.	F: 302 V: 327	Treatment: 10 days Follow up: 30 days	**Initial Clinical Cure** Clinical cure: F: 253 (88%) V: 265 (85%) RR 0.97 95% CI (0.91 to 1.04) **Clinical Recurrence:** F: 39 (15%) V: 67 (25%) RR 0.6 95% CI (0.41 to 0.87) P=0.005 **Global Cure:** F: 214 (74.6%) V: 198 (64.1%) RR 1.16 95% CI (1.15 to 2.34) P=0.006	NS ARR 9.9% NNT 10 ARR 10.5% NNT 9.5	All-Cause Mortality F: 16 (5.3%) V: 21 (6.5%) P=0.6122 Any serious adverse event: F: 25% V:24.1% P=0.852 No subjects discontinued the study as a result of intolerance or allergy to medications	NS NS	Good; Adequate allocation concealment; double blinding, partially ITT analysis Total withdrawals and dropouts: 33 (5%) Funded by Optimer Pharmaceuticals. Intention-to-treat analysis: modified (subjects withdrawing before treatment, had ≤3 bowel motions in 24 hours, or tested negative for C. difficile toxin were excluded) Other medication use that can cause diarrhea not reported at baseline. Patients were allowed to use opioids during hospital stay. Opioid doses used by both groups not reported.

Cornely, et al. Phase III, DB RCT, PG[5] Study: 004	F: Fidaxomicin 200mg PO BID V: Vancomycin 125mg PO QID	Adults with acute symptoms of CDI and a positive result on a stool toxin test in Europe, as well as in Canada and the USA. Mean age: 63, Female: 60.9% **Inclusion: criteria:** • ≥16 y.o, *C.difficile* diagnosis (> 3 unformed stools in 24 h prior randomization, presence of toxin A, or both in stool within 48 h of randomization). **Exclusion criteria:** • Life-threatening *C.dificile* infection, Toxic megacolon, History of UC, Crohn's disease, >1 *C.difficile* infection within 3 months, Use of drugs to control diarrhea or those that affect paristalsis.	F: 270 V: 265	Treatment: 10 days Follow up: 28 days after treatment	**Clinical Cure:** F: 221 (87.7%) V: 223 (86.8%) P=0.754 **Recurrence:** F: 28 (12.6%) V: 60 (27%) RR 0.5 *P*=0.0002 **Global cure**: F: 193 (76.6%) V: 163 (63.4%) RR 1.2 P=0.001	NS ARR 14.4% NNT 7 ARR 13.2% NNT 7	Serious adverse event: F: 70 (26.5%) V: 58 (22.3%) Adverse events leading to discontinuation: F: 16 (6.1%) V: 16 (6.2%)	NS NS	Fair; Adequate allocation concealment; double blinding, partially ITT analysis Total withdrawals and dropouts: 79 (15%) Funded by Optimer Pharmaceuticals. Intention-to-treat analysis: modified (subjects withdrawing before treatment, had ≤3 bowel motions in 24 hours, or tested negative for C. difficile toxin were excluded) Some regional differences in the characteristics and responses of patients

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover. OP=open label. [2]**Results abbreviations**: ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval. [3]**NNT/NNH** are reported only for statistically significant results [4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
CA= concomitant antibiotic, UC=ulcerative colitis, N[5]= number randomized, 6=data from modified intention-to-treat population.

Clinical Efficacy:

In one good quality study and one fair quality study, fidaxomicin was shown to be non-inferior to vancomycin though it was also shown to have significantly lower rates of recurrence and higher rates of global cure. Study 003 enrolled subjects in the US and Canada, while study 004 enrolled subjects in Canada, the US, and Europe. Patients with severe, complicated CDAD were excluded from the clinical trials. Clinical cure was the principal comparison outcome between two treatments.[9] Clinical cure was defined as three or less unformed stools for 2 consecutive days, with maintenance of resolution for the duration of therapy and no further requirement for therapy as of the second day after the end treatment (10days).[9] Results for trial (003) published by Louie et al., showed clinical cure rate in modified intent-to-treat (mITT) population at 88.2% (253/287) in fidaxomicin group compared to 85.8% (265/309) in vancomycin group (RR 0.97; 95% CI 0.91 to 1.04).[4] The lower boundary of the 97.5% confidence interval for the difference of cure rates was at -3.1% points; therefore fidaxomicin met the non-inferiority criteria. [9] The results from trial (004) showed that cure rate for fidaxomicin group was at 86% (217/253) compared to 85% (219/256) in vancomycin group, respectively.[5,9]

In Study 003, Subgroup analyses of the rates of clinical cure according to the patients' age, inpatient vs. outpatient status, prior occurrence, treatment for *C difficile* infection vs. no treatment within 24 hours before the start of the trial, no response vs. response to previous metronidazole therapy and use vs. nonuse of concomitant systemic antimicrobial therapy showed no significant differences between treatments. In trial 004, more patients who received concomitant antibiotics for other infections during the study treatment period achieved clinical cure with fidaxomicin than with vancomycin (90.2% in fidaxomicin vs. 73.3% in vancomycin; p=0.031). For the secondary endpoints of recurrence and sustained

response, fidaxomicin was statistically superior to vancomyin only for patients receiving no concomitant antibiotics during the study. A follow-up study combined the results of these trials to investigate the association between concomitant use of antibiotics (CA) and recurrence rates.[10] Analysis of the pooled phase III data, demonstrated that recurrence rates were lower when patients who required CA were given fidaxomicin; a higher rate was seen in patients on antibiotics historically associated with a high risk of CDI recurrence. Use of concomitant antibiotics and CDI treatment was associated with a lower cure rate, 80% in concomitant antibiotic users versus 93% of nonusers (*P*<0.001). Clinical cure rates in the PP analysis were 87% in concomitant antibiotic users and 93% in nonusers in the fidaxomicin group, and 77% in concomitant antibiotic users and 94% in nonusers in the vancomycin group.[10]

In study 003, there was no significant difference in mean days to resolution of diarrhea (Vancomycin median 3.3 days vs. Fidaxomicin 2.4 days; p=NS). And there was no significant difference in all-cause mortality (7% in vancomycin group vs. 5% in fidaxomicin group). The majority of patients enrolled in the clinical trials were inpatients and the BI/NAP1/027 strain comprised approximately 40% of all isolates. Around 40% of patients in the 003 trial and 30% in the 004 trial were outpatient. In patients with the hyper-virulent strain, there was no significant difference in recurrence rate in either study (fidaxomicin 27.1% vs. vancomycin 20.9%, p=0.42 in study 003, and 22.2% vs. 38%, p=0.079 in study 004).

Safety:

Adverse events were not significantly different between fidaxomicin and vancomycin groups. The occurrence of any serious adverse event was at 25% in fidaxomicin group compared to 24.1% in vancomycin group in study 003.[1,4] However, the fidaxomicin group had significantly more adverse events related to laboratory tests at 4.7% compared to vancomycin group at 1.2% (P=0.01). According to a FDA medical review, which looked at data from both phase III trials, serious adverse events occurred at rate of 25.7% in fidaxomicin treated individuals compared to 23.2% in vancomycin patients.[9] The three severe adverse effects that occurred more frequently in fidaxomicin group were gastrointestinal hemorrhage, megacolon and decrease in WBC counts. Around 3 patients developed megacolon in fidaxomicin group compared to none in vancomycin. The most common adverse events reported in both groups during phase III trials were nausea, vomiting, hypokalemia, headache, abdominal pain, diarrhea, constipation and pyrexia. The incidence of abdominal pain, constipation and hypokalemia was higher in fidaxomicin group. In addition, the rate of deaths in both phase III trials was similar for both groups. Around 36 people died in fidaxomicin group (6.4%) compared to 38 in vancomycin group (6.5%).[9]

Table 3. Adverse event comparison between fidaxomicin and vancomycin[1,9]

	Fidaxomicin (N=564)	Vancomycin (N=583)
Anemia	14 (2.5%)	12 (2.1%)
Neutropenia	14 (2.5%)	6 (1.0%)
Lymphopenia	11 (1.9%)	5 (0.9%)
Gastrointestinal hemorrhage	20 (3.5%)	12 (2.1%)
Nausea	62 (11%)	66 (11.3%)
Vomiting	41 (7.3%)	37 (6.3%)
Constipation	25 (4.4%)	12 (2.1%)
Diarrhea	28 (5%)	39 (6.7%)
Abdominal pain	33 (5.9%)	23 (3.9%)
Hypokalemia	47 (8.3%)	38 (6.5%)
Headache	37 (6.6%)	27 (4.6%)
Pyrexia	24 (4.3%)	31 (5.3%)

Precautions/Contraindications:
Currently there are no contraindications listed for fidaxomicin. The drug should not be used for systemic infections. Also, fidaxomicin should be only used for treatment of *C.difficile* associated infection in order to avoid bacteria resistance. [1]

Tolerability:
According to the FDA review, a total of 57 patients (10.1%) in fidaxomicin group and 58 patients (9.9%) in vancomycin group were withdrawn from phase III trials due to treatment failure or adverse events.[9] During treatment phase in both phase III trials there were 22 patients (3.9%) in fidaxomicin group and 36 patients (6.2%) in vancomycin group who stopped the drug due to adverse event. Around 22 patients (3.9%) taking fidaxomicin and 17 patients (2.9%) taking vancomycin had discontinued therapy during follow-up in both phase III trials. [9]

Pregnancy/Lactation rating:
Pregnancy category B based from animal studies. However, no studies in pregnant women were done. Therefore, the manufacturer recommends using the drug during pregnancy only if clearly needed. It is unknown if fidaxomicin is excreted in milk. Nursing women should use the drug with caution. [1]

Dose Index (efficacy/toxic):
The greatest efficacy in CDI treatment was established with fidaxomicin 200mg twice daily in phase II trial. No drug-related adverse effects were seen in dogs dosed with fidaxomicin tablets at 9600 mg/day. [9]

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for [Fidaxomicin]	None Identified	None Identified	None identified	None Identified	Filgrastim
LA/SA for [Dificid]	None Identified	None Identified	None identified	None Identified	Difiram, Difil-G, Dilaudid, Dilacor XR, Denavir, Dynacin, Diflosid, Digifab,

Allergies/Interactions:

Drug-Drug: Fidaxomicin is poorly absorbed and metabolized primarily by esterase to an active metabolite. There are no known drugs in the market that cause clinically relevant drug interactions by inhibiting esterases; therefore the inhibition of metabolism of fidaxomicin is not anticipated. Fidaxomicin and its main metabolite are substrates of p-glycoprotein. Based on in vivo studies it was concluded that no dose adjustment is warranted when fidaxomicin is co-administered with substrates of p-glycoprotein or CYP enzymes. Also, fidaxomicin may be co-administered with p-glycoprotein inhibitors without dose adjustment. [1]
Food-Drug: Fidaxomicin may be taken with or without food. [1]

Dose and Availability: [1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
200mg	Tablet	Oral	Twice daily	None	None	Not recommended	Adjustment not recommended	None

Appendix 1:

Table 1. Pharmacokinetic comparison of fidaxomicin, metronidazole and vancomycin.

Parameters	Fidaxomicin[1]	Metronidazole[11]	Vancocin*[12,13]
Route of administration	Oral (PO)	Oral (PO)	Oral (PO)
Oral bioavailability	Minimal absorption from GI tract	80%	Poorly absorbed
Cmax (ng/mL)	5.20 + 2.81		
Protein Binding	N/A	< 20%	~ 50%-55%
Half-life (h)	11.7 for drug, 11.2 for active metabolite	~ 8 (range 6-12) Longer in neonates, hepatic and renal impairment.	4-6
Metabolism	Hydrolysis in intestine, has active metabolite	Hepatic (30%-60%)	No apparent metabolism
Elimination	Feces (> 92% unchanged drug, and metabolites).	Renal (60%-80% as unchanged drug), feces (6%-15%).	PO (feces)
Renal Impairment Dose Adjustment	Not recommended	GFR <10mL/min, reduce normal dose by 50% at usual interval.	Recommended
Hepatic Impairment Dose Adjustment	Not evaluated	Recommended for severe impairment	N/A
Food effect on pharmacokinetics	Not clinically significant. May take drug regardless to meals.	Lowers and delays peak concentration. No effect on total drug absorbed.	

*****The parenteral form of Sterile Vancomycin Hydrochloride may be administered orally for treatment of antibiotic-associated psuedomembraneous colitis produced by *C. difficile*. The appropriate dose may be diluted in 1 oz of water and given to the patient to drink. Common flavoring syrups may be added to the solution to improve the taste for oral administration. The diluted solution may be administered via a nasogastric tube.

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Class Update: Second Generation Antidepressant Medications

EXECUTIVE SUMMARY:

Month/Year of Review: April 2012
New Product for review: vilazodone (Viibryd®)
Manufacturer: Forest Laboratories, Inc.
Last Oregon Review: June 2011 (Oregon HRC)

Dossier received: Yes

Source Document: DERP

Table 1. Current Voluntary PDL Preferred/Non-Preferred Antidepressants

Current Preferred Agents:		Current Non-Preferred Agents:
BUPROPION HCL TABLET	MIRTAZAPINE TAB RAPDIS	OLANZAPINE/FLUOXETINE (SYMBYAX)
BUPROPION HCL TABLET ER	MIRTAZAPINE TABLET	Fluoxetine DF (PROZAC WEEKLY)
CITALOPRAM HYDROBROMIDE SOLUTION	PAROXETINE HCL TABLET	Duloxetine (CYMBALTA)
CITALOPRAM HYDROBROMIDE TABLET	SERTRALINE HCL ORAL CONC	EFFEXOR XR
FLUOXETINE HCL CAPSULE	SERTRALINE HCL TABLET	Desvenlafaxine (PRISTIQ)
FLUOXETINE HCL SOLUTION	VENLAFAXINE HCL TABLET	VENLAFAXINE ER
FLUOXETINE HCL TABLET		NEFAZODONE
FLUVOXAMINE MALEATE TABLET		Paroxetine HCL (PAXIL CR)

Reason for Review:[1-6]

The Oregon Evidence-based Practice Center drug effectiveness review project (DERP) published their fifth updated drug class review of second generation antidepressant in March 2011 that included data through September 2010. This was reviewed by the Oregon Health Resources Commission in June 2011 and their conclusions are listed in Appendix 1.[1] This and other previous comparative effectiveness reviews have found that second generation antidepressants do not differ significantly in efficacy of major depressive disorder (MDD). Since the last OR review, however, a new antidepressant, vilazodone (Viibryd®), has been FDA approved and an update to the comparative effectiveness review on second-generation antidepressants in the treatment of adult depression was completed by the Agency for Healthcare Research and Quality (AHRQ).[3] The evidence-based practice guidelines endorsed by the American Psychiatric Association have not been updated since 2010 for the treatment of major

depressive disorder.[4] This update will examine the place in therapy for vilazodone, and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines.

In addition, in August 2011, the FDA issued a Safety Alert regarding the link between abnormal heart rhythms and high dose citalopram (Celexa). Dose limits of 40mg/day have been advised.[5,6]

Issues:

- Is there any new evidence of effectiveness or harms that will support second generation antidepressant management strategies or changes?
- Is there any evidence that vilazodone is more effective or safer than currently available medications in the PDL drug class including subgroups of patients?
- What recommendations for management of the antidepressant class can be made? Should a dose limit be included for citalopram?

Conclusions

- Comparative efficacy and effectiveness of second-generation antidepressants does not differ substantially for treating patients with major depressive disorder (MDD). These findings pertain to patients in the acute, continuation, and maintenance phases; those with accompanying symptom clusters; and subgroups defined by age, sex, ethnicity, or comorbid conditions, although only sparse evidence for these findings exists for subgroups.
- There is fair quality evidence that vilazodone is safe and effective for the treatment of MDD based on short-term placebo controlled trials. There is insufficient evidence to determine comparative effectiveness of vilazodone compared to other antidepressant medications.
- There is insufficient evidence to determine the effectiveness of vilazodone in the maintenance treatment of MDD, for the treatment of generalized anxiety disorder or other indications, as well as in pediatric patients or patients with severe hepatic impairment.
- Citalopram causes dose-dependent QT interval prolongation. The FDA recommends that citalopram should no longer be prescribed at doses greater than 40 mg per day.

Recommendations:

1. 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.
2. Evidence does not support superiority of vilazodone over other agents in this drug class. Recommend that is be listed as a non-preferred agent.
3. Include a dose limit of 40mg/day for citalopram.
4. Due to the need for voluntary compliance with the PDL for this drug class, it is recommended that educational outreach interventions be considered in the management strategy.
    1. As an example, academic detailing can be use to promote appropriate utilization

I. Background

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) (with the exception of premenstrual disorder, which historically was untreated). TCAs and MAOIs sometimes are referred to as traditional or first-generation antidepressants. These drugs are often accompanied by multiple side effects that many patients find intolerable; e.g., TCAs tend to cause anticholinergic effects including dry mouth and eyes, urinary hesitancy, and sometimes retention and constipation and MAOIs have the potential to produce hypertensive crisis if taken along with certain foods or dietary supplements containing excessive amounts of tyramine. Thus, first-generation antidepressants are no longer agents of choice in many circumstances.

Newer treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other second-generation drugs that selectively target neurotransmitters. In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine. Since then, five other SSRIs have been introduced: sertraline, paroxetine, citalopram, fluvoxamine, and escitalopram. The SNRIs were first introduced to the market in 1993 and include venlafaxine, duloxetine, and most recently desvenlafaxine. Other agents used for treatment of MDD include, nefazodone,mirtazapine, and bupropion.

In general, these drugs work through their effect on prominent neurotransmitters in the central nervous system. The SSRIs act by selectively inhibiting the reuptake of serotonin (5-hydroxy-tryptamine, 5-HT) at the presynaptic neuronal membrane. The SNRIs are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Mirtazapine, sometimes characterized as an SNRI, is believed to enhance central noradrenergic and serotonergic activity as a 5-HT2 and 5-HT3 receptor antagonist, nefazodone is believed to inhibit neuronal uptake of serotonin and norepineprhine, and bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine. The recently approved antidepressant, vilazodone, combines properties of a SSRI with 5-hydroxytryptamine-1a ($5\text{-}HT_{1a}$) partial agonist activity. However, the clinical significance of this dual mechanism is unknown and it has not been shown to offer any unique efficacy or safety advantage over currently available treatments. Vilazodone is only approved and studied in the treatment of MDD, while other approved second generation antidepressants have multiple indications including GAD, social anxiety disorder, panic disorder, obsessive compulsive disorder, and post traumatic stress disorder.

SSRI's, SNRI's, and TCA's are also frequently recommended for the treatment of generalized anxiety disorder (GAD). In 2011, the National Institute for Health and Clinical Excellence (NICE) published a guideline on the management of adults with GAD in primary, secondary and community care.[7] These guidelines recommend that if drug treatment is needed, the most cost effective SSRI should be prescribed. NICE specifically recommends sertraline in the UK. If the first SSRI is not effective, recommendations include using an alternative SSRI or an SNRI, taking into account the side-effect profile and drug interaction potential, the risk of suicide and toxicity, and the tendency to produce a withdrawal syndrome when choosing an appropriate medication.

II. **Systematic Reviews**

AHRQ Comparative Effectiveness Review

The AHRQ review assessed evidence on comparative benefits and harms of second-generation antidepressants for treating acute, continuation, and maintenance phases of Major Depressive Disorder.[3] Overall, comparative efficacy and effectiveness of second-generation antidepressants did not differ substantially for treating patients with MDD. This included those with accompanying symptom clusters; and subgroups defined by age, sex, ethnicity, or comorbid conditions, although only sparse evidence for these findings exists for subgroups.
There was moderate quality of evidence that for acute phase treatment of MDD, clinical response and remission rates are similar among second-generation antidepressants. Consistent results from 17 mostly fair-quality studies indicate that the efficacy of second-generation antidepressants regarding quality of life does not differ among drugs. Consistent results from 7 fair-quality trials suggest that mirtazapine has a statistically significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline. Whether this difference favoring mirtazapine can be extrapolated to other second-generation antidepressants is unclear. Most other trials do not indicate a faster onset of action of a particular second-generation antidepressant compared with another. There was also moderate strength evidence based on 5 efficacy studies that demonstrated no statistically significant differences in preventing relapse or recurrence between escitalopram and paroxetine, fluoxetine, and setraline, fluoxeting and venlafaxine, fluvoxamine and sertraline, and trazodone and venlafaxine. Overall, there was low quality of evidence evaluating the management of treatment-resistant depression. Results from 3 trials support modestly better response and remission rates for venlafaxine than with comparator, but differences were generally not statistically significant.

There was high strength of evidence that overall, adverse events profiles are similar among second-generation antidepressants. Differences exist in the incidence of specific adverse events. Discontinuation rates were similar between SSRIs and other second-generation antidepressants (15% to 25%). Duloxetine and venlafaxine have a higher rate of discontinuation due to adverse events and venlafaxine has a lower rate of discontinuation due to lack of efficacy compared to the SSRI class. There was moderate strength evidence that mirtazapine causes greater weight gain than comparators, sertraline as a higher incidence of diarrhea, and trazodone has a higher rate of somnolence than comparators. There was insufficient evidence to draw conclusions on the comparative risk for suicidality, cardiovascular events, or seizures. Limitations of this review were that most trials were conducted in highly selected populations and were relatively short-term trials, publication bias might affect the estimates of some comparisons, and evidence within subgroups was limited.

Overall, 37% of patients with acute-phase MDD who received first-line treatment did not achieve response within 6 to 12 weeks, and 53% did not achieve remission. Current evidence does not warrant recommending a particular second-generation antidepressant on the basis of differences in efficacy or effectiveness and differences in onset of action and adverse events may be considered when choosing a medication.

A recent review by the Cochrane Collaboration assessed the evidence on the efficacy or mirtazapine compared with other antidepressive agents in the acute-phase treatment of MDD and concluded that mirtazapine was significantly more effective at two weeks than SSRI's (OR 1.57, 95% CI 1.3 to 1.88) and at the end of acute-phase treatment (OR 1.19, 95% CI 1.01 to 1.39). Mirtazapine was also more effective than venlafaxine at two

weeks (OR 2.29, 95% CI 1.45 to 3.59) and at the end of acute-phase treatment (OR 1.53, 95% CI 1.03 to 2.25). This was only based on two trials with a total of 415 participants. Mirtazapine was more likely to cause weight gain, increased appetite, and somnolence than SSRIs but less likely to cause nausea or vomiting and sexual dysfunction. One potential reason for these differences in acute-phase treatment of MDD is a faster onset of action when compared to the SSRI's

III. New Drug Review

FDA approved indications: Vilazodone is a selective serotonin reuptake inhibitor indicated for the treatment of major depressive disorder.

Clinical Trial Data

Efficacy: The efficacy of vilazodone was established in two Phase III short term (eight-week), randomized, placebo-controlled, multicenter studies using a dose titrated up to 40 mg/day.[8,9] The trials included a total of 891 adult patients (ages 18-70 years) meeting DSM-IV-TR criteria for MDD, single episode or recurrent. Table 2 provides a summary of the evidence findings for the two studies. There are no head-to-head comparative trials with any other antidepressants. The primary measure used to evaluate efficacy was the Montgomery-Asberg Depression Rating Scale (MADRS). This scale measures the effect of treatment on depression severity by measuring the severity of a number of symptoms at baseline and during the course of treatment. These symptoms include mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness. Limited information is available defining a clinically meaningful change in the MADRAS score. Measurements were conducted at baseline and weeks 1, 2, 3, 6 and 8. Both studies demonstrated a significant improvement in patients on vilazodone according to the MADRS scale compared to placeb. The least-squres mean difference between groups in change from baseline in one study (trial 07) was -2.5 (SE = 0.96; 95% CI, -4.4 to -0.6; p=0.009). In the second study (trial 04) the least squares mean difference from placebo in change from baseline was -3.2 (SE=0.99; 95% CI, -5.1 to -1.2; p=0.001). In the second trial, patients were allowed to stay on the 20 mg/day dose if they could not tolerate 40 mg/day. Forty-one patients were maintained on this dose due to reasons of intolerability (28 in vilazodone group and 13 in placebo group).

Vilazodone has also been studied in five, 8-week Phase II studies in patients with MDD (none are fully published). Three of these studies included active comparators (fluoxetine or citalopram) and all used the change from baseline to endpoint on the Hamilton Depression Rating Scale (HAM-D_{17}) as the primary endpoint. These studies evaluated vilazodone doses ranging from 5 to 100 mg/day, with most patients dosed at ≤ 20 mg/day (however only two used fixed-dose designs that were informative about dose response). No statistically significant differences were observed between vilazodone and placebo or between the active comparator and placebo in the ITT analyses.

Safety and Tolerability: Commonly observed adverse effects (incidence ≥5% and at least twice the rate of placebo) include: diarrhea (28% vilazodone vs 9% placebo), nausea (23% vilazodone vs 5% placebo), vomiting (5% vilazodone vs 1% placebo), and insomnia (6% vilazodone vs 2% placebo). The gastrointestinal adverse events and insomnia tend to occur early in treatment. Other adverse events with an incidence of at least 2% and at least twice the placebo rate include: gastroenteritis, paresthesia, tremor, abnormal dreams, restlessness, decreased libido, abnormal orgasm, delayed ejaculation, erectile dysfunction, feeling jittery, palpitations, and increased appetite.

Pharmacology: Vilazodone is an indolaklylamine that binds with high affinity to the serotonin reuptake site (SSRI). It also has high affinity for 5HT1a Receptors and is a 5HT1A receptor partial agonist. The mechanism of antidepressant effect is not known but is thought to be related to enhancement of serotonergic activity in the central nervous system through its SSRI effect. The net effect of the partial agonist activity is not known.

Consideration in Subpopulations:
Pediatrics: Vilazodone has not been studied in patients less than 18 years of age.
Geriatrics: Vilazodone has not been studied in patients older than 70 years of age. No dose adjusted is necessary for renal impairment or mild to moderate hepatic impairment. Patients with severe hepatic impairment have not yet been studied.
Gender, race, ethnicity: No subgroup analyses have been published.

Comparative Clinical Efficacy:

Relevant Endpoints for Depression:

Response*
Remission*
Relapse
Hospitalization
Quality of Life
Withdrawals due to adverse events
Major adverse events
*Secondary endpoints in vilazodone trials

Study Primary Endpoints:

Khan, et al: Change in baseline at week 8 in Montgomery-Asberg Depression Rating Scale (MADRS)

Rickels, et al: Change in baseline at week 8 in Montgomery-Asberg Depression Rating Scale (MADRS)

Table 2. Vilazodone Comparative Evidence Table

Ref./ Study Design	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
Khan, et al. Multicenter, DB, PC, PG, RCT Vilazodone vs Placebo	1. Vilazodone 40mg 2. Placebo Dosed QD	Adult patients (18-70 yrs); DSM-IV-TR criteria for MDD, single episode or recurrent Mean age 42 y/o 56% female Excluded:	240 241	8-weeks	<u>MADRS total score (change from baseline to week 8):</u> Vilazodone 40mg = -13.3 Placebo = -10.8 Mean difference -2.5 95% CI (-4.4 to -0.6) p-value = 0.009 <u>Response Rate*</u> Vilazodone 101 (43.7%) Placebo 70 (30.3%)	N/A Response: ARR 13.4% NNT=7.5	<u>Discontinuations due to adverse events:</u> Vilazodone: 12 (5.1%) Placebo: 4 (1.7%) RR 3.0, 95% CI (0.9 to 10.9) P=0.042 <u>Severe Adverse events:</u> Vilazodone: 15 (6.4%) Placebo: 13 (5.6%) RR 1.1, 95% CI (0.5 to 2.5)	ARI 3.4% NNH 29 NS	Fair; *Placebo controlled, short-term trial, not head-to-head* *Manufacturer sponsored trial* *No information on methods of allocation concealment*

		Excluded: history of schizophrenia, bipolar, or substance dependence, current psychotherapy within previous 12 weeks			RR 1.44 95% CI (1.1-1.9) P=0.003 <u>Remission Rate**</u> Vilazodone 63 (27.3%) Placebo 47 (20.3%) RR 1.3 95% CI (0.95-1.9) P=0.08 *Response rate defined as ≥50% decrease from baseline in MADRS **Remission rate defined as MADRS score <10	Remission: NS	P=0.7		*Patients with significant comorbid conditions that might interfere with trial participation excluded at the investigator's discretion* *Total Discontinuation Rate 19%(similar between groups)* *No measures of QOL*
Rickels, et al. Multicenter, DB, PC, PG, RCT	1. Vilazodone 40mg 2. Placebo	Adult patients (18-70 yrs); DSM-IV-TR criteria for MDD, single episode or recurrent Mean age 40y/o 63% female Excluded: history of schizophrenia, bipolar, or substance dependence, current psychotherapy, patients with serious suicidal risk, patients with clinically significan cardiac, renal, neurologic, hepatic, metabolic or pulmonary disease	205 205	8-weeks	<u>MADRS total score (change from baseline to week 8):</u> Vilazodone 40mg = -12.9 Placebo = -9.6 Mean difference -3.2 95% CI (-5.1 to -1.2) p-value = 0.001 <u>Response Rate*</u> Vilazodone: 80 (40%) Placebo : 56(28%) RR 1.44 95% CI (1.07-1.9) P=0.01 *Response rate defined as ≥50% decrease from baseline in MADRS	N/A Response ARR 12% NNT=8.1	<u>Discontinuations due to adverse events:</u> Vilazodone: 19 (9.3%) Placebo: 10 (4.9%) RR 1.9, 95% CI(0.9-4.3) P=0.085 <u>Serious adverse events:</u> Vilazodone: 5 (2.4%) Placebo: 5 (2.5%) RR 1.0 95% CI (0.3-4.0) P=0.99	NS NS	Fair; *Placebo controlled, not head-to-head* *No information on methods of allocation concealment* *Manufacturer sponsored tria* *Short-term trial* *Total Dropout rate25% (similar between groups)* *Extensive exclusion criteria* *No measure of QOL*

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Table 3. Vilazodone Dose & Availability

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10mg	Tab	PO	Daily	N/A	N/A (not studied in severe hepatic disease)	Not Established	Not Established	Should be given with food Should be titrated (10mg X 7 days; 20mg X 7 days; then 40mg/day)
20mg	Tab	PO	Daily					
40mg	Tab	PO	Daily					

Table 4. Vilazodone Pharmacokinetics

Parameter	Result
Oral Bioavailability	72% w/food
Tmax	4-5 hours
Protein Binding	96-99%
Elimination	Extensively metabolized Feces 2% Urine 1%
Half-Life	25 hours
Metabolism	CYP3A4 (major); 2C19 (minor); 2D6 (minor) No active metabolites

IV. Safety Alert for Citalopram

In August 2011, the FDA issued a Safety Alert regarding the link between abnormal heart rhythms and high dose citalopram (Celexa). Further clarification of recommendations was posted March 2012.[5,6] Changes in the electrical activity of the heart (prolongation of the QT interval) can lead to an abnormal heart rhythm (including Torsade de Pointes), which can be fatal. Patients at particular risk for developing prolongation of the QT interval include those with underlying heart conditions and those who are predisposed to low levels of potassium and magnesium in the blood. Studies did not show a benefit in the treatment of depression at doses higher than 40 mg per day. Previously, the citalopram drug label stated that certain patients may require a dose of 60 mg per day. The citalopram drug label has been revised to include the new drug dosage and usage recommendations, as well as information about the potential for QT interval prolongation and Torsade de Pointes. The FDA recommends the following:

- Citalopram causes dose-dependent QT interval prolongation.
- Citalopram should no longer be prescribed at doses greater than 40 mg per day.
- Citalopram is not recommended for use in patients with congenital long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure.
- Citalopram use is also not recommended in patients who are taking other drugs that prolong the QT interval.

- The maximum recommended dose of citalopram is 20 mg per day for patients with hepatic impairment, patients who are older than 60 years of age, patients who are CYP 2C19 poor metabolizers, or patients who are taking concomitant cimetidine (Tagamet) or another CYP2C19 inhibitor, because these factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and Torsade de Pointes.

Appendix 1

Previous Conclusions by HRC Second Generation Antidepressants[1,2]:

Drug Classes included in review

- SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline
- SNRIs: desvenlafaxine, duloxetine, venlafaxine
- Others: bupropion, mirtazapine, nefazodone, trazodone

Limitation of the evidence:

- Study durations were short (mostly 6-12 weeks) compared to the usual duration of treatment (9-12 months).
- High dropout rates
- No effectiveness studies
- Depression in children is not as well studied as in adults

Conclusions:

	Good Evidence	Fair Evidence	Insufficient Evidence
Efficacy, Adults	No significant difference in overall efficacy among second generation antidepressants in adults with MDD.	Second generation antidepressants were no better than placebo for MDD in patients with comorbid conditions including methadone maintained opioid addiction, cocaine abuse, HIV, multiple sclerosis, arthritis, diabetes, cancer or substance abuse disorder.	To determine a comparative difference in efficacy among the studied agents for dysthymia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder and late luteal phase dysphoric disorder.
Efficacy, children and adolescents	Citalopram and fluoxetine are the only two agents studied shown to be better than placebo. Sertraline, venlafaxine, and paroxetine were shown to be no better than placebo. In patients ≤18 years the risk of self-harm increased with SSRIs vs. TCAs. There were no statistically significant differences among SSRIs. A systematic review of published and unpublished data suggests that only fluoxetine has a favorable risk/benefit profile in pediatric populations.	Second generation antidepressants were no better than placebo for comorbid alcohol use disorder in adolescents.	

Adverse Effects	Black Box Warning: 1. Nefazone and active liver disease. 2. All included drugs carry a black box warning regarding suicidality. The risk of suicidality is not increased in adult patients ≥ age 18. Higher rate of nausea and vomiting with venlafaxine. Higher rate of discontinuation with venlafaxine and duloxetine.	Sexual Side Effects: 1. Higher risk: paroxetine, sertaline and mirtazapine 2. Lower risk: bupropion and nefazodone Greater weight gain with mirtazapine and paroxetine than with sertraline and fluoxetine.	
Subgroups	A large meta-analysis of paroxetine vs. placebo suggests that the response rate is lower in Hispanic and Asian populations compared to White and Black populations for MDDs in adults, anxiety disorders, and post menstrual dysphoric disorder.	A retrospective cohort study of women ≥66 years with breast cancer shows that use of paroxetine increased the risk of death from breast cancer among women taking tamoxifen. There is insufficient data to assess the risk for other medications in this class.	To determine a comparative difference among agents in this class based on subpopulations of age, comorbidities, ethnicity or gender.

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Tobacco Cessation Medication Review

Month/Year of Review: April 2012

FDA Approved Medications		Non FDA-approved Alternatives
Nicotine transdermal patch	Bupropion sustained –release	Clonidine
Nicotine lozenge	Varenicline (Chantix®)	Nortriptyline
Nicotine gum		
Nicotine inhaler (Nicotrol®)		
Nicotine nasal spray (Nicotrol®)		

*See Appendix 2 for dosing, duration and administration information

Reason for Review:
Smoking is a significant public health problem that can be associated with substantial health care costs and can cause many preventable diseases including cancers, chronic obstructive pulmonary disease (COPD), and cardiovascular disease. This review will evaluate current comparative effectiveness evidence to assist in establishing recommendations for the therapeutic agents indicated for smoking cessation.

Issues:

1. What is the comparative efficacy of smoking cessation products in promoting long-term tobacco abstinence?
2. Is there any evidence that there is a meaningful difference in agents in safety that would favor one agent over another?
3. Is there any evidence that there is a difference in efficacy or safety in special populations?

Methods:

Search Strategy

An Ovid MEDLINE search was conducted using the following search terms:
Varenicline; bupropion; nicotine replacement therapy; nicotine patch; nicotine gum; nicotine lozenge; nicotine nasal spray; nicotine inhaler; smoking cessation; tobacco abstinence. The search was limited to controlled trials conducted with humans in English language publications from 2010 to present. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, 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.

Results:

The MEDLINE search retrieved 181 full citations. After a full evaluation of citations and abstracts, 8 head-to-head trials using FDA approved agents were identified for further review and three potentially relevant articles were included here. One trial evaluated the effects of varenicline on cardiovascular risk and two articles evaluated varenicline dosing. The majority of the RCTs identified were excluded for wrong study type (observational, case study), the wrong endpoint (smoking reduction, decreased disease occurrence), wrong duration (trials less than 6 weeks), for very specific subpopulations (chronic binge drinkers, Japanese men over 40) or for duplication (already included in another article or review).

Conclusions:

The collective conclusions of the Canadian Agency for Drugs and Technologies in Health[1], U.S. Department of Health and Human Services[2], and the Cochrane Collaboration systematic reviews[3-8], as well as the guidelines of the UK's National Institute for Clinical Excellence[9] and the US Preventive Task Force[10] share many similar recommendations. There is strong evidence that all of the FDA approved smoking cessation products are efficacious compared with placebo in terms of abstinence rates. There is strong evidence that bupropion and nicotine replacement therapy (NRT) formulations are equally effective for tobacco abstinence rates. There is moderate to strong evidence that varenicline has the higher rate of abstinence success when compared with bupropion or NRTs. There is strong evidence that combining the nicotine patch with another NRT therapy improves abstinence rates over NRT monotherapy. There is strong evidence that clonidine is efficacious compared with placebo for tobacco cessation and moderate to strong evidence that nortriptyline is effective compared with placebo for tobacco cessation. There is strong evidence that combining behavioral therapy with tobacco cessation medications increase the rate of long-term (greater than 6 months) abstinence. There is inconclusive evidence that combining bupropion with NRT is more effective than monotherapy and there is insufficient evidence to recommend any medication for special populations including pregnant or lactating women, adolescents or the mentally ill.

Varenicline has some safety issues not seen with bupropion or NRT products.[11-12] From systematic reviews, there is strong evidence that varenicline is safe to use over a 12 week period, although limitations may be appropriate in patients with a neuropsychiatric or cardiovascular history. A small

increase in risk of serious cardiovascular events may exist for patients with cardiovascular disease taking varenicline; however the evidence is insufficient to form a conclusion. There is a black box warning for potential serious neuropsychiatric events (depression and suicidal tendencies) especially in those patients with a history of mental illness (bupropion also carries this warning). A recent study however, found no difference in the rates of neuropsychiatric hospitalizations between NRT and varenicline patients.[13] Post-marketing trials on psychiatric safety of varenicline are currently ongoing.

Recommendations:

1. Add Nicotine replacement therapy (NRT) products including the patch, gum and lozenges as preferred drugs on the PDL with an age restriction to adults.
2. Due to no differences in safety or efficacy between the NRT products, evaluate comparative costs for further decisions.
3. Make buproprion sustained release (generic Zyban) a preferred medication with an age restriction for adults.
4. Make varenicline a preferred agent on the PDL with a quantity limit for twelve weeks of treatment and with restriction to adults without a history of cardiovascular or neuropsychiatric events.

I. BACKGROUND/CURRENT LANDSCAPE/SUMMARY

Cigarettes are responsible for more than 443,000 deaths annually. One in every five deaths last year was smoking related, and according to the US Department of Health and Human Services, more than 50% of long-term cigarette smokers are killed from smoking-related diseases. Smoking cigarettes can negatively affect every physiological system in a smoker's body. Unfortunately, smoking doesn't only affect the person smoking. Thousands of non-smoking Americans die from heart and lung disease associated with second-hand smoke. Children exposed to second-hand smoke are at higher risk for sudden infant death syndrome (SIDS), respiratory diseases, long term ear infections and other health issues. More than 193 billion dollars in health care costs and lost productivity is spent annually on chronic diseases caused by tobacco use.[14-15]

Although cigarette smoking rates have dropped by more than half since the 1960s, approximately 20% of American adults and teenagers are current smokers.[15] Among those, about 70% express an interest in quitting. In 2010, about half of all adult smokers made an attempt to stop smoking, but only 6.2% reported remaining smoke-free after one year. Among those who attempted to quit and those successfully quit in the last two years, 31.7% used either counseling or medications and 4.3% used both.[14]

The consequences of tobacco addiction are a large problem in the Medicaid population. The prevalence of smokers in the Medicaid population is nearly twice that of the general population. In Oregon, three times as many adult Medicaid patients smoke compared with the general population.[16]

Rates of tobacco cessation in the Medicaid population remain especially low. Patients with private health plans are 41% more likely to have quit smoking than Medicaid patients.[14] The estimated annual cost to the state is $290 million dollars.[16] A recent cost-benefit analysis looked at what savings smoking cessation programs might bring state Medicaid programs. The analysis estimated the short-term return on investment of the savings attached to reduced cardiovascular hospital admissions and found for every dollar spent in the smoking cessation program (medications, counseling, etc.) $3.12 was saved from reduced admissions. A potential annual savings of $388 per patient.[17]

Seven medications are FDA approved for treatment of tobacco dependence. Five are nicotine replacement therapy (NRT) available in various formulations. As the name implies, NRT contain a measured amount of nicotine and are designed to help a smoker gradually wean themselves off nicotine while abstaining from cigarette smoking. Depending on the formulation, these agents can help with the withdrawal symptoms (the patch, gum and lozenge) and help with more immediate nicotine cravings (inhaler, nasal spray, gum, and lozenge). All five are meant for short-term use (12-24 weeks or less). The nasal spray and inhaler agents are available by prescription only. Safety concerns include use in cardiovascular patients, pregnancy and breast-feeding women, and minors.[18]

There are two agents approved that are non-nicotine products. Bupropion is an anti-depressant medication that has affects on dopamine receptors in the central nervous system (CNS). It is thought to affect the pleasure-seeking center in the brain, although its mechanism of action in smoking cessation is unknown. It has been used in combination with some of the NRT products. Bupropion can increase the seizure threshold and shouldn't be used in patients prone to seizures. It also has not been approved for pregnancy/breastfeeding or minors. Varenicline (Chantix®) is a partial nicotinic agonist approved to treat smoking dependence. It acts at the same receptors nicotine occupies but without the receptor stimulation nicotine provides. Patients therefore experience less craving and withdrawal symptoms. Varenicline is the newest medication for tobacco dependence and has less safety data than the alternative agents. Choosing among medications requires consideration of the benefits and risks, with attention to each patient's medical and psychiatric status. In 2009, the FDA issued a boxed warning for both varenicline and bupropion concerning neuropsychiatric symptoms, depressed mood, and suicidal thoughts and behavior.[19] Also, a recent drug-safety communication noted that it may be associated with a small increase in the risk of cardiovascular events. Varenicline should not be used with NRT agents.[18]

Many medications have been prescribed for tobacco dependence as off-label agents. These non-FDA approved medications have a wide range in the amount of evidence supporting their use. Two medications, clonidine (an anti-hypertensive) and nortriptyline (an antidepressant) have the most data supporting their use. However, evidence is limited for their use and both should be considered as second-line agents after the FDA-approved medications discussed above. Other medications including the SSRIs (i.e. fluoxetine) and naltrexone have little to no data supporting their use in tobacco dependence and are not recommended for use.[18]

II. **Systematic Reviews:**

Canadian Agency for Drugs and Technologies in Health (CADTH) [1]*:*

The Canadian Agency for Drugs and Technologies in Health (CADTH) provided a technology report in September 2010 (updated October 2011) to assess the clinical effectiveness and cost effectiveness of medications for smoking cessation. The review evaluated the comparative clinical effectiveness of varenicline, bupropion and NRT agents, the effectiveness of combining various agents, the effectiveness of adding behavioral support therapy to drug therapy, and the effectiveness of treating special populations (including adolescents, those who are pregnant and those with psychiatric disorders).

More than 3500 citations were originally identified and 143 included in the meta-analysis. Articles were included for clinical evaluation if they met the following criteria: the article was a randomized control trial with a follow up of at least six months; the population was smokers that mirrored the general population (both genders, all ages, multiple ethnicities) unless a specific population was studied (adolescents); the intervention studied was bupropion, varenicline, NRT or behavioral support therapy with an active or placebo comparator; and the outcome was biochemically identified smoking abstinence.

After screening for criteria, 143 articles were included for analysis. Quality ratings were assigned to each article after review using a combination of the Jadad and Hailey scales. Ratings ranged from high to poor quality, although the majority of articles (53% were given the highest rating.

All seven medications were more effective than placebo at helping patients remain tobacco free after six months and one year. Comparing bupropion with NRT treatment showed no difference in abstinence rates one year after quitting (OR 1.03, 95% CI 0.84-1.27). Among individual nicotine replacement products, no difference was found between abstinence rates after one year. Patients on varenicline had the highest odds of being tobacco free one year after quitting versus placebo (OR 2.7, 95% CI 2.25- 3.24), bupropion (OR 1.43, 95% CI 1.11-1.84) , and NRT (OR 1.47, 95% CI 1.2-1.82). Most combinations of medications showed no improvement over monotherapy in abstinence rates. The exception was two combinations of NRT formulations: using the nicotine patch with the nicotine gum or nasal spray was more effective than the patch alone (at six months, patch + gum: OR 2.1, 95% CI 1.18- 3.71; patch + spray: OR 2.4, 95% CI 1.27-4.5).

All medications were associated with higher numbers of adverse events compared with placebo and the nicotine spray seemed to be associated with more adverse events than nicotine patch (OR 3.83, 95% CrI 1.07 to 13.76) or nicotine inhaler (OR 5.12, 95% CrI 1.28 to 20.48). The nicotine patch, bupropion, and varenicline showed a higher proportion of withdrawals due to adverse events compared with placebo with pooled OR's of 1.41 (95% CI 1.02 to 1.94), 1.74 (95% CI 1.31 to 2.31), and 1.52 (95% CI 1.09 to 2.12) respectively. More studies are needed to see what therapy, if any works best in special populations including pregnancy and the mentally ill; one study showed the use of the nicotine patch in adolescents improved tobacco

abstinence rate compared with placebo for up to six months (OR 4.93, 95% CI 0.95- 25.57). There was no analysis for smoking cessation agents in patients with cardiovascular disease. The evidence of head-to-head comparisons between medications is limited.

Conclusions:

1. There is high quality evidence NRT, bupropion and varenicline are all efficacious compared with placebo in treating tobacco dependence and promoting long-term cessation.
2. There is high quality evidence that there is no difference in efficacy in varenicline, bupropion and NRT in tobacco abstinence rates.
3. There is high quality evidence that there is no difference between NRT formulations in smoking abstinence rates.
4. There is high quality evidence that all seven tobacco cessation products have higher relapse rates than placebo.
5. There is high to good quality evidence that combining the nicotine patch with the nicotine gum or nasal spray was more efficacious than the patch alone.
6. There is good to fair quality evidence that adding the nicotine patch or gum to behavioral therapy was more effective than behavioral therapy alone.
7. In special populations, there is high to fair quality, limited evidence that there is no difference in smoking abstinence rates between NRT, NRT + behavioral therapy, or behavioral therapy alone vs. placebo in pregnant woman
8. In special populations, there is good to fair quality, limited evidence that the nicotine patch is more effective than placebo in adolescents.
9. In special populations, there is good to poor quality evidence that none of the current medications available are more effective than placebo in patients with mental illness.

US Department of Health and Human Services[2]:

A meta-analysis by the US Department of Health and Human Services assessed randomized trials to create a public health service-sponsored clinical practice guideline in May 2008. This clinical practice guideline and systematic review was sponsored by a group effort of Federal Government agencies and nonprofit organizations including the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control (CDC), the National Heart, Lung and Blood Institute (NHLBI), and the National Cancer Institute (NCI). The review focuses on eleven topics including the effectiveness of combining counseling and medication relative to either counseling and medication alone, effectiveness of varenicline, effectiveness of medication combinations, effectiveness of long-term use, and effectiveness in special populations (including adolescents, those who are pregnant and those with psychiatric disorders).

Articles were included if they were a randomized, placebo/comparison controlled trial of a tobacco use treatment intervention with follow-up results at least 5 months after the quit date; was published between January 1975 and June 2007 in English in a peer-reviewed journal; and addressed one of

the 11 topics chosen for review. Recommendations based on the articles were given a strength of evidence (A, B, or C) rating based on the quality and quantity of data.

Seven FDA indicated medications were evaluated in the systematic review. Other medications used off-label for tobacco dependence were also included. 83 trials were included in a meta-analysis comparing the effectiveness of smoking cessation medications with respect to the rate of abstinence 6 months after treatment. This review identified all seven medications effective in increasing the odds of achieving abstinence compared to placebo. A meta-analysis was performed to allow for comparisons of medications between other active medications. Varenicline 2mg/day (number of trials, N=5) demonstrated the greatest odds of remaining tobacco free six months after quitting (OR 3.1 , 95% CI 2.5-3.8) and was associated with an estimated abstinence rate of 33%. Combination NRT was also associated with a higher estimated abstinence rate of 37% (most pharmacotherapies showed an estimated rate of 19% to 26%). Subjects on all forms of NRT, except for the lozenge formulation, were more likely to be tobacco free compared to placebo. The nicotine nasal spray and the high dose (>25mg) nicotine patch shared the second highest odds after varenicline (both: OR 2.3, 95% CI 1.7-3.0). Bupropion SR (N=26) use was also associated with greater odds of being tobacco free compared with placebo at six months (OR 2.0, 95% CI 1.8-2.2). Clonidine (N=3) and nortriptyline (N=5) are used off-label to treat tobacco dependence; patients in both treatment arms were more likely to still be tobacco free at six months than their placebo counterparts. Combination therapy that included the nicotine patch was shown to be very effective. The patch when combined with the nicotine inhaler (OR 2.2, 95%CI 1.3-3.6), bupropion SR (OR 2.5, 95%CI 1.9-3.4), nortriptyline (OR 2.3, 95%CI 1.3-4.2), or the nicotine gum/inhaler (OR 3.6, 95%CI 2.5-5.2) showed improved effectiveness at 6 months compared with placebo.

Conclusions:

1. There is evidence that first-line medications varenicline, bupropion, nicotine patch, gum, inhaler and nasal spray appear to be effective smoking cessation treatments. (Strength of evidence A)
2. There is evidence that the nicotine lozenge is an effective smoking cessation treatment. (Strength of evidence B)
3. There is evidence that second-line smoking cessation medications, clonidine and nortriptyline, appear to be effective smoking cessation treatments when used under a physician's supervision. (Strength of evidence A)
4. There is evidence that using a combination of the nicotine patch and other NRT or bupropion appear to be effective smoking cessation treatments. (Strength of evidence A)
5. There is evidence that the combination of counseling and medication is more effective for smoking cessation than either medication or counseling alone. (Strength of evidence A)
6. There is insufficient evidence supporting the use of smoking cessation medications in the following special populations: pregnant women, adolescents, smoke-less tobacco users, and light smokers who smoke less than 10 cigarettes per day.

The Cochrane Collaboration[3-8]*:*

In 2008, a systematic review evaluated if nicotine replacement therapy is more effective than placebo at achieving abstinence from smoking. Thirteen other objectives were analyzed including if one NRT formulation is more effective than the others, if combination NRT is more effective than monotherapy, or if NRT is more effective than other smoking cessation treatment.
Articles were included if they were an RCT where a NRT was compared with placebo, an active comparator, or no treatment at all. The primary outcome was abstinence from smoking with a follow up of at least six months. A meta-analysis was performed on the 111 articles selected for review. All forms of NRT were shown to be more effective than placebo in maintaining tobacco abstinence (RR 1.58, 95% CI 1.5-1.66) at six months. Of the five forms of nicotine products, patients on the nasal spray (number of trials, N=4) and the lozenge (N=6) had the greatest probability of remaining smoke-free (RR 2.02, 95% CI 1.49-3.73; RR 2.0, 95% CI 1.63-2.45 respectively). The inhaler (N=4; RR 1.9, 95% CI 1.36-2.67), the patch (N=41; RR 1.66, 95% CI 1.53-1.81), and the gum (N=53; RR 1.43, 95% CI 1.33-1.53) were also found more efficacious than placebo. Only three trials directly compared NRT therapies; none of the three found any significant difference between formulations. Two trials looked at NRT versus bupropion but neither found a significant difference in sustained quit rates. Seven trials compared combination therapy (patch + another NRT agent) with NRT monotherapy. Patients using combination therapy had higher rates of abstinence at six months than patients using one NRT (RR 1.35, 95% CI 1.11 to 1.63).

A 2009 review looked at whether anti-depressant use helps in quitting tobacco. Twelve antidepressants were assessed in this systematic review for effectiveness in tobacco cessation. FDA-approved atypical antidepressant bupropion; SSRIs fluoxetine, sertraline and paroxetine; MAO inhibitors mocolobemide, and selegiline; tricyclics nortriptyline, doxepin and imipramine; venlafaxine; tryptophan; and St. John's Wort were all included. Other inclusion criteria were RCT with a placebo or active comparator and at least six months follow up.
A meta-analysis was conducted with the data gathered from the 66 articles which met criteria. The majority of articles evaluated bupropion (number of articles, N=49) or nortriptyline (N=9). Both were found to be efficacious in helping patients remain tobacco free at six months (bupropion RR 1.69, 95%CI 1.53-1.85; nortriptyline RR 2.03 95%CI 1.48-2.78). Adding bupropion or nortriptyline to NRT was not more effective than either anti-depressant alone, and in direct comparator trials both were as effective as NRT as monotherapy. Three trials compared bupropion to varenicline. Patients in the bupropion arms had lower quit rates at six months than those in the varenicline groups (RR 0.66, 95% CI 0.53-0.82). No treatment effects were seen with venlafaxine, the SSRIs or the MAO inhibitors. No long-term data was found for St. John's Wort, tryptophan, doxepin and imipramine.

In 2011 a systematic review examined varenicline and its effectiveness as a smoking cessation agent. Articles were included if they were a RCT which compared varenicline to placebo, bupropion or NRT. All trials were required to have a follow-up period of at least six months. Fourteen trials were identified for inclusion; the majority had a placebo control (number of trials, N=11), three trials compared varenicline to bupropion and two open-label trials had a NRT comparator. The varenicline patients in all comparator trials had higher rates of tobacco abstinence: vs. placebo at six months (RR 2.31, 95% CI 2.01-2.66), vs. bupropion at one year (RR 1.52, 95% CI 1.22-1.88), and vs. NRT at six months (RR 1.13, 95% CI 0.94-1.35; not significant).

Clonidine, an alpha-2 receptor agonist, is often used off-label for smoking cessation. A 2008 updated systematic review analyzed the effectiveness of clonidine for this. Six trials were included for meta-analysis; three used transdermal clonidine and three used the oral form. All trials were RCT, placebo controlled with at least six months follow-up. Patients using clonidine had higher rates of quitting at six months than those receiving placebo (RR 1.63, 95% CI 1.22-2.18).

Patients with mental illness have higher rates of tobacco dependence than the general population. They are also more difficult to treat because of their mental illness. A 2010 systematic review evaluated smoking cessation trials in schizophrenic populations. Articles were included if they were a RCT with a schizophrenic or schizoaffective adult smoker population. Any tobacco intervention was acceptable for inclusion, although a placebo or active control was required. Unlike many tobacco cessation reviews, reduction in smoking was an outcome along with abstinence. A total of 21 articles were included for analysis; 11 trials used smoking cessation as an outcome. Of those, seven compared bupropion with placebo and found bupropion use was associated with higher quit rates at the end of treatment (RR 2.84, 95% CI 1.66-4.99) and at six months follow-up (number of trials, N=5), (RR 2.78, 95% CI 1.02-7.58). No significant differences were seen in schizophrenic symptoms (positive or negative) between the placebo and bupropion groups. Three trials compared NRT plus behavioral therapy versus routine care or placebo. No significant difference in cessation or smoking reduction was seen. Results were similar in two cross-over nicotine patch studies: no difference was seen between the patch and placebo groups. Other pharmacological interventions examined: topiramate, clozapine, atomoxetine, and galantamine were found to be either inconclusive or ineffective.

Pregnant smokers are an often targeted population for smoking cessations interventions. Smoking during pregnancy can cause demonstrated harm to the fetus and mother. Use of pharmacological tobacco abstinence agents is controversial during pregnancy, leaving behavioral therapy as the treatment of choice. A 2009 systematic review examined smoking cessation interventions during pregnancy and their success rates. Articles were included if they were a RCT with pregnant adult smokers and had a primary outcome of smoking cessation. In the 65 articles included for analysis, patients who were targeted with a smoking cessation intervention were less likely to continue smoking in the third trimester than those with no intervention (RR 0.94, 95% CI 0.92-0.96). Five of the trials employed NRT as the intervention. Using NRT did not appear to have any more efficacy than other non-pharmacologic interventions, but did cause greater safety concerns. One NRT trial was discontinued early due to large statistically significant difference between the NRT and placebo groups in adverse events, including fetal death.

Conclusions:

1. There is high quality evidence that the nicotine inhaler, nasal spray and patch are effective medications for smoking cessation.
2. There is good quality evidence that the nicotine gum and lozenge are effective medications for smoking cessation.
3. There is good quality evidence to conclude that combination NRT that includes the nicotine patch is more effective than monotherapy.
4. There is insufficient evidence to conclude if bupropion is more effective than NRT.
5. There is good quality evidence that bupropion is an effective medication for smoking cessation.
6. There is good quality evidence that nortriptyline is an effective medication for smoking cessation.

7. There is limited good-to-fair quality evidence that SSRIs fluoxetine, paroxetine, and sertraline are not effective medications for smoking cessation.
8. There is good quality evidence that varenicline is an effective medication for smoking cessation.
9. There is limited good quality evidence that varenicline is a more effective medication for smoking cessation than bupropion.
10. There is limited fair-to-poor quality evidence that varenicline is a more effective medication for smoking cessation than NRT.
11. There is limited good-to-fair quality evidence that clonidine is an effective medication for smoking cessation.
12. There is fair quality evidence that bupropion is an effective medication for smoking cessation in schizophrenic and schizoaffective populations.
13. There is insufficient evidence to conclude if NRT is an effective smoking cessation therapy in schizophrenic and schizoaffective populations.
14. There is fair-to-poor quality evidence that smoking cessation interventions in pregnant women decrease smoking rates.
15. There is insufficient evidence to conclude if NRT is a safe or effective smoking cessation therapy in pregnant populations.

Remaining Issues:

- Further studies are needed to assess the relative effectiveness and safety of the seven FDA-approved medications for long-term treatment, in general and for specific subpopulations (women; adolescents; older smokers; smokeless tobacco users; individuals with psychiatric disorders, including substance use disorders; post-myocardial infarction patients).
- Further studies are needed to evaluate the use of combined tobacco dependence medications in general and for specific subpopulations (e.g. highly dependent smokers).
- Further studies are needed to assess the effectiveness of pre-quit NRT use in increasing abstinence rates.
- Further studies are needed to address the comparative efficacy of OTC treatments versus prescription treatment
- Further study is needed to determine if smoking for a longer duration after starting varenicline is more effective at improving long-term abstinence than the original varenicline packaging recommendation of one week.

III. Guidelines

1. Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities.[9]

Developer:
National Institute for Health and Clinical Excellence

Published:
2008

Recommendations:

i. There is high quality evidence that brief interventions by healthcare professionals to advise and discuss smoking are effective in helping smoking cessation.
ii. There is high quality evidence that individual or group behavioral counseling is effective in aiding tobacco cessation.
iii. There is high quality evidence that medications available for tobacco dependence (bupropion, varenicline, and nicotine replacement therapy) are effective in assisting smoking cessation.
iv. The guideline recommends using professional judgment when prescribing tobacco cessation medication in special populations including pregnant or breastfeeding mothers and adolescents.

Critique:

The NICE smoking cessation guideline is aimed at a large target audience and is expansive in scope.
Search criteria are given in broad descriptions, but with direction to appendices with more detailed information. Internal and external peer reviews were conducted to validate the guideline. A hierarchy of Evidence Rating system was used to assess the quality and strength of the evidence
This guideline is funded by the Government of the United Kingdom.

2. Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: U.S. Preventive Services Task Force reaffirmation recommendation statement[10]

Developer:
U.S. Preventive Services Task Force

Published:
Update 2009

Recommendations:

i. There is high quality evidence that clinicians ask all adults about tobacco use and provide tobacco cessation interventions for those who use tobacco products
ii. There is high quality evidence that clinicians ask all pregnant women about tobacco use and provide augmented, pregnancy tailored counseling for those who smoke.

iii. There is evidence that combination of medication and counseling therapy is more effective at increasing cessation rates of either alone.

Critique:
The Task Force is an independent expert panel funded by the US Government. The target audiences for this guideline are healthcare providers in the primary care setting. Expert opinion consensus is given great weight in the guideline, particularly for subjects such as screening which are difficult to quantify using RCTs. Evidence is ranked on the strength and source of data as "high, moderate and low certainty of net benefit" and then graded through the panels consensus on the degree of magnitude of that benefit: grade A is thought to provide substantial benefit while grade D provides no benefit.

IV. FDA Safety Alerts

In 2011, the FDA reviewed new safety information for varenicline concerning cardiovascular and neuropsychiatric adverse events.[11-12] Varenicline (Chantix ®) may be associated with an increased risk of cardiovascular adverse events. The new data on cardiovascular safety came from a recent RCT evaluating the safety and efficacy of varenicline. The trial was twelve weeks of treatment with varenicline or placebo and then 40 weeks of follow-up in a population of stable cardiovascular disease patients. The continuous abstinence rate from week 9 to week 52 showed the varenicline arm was significantly more likely to remain tobacco free (OR 3.14, 95% CI 1.93- 5.11; *P*= 0.0001). However, a small number of participants experienced a serious cardiovascular adverse event, more often to the varenicline group than the control: nonfatal MI 2.0% vs. 0.9%, need for coronary revascularization 2.3% vs. 0.9%, new diagnosis of PVD 1.4% vs. 0.9%. The trial was not powered to quantify the statistical differences seen.[13]

The FDA instructed Pfizer to add the new cardiac safety information to the "Warnings and Precautions" in Chantix labeling and prescribing information. Given the risk of serious cardiovascular events occurring in this population (patients with cardiovascular disease who continue to smoke), the FDA advises weighing the risks and benefits for individual patients before treating CVD patients with varenicline. They have instructed Pfizer to conduct a large meta-analysis of RCT and will issue another update when reviewed.[12]

The FDA did not require Pfizer to alter labeling for the risk of neuropsychiatric adverse events. Two large VA and Department of Defense sponsored observational studies were recently reviewed by the FDA. Both studies compared varenicline and nicotine replacement therapy (NRT); adverse safety outcomes included hospitalizations due to neuropsychiatric events. Neither study found a difference in rates of neuropsychiatric hospitalizations between varenicline and NRT; because of this, the FDA did not advise any change to the labeling of Chantix. The FDA noted some concerns with the two studies. They were not powered to detect very rare adverse events and adverse events were tracked only when they resulted in hospitalizations. Pfizer is currently conducting a large clinical trial focused on neuropsychiatric safety. Results are anticipated in 2017.[13]

A recent clinical trial was the impetus for a change in the dosing recommendations for varenicline by Pfizer. Previously varenicline has been dosed so to allow the patient to smoke concurrently with the first week of taking varenicline and instruct patients to quit on the eighth day of varenicline use. The new alternative instructions allow patients to quit anytime between day 8 and day 35 after varenicline is started. [20]

The trial was a double-blind randomized controlled trial (n=659) comparing varenicline or placebo. Subjects received treatment for 12 weeks and were followed for an additional 24 weeks. They were instructed to quit smoking sometime between day 8 and day 35; endpoints were abstinence at weeks 9 to 12 and weeks 9 to 24. Patients in the varenicline group were more likely than the placebo subjects to be tobacco abstinent through weeks 9 to 12 (53.1% vs. 19.3%; OR 5.9, 95% CI 3.7-9.4) and weeks 9 to 24 (34.7% vs. 12.7%; OR 4.4, 95% CI 2.6-7.5). Adverse events were minor and were similar among both arms. The trial was of good to fair quality.[21]

On the basis of the success of the flexible-date trial, a small UK study set out to see if continued tobacco use for an additional three weeks after starting varenicline improved outcomes. Unlike the previous trial, this study had set quit dates. Patients were randomized to receive varenicline (n=52) or placebo (n=48) for the initial three weeks of treatment, during this time they continued smoking. After week three, all subjects were receiving varenicline and at the end week four all subject were to stop smoking. Patients who smoked during the initial four weeks of varenicline had an increased sustained abstinence rate at 12 weeks (47.2% vs. 20.8%, p=0.005) than the placebo subjects.[22] Although small, this trial was of good to fair quality. More studies are needed, however, to establish if this dosing regimen or flexible dosing improves the effectiveness of varenicline.

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Appendix 2: Medication Information

NAME	STRENGTH	FORM	ROUTE	FREQUENCY
Nicotine[23] Transdermal Patch	21 mg 14 mg 7 mg	Patch	Transdermal	Over 10 cigs/day: use one 21 mg patch/day for 4-6 wk, then use one 14 mg patch/day for 2 wk, then use one 7 mg patch/day for 2 wk 10 or less cigs/day: use one 14 mg patch/day for 6 wk, then use one 7 mg patch/day for 2 wk
Nicotine[23] inhaler (Nicotrol®)	10 mg	Inhaler	Inhalation	Inhale with continuous puffing over 20 min; initial, 6 to 16 cartridges/day for up to 12 weeks, then gradually discontinue over 6 to 12 weeks; MAX 16 cartridges/day
Nicotine nasal spray[23] (Nicotrol®)	100 mg	Nasal spray	Intranasal	1 spray in each nostril initially 1 to 2 times per hour, at least 8 times/day up to MAX of 5 doses/h, 40 doses/24 h; gradually discontinue; MAX duration, 3 months
Nicotine lozenge[24]	4 mg 2 mg	Lozenge	Buccal	Patients who smoke first cigarette >30 minutes after waking: One 2-mg lozenge every 1–2 hours during weeks 1–6; then one 2-mg lozenge every 2–4 hours during weeks 7–9; and once 2-mg lozenge every 4–8 hours during weeks 10–12. Patients who smoke first cigarette ≤30 minutes after waking: One 4-mg lozenge every 1–2 hours during weeks 1–6; then one 4-mg lozenge every 2–4 hours during weeks 7–9; and one 4-mg lozenge every 4–8 hours during weeks 10–12
Nicotine gum[24]	4 mg 2 mg	Gum	Buccal	Patients who smoke <25 cigarettes daily: Chew a 2-mg piece of gum every 2 hours during weeks 1–6; chew a 2-mg piece every 2–4 hours during weeks 7–9; and chew a 2-mg piece every 4–8 hours during weeks 10–12 of therapy. Alternatively, chew a 2-mg piece of gum whenever the urge to smoke occurs; do not exceed 2 pieces (4 mg) per hour Patients who smoke ≥25 cigarettes daily: Chew a 4-mg piece of gum every 2 hours during weeks 1–6; chew a 4-mg piece every 2–4 hours during weeks 7–9; and chew a 4-mg piece every 4–8 hours during weeks 10–12 of therapy Alternatively, chew a 4-mg piece whenever the urge to smoke occurs; do not exceed 2 pieces (8 mg) per hour
Bupropion[25] Sustained-release	150 mg	Tablet	Oral	150 mg orally in the morning for 3 days, then increase to 150 mg 2 times a day (MAX dose 300 mg/day) for 7-12 weeks; treatment should begin 1 week before the patient stops smoking
Varenicline[26]	1 mg 0.5 mg	Tablet	Oral	Initial, 0.5 mg orally once daily for days 1 through 3, then 0.5 mg twice daily for days 4 through 7, then 1 mg twice daily; duration of treatment is 12 weeks; an additional 12 weeks in patients who have successfully stopped smoking may increase the likelihood of long-term abstinence
Clonidine[27]	0.3 mg 0.2 mg 0.1 mg	Tablet Patch	Oral Transdermal	Oral: Initial: 0.1 mg twice daily; titreate by 0.1 mg/day every 7 days if needed; dosage range used in clinical trials: 0.15-0.75 mg/day; duration of therapy ranged from 3-10 weeks in clinical trials Transdermal: Initial: 0.1 mg/24 hour patch applied once every 7 days and increase by 0.1 mg at 1-week intervals if necessary; dosage range used in clinical trials: 0.1-0.2 mg/24 hour patch applied once every 7 days; duration of therapy ranged from 3-10 weeks in clinical trials
Nortriptyline[28]	75 mg 50 mg 25 mg	Capsule	Oral	25 mg daily, and then gradually increase to a target dosage of 75–100 mg daily Initiate nortriptyline therapy 10–28 days before date set for cessation of smoking Nortriptyline was continued for approximately 12 weeks in clinical studies

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Month/Year of Review: April 2012
PDL Classes: Pulmonary Arterial Hypertension Agents
Date of Last Review: September 2010
Source Document: Provider Synergies

Current Preferred Agents:	Current Non-Preferred Agents*:
Oral Agents Bosentan (Tracleer®) Sildenafil (Revatio®) Tadalafil (Adcirca®)	Oral Agents Ambrisentan (Letairis®) Inhalation Agents Iloprost (Ventavis®) Treprostinil (Tyvaso®)

***** Home administered IV's are non-preferred (Epoprostadil, Revatio, Veletri, Flolan, Remodulin)

Previous Recommendations:
1. There is no evidence found to support a difference in efficacy/effectiveness between members of this class.
2. There was no evidence found to support a difference in harms between members of this class.
3. Consideration should be given to including at least on medication from each dosage form (oral and inhalation).
4. Prior Authorization (PA) criteria should be considered for appropriate patient selection.

PA Criteria/QL: Prior Authorization is required for non preferred agents on PDL to ensure appropriate use for pulmonary arterial hypertension (Appendix 1). This requires the patient have a World Health Organization Functional Class (WHO-FC) of II-IV and the drug prescribed by a pulmonologist or cardiologist. Revatio and Adcirca have the FDA indication for pulmonary hypertension and should not be used for erectile dysfunction.

Methods:
A MEDLINE OVID search was conducted using all included oral and inhalation drugs in pulmonary arterial hypertension and limits for humans, English language, and controlled clinical trials or meta-analysis from 2010 to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, 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:
A Meta -analysis was performed and reviewed by the Centre for Reviews and Dissemination and met their criteria for inclusion.[1] Twenty-four RCTs (3,758 participants) were included. This review concluded that prostanoids, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors all had benefits in people with pulmonary arterial hypertension. Only intravenous prostanoids had a proven benefit on mortality, particularly in people with severe disease (RR 0.49, 95% CI 0.29 to 0.82; 10 trials). Compared to placebo, endothelin receptor antagonists (8 studies) and PDE5 inhibitors (3 trials) had no statistically significant effect on mortality. Endothelin receptor antagonists were associated with statistically significant improvements in six-minute walk distance (38 meters, 95% CI 27.2 to 48.7; seven trials), functional class (six trials), Borg score (five trials) and most hemodynamic changes (five trials). PDE5 inhibitors were associated with statistically significant improvements in six-minute walk distance (33.7 meters, 95% CI 22.5 to 44.8; three trials) and all reported hemodynamic parameters (two trials). Available data was based on studies of short duration (12 -16 weeks) and authors agreed that longer term studies were needed to confirm results.

New Trials:
A total of 30 citations resulted from the initial MEDLINE search and after review for inclusion, four potentially relevant clinical trials were identified (Appendix 2). These trials are briefly described in Table 1.

Table 1: Study details

Study	Comparison	Population	Primary Outcome	Results
McLaughlin, 2010[2] DB, MC, PC, RCT TRIUMPH-1	Treprostinil inhaled four times daily vs. placebo in patients already on either bosentan or sildenafil therapy	Adults with PAH, baseline 6MWD between 200 and 450m, receiving bosentan 125mg daily or any prescribed dose of sildenafil for at least 3 months N=235	Change in 6MWD measured at peak (10 to 60 minutes after inhalation)	<u>Change in 6MWD at 12 weeks:</u> • Between-treatment median difference in change from baseline in peak 6MWD was 20 m (*P*=0.0004). • Between-treatment median difference in change in peak 6MWD was 25 m (*P*=0.0002) in patients receiving background bosentan therapy and 9 m in patients taking sildenafil background therapy (*P* value not significant). • There was no difference in time to clinical worsening between treatment groups
Barst, 2011[3] DB, PC	Tadalafil 2.5mg vs. 10mg vs. 20mg vs. 40mg vs. placebo stratified by background bosentan	Patients with PAH with the option of background bosentan	Change in 6-minute walk distance (6MWD)	<u>PBO-adjusted change in 6MWD from baseline at week 16 (meters)</u> *Bosentan background* 20mg: 22.6; 95 % CI (-0.5 to 45.7), p=NS 40mg: 22.7; 95% CI (-2.4 to 47.8), p=NS *Treatment-naïve* 20mg: 32.4; 95% CI (6.8 to 58.1), p=NS 40mg: 44.3; 95% CI (19.7 to 69.0), p<0.01
Sun, 2011[4] Open-label, uncontrolled, prospective	Low dose iloprost (2.5 ug per inhalation, 6 x daily) x 24 weeks	Adults patients with PAH (n=62), 95% in WHO-FC classes II and III	Change in 6-minute walk distance (6MWD)	<u>Change in 6MWD from baseline</u> + 57 meters; 95% CI (26.59-87.82), p<0.001 *The WHO_FC was improved significantly (p=0.006), no significant in change in systemic arterial oxygen saturation and systemic arterial pressure **14 patients (22.6%) discontinued the study prematurely
Barst, 2012[5] DB, PC, RCT	Low-dose vs. medium-dose vs. high-dose sildenafil vs. placebo	Treatment-naïve children, aged 1-17	% change from baseline in peak oxygen consumption (PVo2) to week 16	<u>% change from baseline inPVo2</u> Low: 3.8<u>+</u>5.0% [95% CI, -6.1% to 13.7%] Med: 11.3 <u>+</u> 4.8% [95% CI, 1.7–20.9%] high: 8.0 <u>+</u> 4.9% [95% CI, -1.6% to 17.6%] Combined sildenafil: 7.7 <u>+</u> 4.0% (95% CI, -0.2% to 15.6%);p=0.056

New drugs:
None

New Formulations:
None

New FDA safety alerts:
On March 4, 2011, the Food and Drug Administration removed a boxed warning about a potential for liver injury from the prescribing information for ambrisentan based on the review of post-marketing data; monthly liver function monitoring is no longer required.[6] Healthcare professionals should still order liver enzyme tests when they consider it clinically necessary. Bosentan, however, is still not recommended in patients with liver impairment.

References:

1. Ryerson CJ, Nayar S, Swiston JR, Sin DD. Pharmacotherapy in pulmonary arterial hypertension: a systematic review and meta-analysis. *Respir. Res.* 2010;11:12.

2. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J. Am. Coll. Cardiol.* 2010;55(18):1915–1922.

3. Barst RJ, Oudiz RJ, Beardsworth A, et al. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. *J. Heart Lung Transplant.* 2011;30(6):632–643.

4. Sun Y-J, Xiong C-M, Shan G-L, et al. Inhaled Low-Dose Iloprost for Pulmonary Hypertension: A Prospective, Multicenter, Open-Label Study. *Clinical Cardiology*. 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22488211. Accessed April 20, 2012.

5. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. *Circulation*. 2012;125(2):324–334.

6. FDA Drug Safety Communication. Liver injury warning to be removed from Letairis (ambrisentan) tablets. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm245852.htm. Accessed April 24, 2012.

Pulmonary Arterial Hypertension

Goal(s): To ensure appropriate drug use for pulmonary arterial hypertension (PAH) by utilization in specified patient population.

Length of Authorization: 1 year

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

* Note: Revatio and Adcirca have the FDA indication for pulmonary hypertension and should not be used for Erectile Dysfunction (ED). Viagra® and Cialis® are FDA-approved for ED and not covered by OHP.

Requires PA:

GSN	Drug Name	Brand Name
	Bosentan	Tracleer
	Iloprost	Ventavis
	Treprostinil	Tyvaso

Approval Criteria		
1. What is the diagnosis?	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. Does the patient have a diagnosis of pulmonary arterial hypertension (PAH)?	**Yes:** Go to #4	**No:** Pass to RPh. RPh go to #8
4. Is this renewal of current therapy?	Yes: Go to bottom section titled "renewal"	No: go to #5
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml. Approve for 1 year.	**No:** Go to #6
6. Does the patient have a WHO FC Classification of II-IV?	**Yes:** Go to #7	**No:** Deny (Medical Appropriateness)

7. Is the drug being prescribed by a pulmonologist or a cardiologist?	**Yes:** Approve for 1 year	**No:** Deny (Medical Appropriateness)

8. RPh Only; All other indications need to be evaluated as to whether they are above the line or below the line diagnosis.

- **If above the line or clinic provides supporting literature:** approve for length of treatment.
- **If below the line:** Deny, (Not Covered by the OHP).

Renewal		
1. Does the patient have PAH with a WHO FC Classification of II-IV?	**Yes:** Go to #2	**No:** Deny (Medical Appropriateness)
2. Is the drug being prescribed by a pulmonologist or a cardiologist?	**Yes:** Approve for 1 year	**No:** Deny (Medical Appropriateness)

DUR Board Action: *9/16/10 (KS)*
Revision(s):

Appendix 2: Trial Abstracts

1. McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, Robbins IM, Olschewski H, Rubenfire M, Seeger W. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol. 2010 May 4;55(18):1915-22.

OBJECTIVES: This study assessed the efficacy and safety of inhaled treprostinil in pulmonary arterial hypertension (PAH) patients receiving therapy with either bosentan or sildenafil. BACKGROUND: There is no cure for PAH, despite effective treatments, and outcomes remain suboptimal. The addition of inhaled treprostinil, a long-acting prostacyclin analog, might be a safe and effective treatment addition to other PAH-specific oral therapies. METHODS: Two hundred thirty-five PAH patients with New York Heart Association (NYHA) functional class III (98%) or IV symptoms and a 6-min walk distance (6MWD) of 200 to 450 m while treated with bosentan (70%) or sildenafil were randomized to inhaled treprostinil (up to 54 mug) or inhaled placebo 4 times daily. The primary end point was peak 6MWD at 12 weeks. Secondary end points included time to clinical worsening, Borg Dyspnea Score, NYHA functional class, 12-week trough 6MWD, 6-week peak 6MWD, quality of life, and PAH signs and symptoms. The biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) was assessed. RESULTS: Twenty-three patients withdrew from the study prematurely (13 treprostinil, 10 placebo). The Hodges-Lehmann between-treatment median difference in change from baseline in peak 6MWD was 19 m at week 6 ($p = 0.0001$) and 20 m at week 12 ($p = 0.0004$). Hodges-Lehmann between-treatment median difference in change from baseline in trough 6MWD at week 12 was 14 m ($p = 0.0066$). Quality of life measures and NT-proBNP improved on active therapy. There were no improvements in other secondary end points, including time to clinical worsening, Borg Dyspnea Score, NYHA functional class, and PAH signs and symptoms. Inhaled treprostinil was safe and well-tolerated. CONCLUSIONS: This trial demonstrates that, among PAH patients who remain symptomatic on bosentan or sildenafil, inhaled treprostinil improves exercise capacity and quality of life and is safe and well-tolerated. (TRIUMPH I: Double Blind Placebo Controlled Clinical Investigation Into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients With Severe Pulmonary Arterial Hypertension; NCT00147199).

2. Barst RJ, Oudiz RJ, Beardsworth A, Brundage BH, Simonneau G, Ghofrani HA, Sundin DP, Galiè N; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension.

BACKGROUND: Tadalafil 40 mg orally once daily, was shown to be well-tolerated and efficacious for pulmonary arterial hypertension in a 16-week, double-blind, placebo (PBO)-controlled trial. Inclusion criteria included the option for background bosentan. Analyses of tadalafil in treatment-naive patients and as add-on to bosentan were pre-specified. Objectives were to provide safety and efficacy data for both groups.METHODS: Groups analyzed included: treatment-naive + PBO; treatment-naive + tadalafil; background bosentan + PBO; and background bosentan + tadalafil. Patients randomized to tadalafil or PBO (N = 405) were analyzed by bosentan use (yes = 216, no = 189). Treatment differences in 6-minute walk distance (6MWD, PBO-adjusted), functional class (FC), clinical worsening (CW) and adverse events were assessed. Hazard ratios (HRs) with 95% confidence intervals (CIs) are presented for FC and CW.RESULTS: At Week 16, PBO-adjusted 6MWD increases were 44 m (CI: 20 to 69 m; n = 37) for tadalafil 40 mg in treatment-naive patients and 23 m (CI: -2 to 48 m; n = 42) for tadalafil 40 mg add-on to bosentan. The 6MWD for treatment-naive and background bosentan PBO patients decreased by 3 m and increased by 19 m, respectively, at Week 16 compared with baseline. Two (5%) treatment-naive patients had CW with tadalafil 40 mg vs 8 (22%) with PBO (HR = 3.3, CI: 1.1 to 10.0). Two (5%) background bosentan patients had CW with tadalafil 40 mg add-on vs 5 (11%) for PBO add-on (HR = 1.9, CI: 0.4 to 10.2). Adverse events for tadalafil monotherapy and as add-on were similar.CONCLUSION: Tadalafil 40 mg was well-tolerated and provided clinical benefit in patients as monotherapy. It was also well-tolerated when added to background bosentan, but data are insufficient to conclude additional benefit.

3. Sun YJ, Xiong CM, Shan GL, Gu Q, Zeng WJ, Lu XL, Zhu F, Liu ZH, Ni XH, He JG; on behalf of the Iloprost Therapy on Pulmonary Hypertension Study Group. Inhaled Low-Dose Iloprost for Pulmonary Hypertension: A Prospective, Multicenter, Open-Label Study. Clin Cardiol. 2012 Apr 9. doi: 10.1002/clc.21987. [Epub ahead of print]

BACKGROUND: Inhaled iloprost (average >30 μg/d) has been considered an effective treatment for severe pulmonary hypertension (PH). Further evidence also showed that low-dose iloprost given intravenously was equally effective as high-dose iloprost in the therapy of systemic sclerosis. HYPOTHESIS: Patients with pulmonary hypertension will benefit from inhalation of low-dose iloprost. METHODS: Sixty-two patients with PH were enrolled and initiated with neubulizedlow-dose iloprost (2.5 μg per inhalation, 6× daily) for 24 weeks in 13 medical centers in China. Efficacy endpoints included changes in 6-minute walk distance (6MWD), World Health Organization functional class (WHO-FC), and hemodynamic parameters.RESULTS: Fourteen patients (22.6%) prematurely discontinued the study: 8 due to clinical worsening (6 in WHO-FCIII-IV at baseline), 4 because of protocol change, and 2 patients lost during follow-up. In the remaining 48 patients, 6MWD was increased from 356 ± 98 meters to 414 ± 99 meters ($P < 0.001$) and WHO-FC improved significantly ($P = 0.006$) after 24-week inhalation therapy. Cardiac output, cardiac index, and mixed venous oxygen saturation improved significantly compared with baseline ($n = 34$, $P < 0.05$). Most of the hemodynamic parameters improved significantly in patients in WHO-FC II ($P < 0.05$) but not in patients in WHO-FCIII-IV. CONCLUSIONS: Low-dose iloprost inhalation significantly improved exercise capacity and functional status in patients with PH. It was well tolerated. The improvement of hemodynamics was confirmed in patients with WHO-FCI-II but not in patients with WHO-FCIII-IV, suggesting the importance of early treatment in patients with advanced disease stages. Clin. Cardiol. 2012 DOI: 10.1002/clc.21987 This study was supported by National Grant from the Ministry of Science and Technology (Beijing, China, project number 2006BAI01A07) and the Capital Development Scientific Fund (Beijing, China, project number 2005-1018). The authors have no other funding, financial relationships, or conflicts of interest to disclose.

4. Barst RJ, Ivy DD, Gaitan G, Szatmari A, Rudzinski A, Garcia AE, Sastry BK, Pulido T, Layton GR, Serdarevic-Pehar M, Wessel DL. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension.

BACKGROUND: Safe, effective therapy is needed for pediatric pulmonary arterial hypertension. METHODS AND RESULTS: Children (n=235; weight ≥8 kg) were randomized to low-, medium-, or high-dose sildenafil or placebo orally 3 times daily for 16 weeks in the Sildenafil in Treatment-Naive Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension (STARTS-1) study. The primary comparison was percent change from baseline in peak oxygen consumption (PV(O(2))) for the 3 sildenafil doses combined versus placebo. Exercise testing was performed in 115 children able to exercise reliably; the study was powered for this population. Secondary end points (assessed in all patients) included hemodynamics and functional class. The estimated mean±SE percent change in PV(O(2)) for the 3 doses combined versus placebo was 7.7±4.0% (95% confidence interval, -0.2% to 15.6%; P=0.056). PV(O(2)), functional class, and hemodynamics improved with medium and high doses versus placebo; low-dose sildenafil was ineffective. Most adverse events were mild to moderate in severity. STARTS-1 completers could enter the STARTS-2 extension study; patients who received sildenafil in STARTS-1 continued the same dose, whereas placebo-treated patients were randomized to low-, medium-, or high-dose sildenafil. In STARTS-2 (ongoing), increased mortality was observed with higher doses. CONCLUSIONS: Sixteen-week sildenafil monotherapy is well tolerated in pediatric pulmonary arterial hypertension. Percent change in PV(O(2)) for the 3 sildenafil doses combined was only marginally significant; however, PV(O(2)), functional class, and hemodynamic improvements with medium and high doses suggest efficacy with these doses. Combined with STARTS-2 data, the overall profile favors the medium dose. Further investigation is warranted to determine optimal dosing based on age and weight.

Drug Use Research & Management Program
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Month/Year of Review: April 2012
PDL Classes: DPP4 Inhibitors
GLP-1 agonists and analogs
Oral Hypoglycemics
Thiazolidinediones

Date of Last Review: June 2009
Source Document: DERP Report (June 2009)

Current Preferred Agents:

Dipeptidyl peptidase (DPP4) Inhibitors
Sitagliptan/metformin (Janumet®)
Sitagliptan (Januvia®)

Glucagon-like peptide (GLP)-1 Analogs
Pramlintide (Symlinpen 60 and 120®)

Thiazolidinediones (TZD's)
Pioglitazone (Actos®)

Oral hypoglycemics
Glimepiride
Glipizide
Glyburide
Metformin
Metformin ER

Current Non-Preferred Agents:

Oral hypoglycemics
Glyburide micronized
Chlorpropamide
Tolbutamide
Repaglinide (Prandin®)
Nateglinide (Starlix®)
Tolazamide

Thiazolidinediones
Rosiglitazone (Avandia®)

DPP4 Inhibitors
Linagliptan (Tradjenta®)
Saxagliptan (Onglyza®)

GLP-1 Analogs
Exenatide (Byetta®)
Liraglutide (Victoza®)

Combination Products
Rosiglitazone/Glimepiride (Avandaryl®)
Pioglitazone/Glimepiride (Duetact®)
Pioglitazone/metformin (Actoplus Met®)
Rosiglitazone/metformin (Avandamet®)
Glyburide/metformin
Glipizide/metformin
Repaglinide/metformin (Prandimet®)
Saxagliptan /metformin (Kombiglyze XR®)
Linagliptan/metformin (Jentadueto®)
Sitagliptan/metformin (Janumet XR®)

Previous Recommendations:

Oral Hypoglycemics

1. 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 A1c (HbAlc).
2. 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.
3. There is insufficient evidence on other sulfonylureas and nonsulfonylureas secretagogues to identify a difference in progression or occurrence of clinically relevant outcomes.
4. 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.

TZDs

1. Good quality evidence shows that pioglitazone and rosiglitazone have similar effects on A1C, yielding a decrease of approximately 1%. There are no significant differences between these two drugs for effect on A1c .
2. TZDs have a similar effect on A1C as metformin, glibenclamide, or glimepiride.

3. There is no difference between TZDs and metformin or sulfonylureas in their ability to lower A1c.

DPP4-Inhibitors
1. Data are insufficient to determine the long term clinical effectiveness of sitagliptin.
2. No studies provided evidence on benefits or harms for follow-up periods longer than 52 weeks.
3. There was no evidence of increased adverse events for sitagliptin vs. placebo.
4. Sitagliptin had lower rates of abdominal pain, nausea, vomiting and diarrhea than metformin.
5. Sitagliptin and metformin as monotherapy or in combination have a lower incidence of hypoglycemia than glipizide.

GLP-1 agonists and analogs
1. Data are insufficient to determine long term effectiveness of pramlintide in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy.
2. Pramlintide + insulin treated patients had an increased incidence of nausea, vomiting and anorexia than insulin treated patients.
3. Data are insufficient to determine long term clinical effectiveness of pramlintide in Type 2 Diabetes when added to prandial insulin compared to conventional insulin therapy with or without concurrent oral agents.
4. No studies meeting inclusion criteria examined exenatide as monotherapy or combined therapy for long term health outcomes.
5. Nausea and vomiting were more common in exenatide vs. insulin groups.

PA Criteria/QL: Prior Authorization criteria for incretin enhancers, incretin mimetics, and amylin analogs to promote use of preferred agents and require a trial of metformin and sulfonylurea therapy or have contraindications before approval of a non-preferred agent in these classes.

Methods:
A MEDLINE OVID search was conducted using all included drugs in adults and limits for humans, English language, and controlled clinical trials or meta-analysis from July 2010 (end of literature search in recent systematic review) to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, 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:
The Oregon Evidence-based Practice Center (EPC) for the Drug Effectiveness Review Project (DERP) produced an original report on newer diabetes medications, TZD's, and combinations in February 2011.[1] The full report can be found on the Evidence-based Practice Center website: http://derp.ohsu.edu/about/final-document-display.cfm. This review compared the effectiveness and adverse event profiles of amlyin agonists, DDP-4 inhibitors, incretin mimetics, TZDs, and certain combination products for people with type 2 diabetes and for people with type 1 diabetes for pramlintide only.

Most of the evidence was limited to adult populations which evaluated intermediate outcomes, such as HbA1c or weight. Very few studies reported health outcomes or were longer than 6 months. All of the included medications were found to be efficacious for reducing HbA1c and none of the newer medications appeared to cause weight gain. Little data was available to evaluate the long-term effectiveness of the newer medications compared with more established treatments. Overall, there was insufficient evidence to determine how fixed-dose combination products (FDCPs) compared with other treatments for their impact on health outcomes and there were no head-to-head trials that compared 2 FDCPs. There was insufficient evidence to draw conclusions based on subgroups of patients based on demographics, comorbidities, or other medications. The following additional conclusions were made for each drug class.

Amylin Agonists

There was insufficient evidence to determine how pramlintide compares with other treatments for their impact on health outcomes. There was moderate strength evidence that a greater reduction in HbA1c was demonstrated with pramlinitde added to fixed doses of insulin compared with placebo and insulin (range 0.13% to 0.4%) and low evidence that there is no statistically significant differences when added to insulin glargine or determir compared with rapid acting insulin (1.1% vs. 1.3%, p=0.46).[1] There was moderate strength evidence demonstrating nausea as the most commonly reported adverse event which occurred more frequently with pramlintide plus insulin than with placebo plus insulin.

DPP-IV Inhibitors

There was insufficient evidence to compare the direct effectiveness of sitagliptan and saxagliptin and all included studies focused on intermediate outcomes.. There was low quality evidence that sitagliptin monotherapy resulted in slightly less HbA1c reduction than either metformin monotherapy over 54 weeks (between group difference −0.16 for metformin 1000 and −0.47 for metformin 2000 mg/d) or glipizide monotherapy over 12 weeks (between group difference −0.22%). [1] There was moderate strength evidence that there is no significant difference in reduction in HbA1c between rosiglitazone and sitagliptin when added to metformin therapy.

GLP-1 Agonists

No studies examined the impact of treatment on health outcomes as the primary outcomes. One head-to-head trial demonstrated low quality evidence that liraglutide 1.8mg once daily reduced mean HbA1c significantly more than exenatide 10 mcg twice daily (treatment difference -0.33%; 95% CI -0.47 to -0.18) and resulted in similar weight loss.[1] This trial also demonstrated no significant difference in withdrawal rates between groups. There is moderate strength evidence that there is no significant difference in reduction in HbA1c between exenatide and insulin when also taking oral diabetic agents (exenatide range -1.0% to -1.4%, insulin range -0.9% to -1.4%)

TZDs:

Moderate evidence from a meta-analysis of 8 head-to-head randomized controlled trials suggests no statistically significant difference between pioglitazone and rosiglitazone for their ability to improve glycemic control (mean difference in reduction in HbA1c -0.09, 95% CI -0.23 to 0.05) when used in either monotherapy or combination therapy.[1] There is also moderate strength evidence that there is no difference between pioglitazone or rosiglitazone and sulfonylureas for reduction in HbA1c and high quality evidence for no difference between pioglitazone and metformin. There is high quality evidence that both TZDs increase the risk of heart failure (Odds ratio from 1.32 to 2.18) and the risk of edema (Odds ratio from 2.26 to 2.18).[1] There is low strength evidence that there is no increased all-cause mortality or cardiovascular mortality with pioglitazone. There is also moderate strength evidence that the risk of fractures is increased among patients exposed to TZDs (OR 1.45, 95% CI 1.18 to 1.79, from meta-analysis of 10 randomized controlled trials with 13,715 patients). This risk appears to be increased among women compared to men.[1]

<u>Agency for Healthcare Research and Quality</u>

The Agency for Healthcare Research and Quality (AHRQ) published an update to the comparative effectiveness review on Oral Diabetes Medications for Adults with Type 2 Diabetes in March 2011 to summarize the benefits and harms of medications as monotherapy and in combination, for the treatment of adults with type 2 diabetes.[2] There was low or insufficient evidence for all comparisons when focusing on long term clinical outcomes of all-cause mortality, cardiovascular disease, nephropathy, and neuropathy, as most studies were generally of short duration and had few long-term events. Metformin was associated with slightly lower all-cause mortality and cardiovascular disease mortality than the sulfonylureas. There was moderate strength evidence from two larger trials that pioglitazone is better than metformin at reducing short-term nephropathy. In both trials, the urinary

albumin-to-creatinine ratio declined in patients receiving pioglitazone by 15 percent and 19 percent, respectively but remained unchanged in patients with metformin with statistically significant differences between groups in both trials.[2]

Intermediate outcomes were the most frequently evaluated outcomes. Most diabetes medications reduced HbA1c to a similar degree, by about 1 absolute percentage point (moderate to high strength of evidence). There was moderate strength of evidence that metformin was more efficacious than the DPP-4 inhibitors in lowering HbA1c (by about 0.4 absolute percentage points, 95% CI -0.5% to -0.2%) based on three randomized controlled trials.[2] There was high strength of evidence that TZD's and sulfonylureas had a more unfavorable effect on weight compared to metformin (mean difference of -2.6kg; 95% CI -4.1 kg to -1.2 kg, mean difference of -2.7kg; 95% CI -3.5 kg to -1.9 kg for TZDs and sulfonylureas, respectively).[2] Three RCTs comparing rosiglitazone directly with pioglitazone showed a greater increase in LDL with rosiglitazone, (pooled between-group difference of 14.3 mg/dL, 95 percent CI 5.8 mg/dL to 22.7 mg/dL) and that pioglitazone increased HDL more than rosiglitazone (pooled between group difference of -2.3 mg/dL, 95 percent CI -3.5 mg/dL to -1.2 mg/dL).[2] All comparisons with the GLP-1 agonists were based on insufficient or low evidence. Comparisons of two-drug combinations showed little to no difference in HbA1c reduction, but some combinations increased risk for hypoglycemia and other adverse events.

Metformin was associated with high risk of gastrointestinal side effects than all other medications and there was high strength of evidence that TZDs were associated with a 1.5-fold higher risk of bone fractures than was with metformin alone or in combination with a sulfonylurea and women were taking rosiglitazone were at higher risk for bone fractures than men.[2] No other conclusions regarding differences in subgroups of patients could be made. Sulfonylureas had a fourfold higher risk of mild/moderate hypoglycemia compared with metformin alone, and, in combination with metformin, had more than a fivefold increased risk compared with metformin plus TZDs. TZDs also had an increased risk of congestive heart failure relative to sulfonylureas and bone fractures relative to metformin.

Other

Another meta-analysis was performed that included 43 randomized (n=19,101) controlled trials lasting at least 12 weeks involving DPP-4 inhibitors.[3] Of participants evaluated for the primary endpoint, 10,467 were treated with a DPP-4 inhibitor and 8,634 treated with placebo or a comparator drug. DPP-4 inhibitors showed a statistically significant reduction in HbA1c compared to placebo and approximately 40 percent of participants achieved the HbA1c goal of < 7 percent, which was associated with weight neutrality and no greater hypoglycemia. Baseline HbA1c was the best predictor for achievement of HbA1C target ($p<0.001$).[3]

New Trials:

A total of 233 citations resulted from the original Medline literature search. After title and abstract review, 43 citations resulted and after further review for inclusion of population and outcomes, eleven potentially relevant clinical trials were identified (Appendix 1). Four trials evaluated linagliptin and are included in the individual drug monograph. The table below briefly describes the identified clinical trials.

Study	Comparison	Population	Primary Outcome	Results
Yang, 2011[4] R, PC, DB	saxagliptin 5mg + metformin vs. placebo + metformin (n = 570).	Asian patients with type 2 diabetes with inadequate control on metformin alone	HbA1c change from baseline to week 24	Adjusted mean decrease in HbA1c: Sax/Met: -0.78% Pla/met: -0.37% P<0.0052
Nowicki, 2011[5] RCT, DB	Saxagliptin 2.5 mg vs. placebo added to other	Type 2 diabetes and renal impairment	Change in HbA1c and fasting plasma glucose	mean decrease in HbA1c: Sax: -1.08%; 95% CI (-1.37 to -0.8%) Pla: -0.36%%; 95% CI (-0.63 to -0.08%)

	antidiabetic drugs (n=170)		(FPG) at week 52	Diff -0.73%; 95% CI -1.11% to -0.34% P<0.001 Reductions similar in patients with ESRD	
Borges, 2011[6] RCT, PG, DB	Avandamet (AVM) vs. metformin N=688	Type 2 diabetes, drug naive	Two hour pain relief	<u>Reduction in HbA1c:</u> AVM: Met: P<0.0001	<u>Reduction in FPG:</u> AVM: Met: P<0.001
Goke, 2010[7] RCT	saxagliptin 5 mg or glipizide from 5 to 20 mg x 52 weeks.	Type 2 diabetes with inadequate control on metformin alone N=858	Change from baseline in HbA1c; Non-inferiority	<u>Adjusted mean decrease in HbA1c:</u> Sax/Met: -0.74% Glp/Met: -0.80% Diff 0.06% (95% CI -0.05% to 0.16) *Discontinuation rates due to adverse events similar between groups (~4%)	
Reasner, 2010[8] RCT, DB	Sitagliptin/ Metformin 50/500 bid vs. metformin 500 bid (N=1250)	Type 2 diabetes, drug naïve Mean baseline HbA1c 9.9%	Mean reduction in HbA1c at week 18	<u>Mean change in HbA1c</u> Sita/met: -2.4% Met: -1.8% p < 0.001	
Hollander, 2011[9] DB, PC	Saxagliptin (SX) 2.5mg vs. SX 5mg vs. placebo added to TZD	Type 2 diabetes with inadequate control on TZD monotherapy N=565	Mean reduction in HbA1c at week 18 at 76 weeks	<u>Mean change in HbA1c</u> SX 2.5mg: -0.59% SX 5 mg: -1.09% PLA: -0.2% P=0.0019 for SX 2.5mg vs. placebo p < 0.0001 for SX 5 mg vs. placebo *Only 63.8% of patients completed the study	
Buse, 2011[10] RCT, DB, PC	Exenatide vs. placebo	Type 2 diabetes, HbA1c 7.1 to 10.5% on insulin glargine alone or in combination with metformin and/or pioglitazone	Mean reduction in HbA1c at week 30 weeks	<u>Mean change in HbA1c</u> Exen: -1.74% Pla: -1.04% P<0.001 <u>Achieved HbA1c <7.0%</u> Exen: 60% Pla: 35% * Thirteen exenatide patients and one placebo patient discontinued due to adverse events (p<0.010).	

New drugs:

Linagliptin (Tradjenta) is a dipeptidyl peptidase-4 (DPP-4) Inhibitor FDA approved in 2011 and used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. See full drug monograph for further information and details (http://pharmacy.oregonstate.edu/drug_policy/meetings).

New Formulations:

Exenatide extended–release (Bydureon), once weekly injection (EQW) is a glucagon-like peptide-1 (GLP-1) agonist approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. EQW is an extended release formulation of the twice daily injectable product exenatide (Byetta) which was FDA approved in 2005. See full drug summary for further information and details (http://pharmacy.oregonstate.edu/drug_policy/meetings).

New Combination Products:

Sitagliptin/simvastatin (Juvisync) is a new combination product that combines a DPP-4 Inhibitor with the cholesterol lowering agent, simvastatin. It was FDA approved in October 2011 for patients in whom treatment with

both sitagliptin and simvastatin is appropriate.[11] Sitagliptin/simvastatin was approved based on studies demonstrating its bioequivalence to the single agents administered together. In a randomized open-label, crossover study (n=29), steady-state sitagliptin did not alter the pharmacokinetics of a single dose of simvastatin. This study did not specifically evaluate the effects of simvastatin on sitagliptin pharmacokinetics, although none is expected. It has not been studied in patients with a history of pancreatitis and use is not recommended in patients with moderate or severe renal impairment or end stage renal disease (ESRD) since doses appropriate for these patients are not available in this combination product.[11]

Linagliptan/metformin (Jentadueto) is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product approved in January, 2012 and indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.[12] It is not indicated for the treatment of type 1 diabetes or diabetic ketoacidosis. Jentadueto has not been studied with insulin. There have been no clinical efficacy studies performed with linagliptin/metformin (Jentadueto). However, coadministration of the single entity medications has been studied in type 2 diabetes mellitus patients who were not well controlled in their diet and exercise and in combination with a sulfonylurea.[12] The bioequivalence of Jentadueto to linagliptin and metformin administered together as single entities was demonstrated in healthy subjects. There are currently three additional biguanide/DDP-4 combination products available.

New FDA safety alerts:
In September 2010, the FDA restricted access for rosiglitazone and combination products that contain rosiglitazone due to an increased risk of cardiovascular adverse events as a result of review of cardiovascular safety data from the long-term clinical study, Rosiglitazone Evaluted for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD).[13]

In May 2011, the FDA outlined the risk evaluation and mitigation strategy (REMS), which applies to all rosiglitazone-containing products.[14] Under the REMS, healthcare providers and patients must enroll in a special program in order to prescribe and receive these drugs. The REMS, called the Avandia-Rosiglitazone Medicines Access Program, limits the use of rosiglitazone medicines to patients already being successfully treated with these medicines and patients whose blood sugar cannot be controlled with other anti-diabetic medicines and who, after consulting with their healthcare provider, do not wish to use pioglitazone-containing medicines. As of November 18, 2011, rosiglitazone medicines are no longer available through retail pharmacies.

In June 2011, the FDA issued a safety announcement that the use of pioglitazone (Actos) for more than one year may be associated with an increased risk of bladder cancer based on two three-year trials demonstrating increased reports of bladder cancer in patients taking pioglitazone compared to placebo or glyburide (44% vs. 14%).[15] Consequently, pioglitazone should not be used in patients with active bladder cancer and should be used with caution in those with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.

In 2011, the REMS requirement for exenatide, sitagliptin and sitagliptin/metformin were removed by the FDA.

Recommendations:
1) No further review or research needed.
2) Maintain new combination products sitaglipin/simvastatin and linagliptin/metformin as non-preferred agents on the PDL.

References:

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2. Bennett W, Wilson L, Bolen S, et al. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 27. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 11-EHC038-EF. Rockville, MD: Agency for Healthcare Research and Quality. 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

3. Esposito K, Cozzolino D, Bellastella G, et al. Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2011;13(7):594–603.

4. Yang W, Pan CY, Tou C, Zhao J, Gause-Nilsson I. Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial. *Diabetes Res. Clin. Pract.* 2011;94(2):217–224.

5. Nowicki M, Rychlik I, Haller H, et al. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. *Int. J. Clin. Pract.* 2011;65(12):1230–1239.

6. Borges JLC, Bilezikian JP, Jones-Leone AR, et al. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naïve type 2 diabetes mellitus patients. *Diabetes Obes Metab*. 2011;13(11):1036–1046.

7. Göke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. *Int. J. Clin. Pract.* 2010;64(12):1619–1631.

8. Reasner C, Olansky L, Seck TL, et al. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2011;13(7):644–652.

9. Hollander PL, Li J, Frederich R, Allen E, Chen R. Safety and efficacy of saxagliptin added to thiazolidinedione over 76 weeks in patients with type 2 diabetes mellitus. *Diab Vasc Dis Res*. 2011;8(2):125–135.

10. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann. Intern. Med.* 2011;154(2):103–112.

11. Juvisync. Prescribing Information. Merck & Co., Inc. Available at: http://www.merck.com/product/usa/pi_circulars/j/juvisync/juvisync_pi.pdf.

12. Jentadueto prescribing information. Ridgefield, CT; Boehringer Ingelheim Pharmaeuticals.

13. FDA Drug Safety Communication. Ongoing review of Avandia (rosiglitazone) and cardiovascular safety. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm201418.htm.

14. FDA Drug Safety Communication. Updated Risk Evaluation and Migitation Strategy (REMS) to Restrict access to rosiglitazone-containing medicines ncluding Avandia, Avandamet, and Avandaryl. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm255005.htm.

15. FDA Drug Safety Communication. Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm.

Appendix 1: New Trials

1. Yang W, Pan CY, Tou C, Zhao J, Gause-Nilsson I. Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Res Clin Pract. 2011 Nov;94(2):217-24. Epub 2011 Aug 26.

To assess efficacy and safety of saxagliptin added to metformin versus placebo plus metformin in Asian patients with type 2 diabetes mellitus (T2DM) and inadequate glycemic control on metformin alone. METHODS: Adults (HbA(1c) 7.0-10.0%, on stable metformin ≥ 1500 mg/day) were randomized 1:1 to saxagliptin 5mg daily plus metformin (n = 283) or placebo plus metformin (n = 287). The primary end point was HbA(1c) change from baseline to Week 24. RESULTS: Saxagliptin plus metformin provided significant adjusted mean decreases versus placebo plus metformin ($p \leq 0.0052$) in HbA(1c) (-0.78% versus -0.37%), fasting plasma glucose (-1.14 mmol/L versus -0.58 mmol/L), and postprandial glucose area under the curve from 0 to 180 min (-315 mmol min/L versus -160 mmol min/L). Significantly more saxagliptin-treated patients achieved a therapeutic glycemic response (HbA(1c)<7.0%) (46.5% versus 30.5%; $p = 0.0001$). The proportion of patients experiencing adverse events (excluding hypoglycemia) was similar for saxagliptin plus metformin (42.8%) versus placebo plus metformin (40.8%). Hypoglycemic events were reported in 1.4% of patients in each group. CONCLUSION: Saxagliptin added to metformin significantly improved glycemic control and was well tolerated in Asian patients with T2DM who had inadequate glycemic control with metformin and diet and lifestyle modification.

2. Nowicki M, Rychlik I, Haller H, Warren M, Suchower L, Gause-Nilsson I, Schützer KM. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. Int J Clin Pract. 2011 Dec;65(12):1230-9. doi: 10.1111/j.1742-1241.2011.02812.x. Epub 2011 Oct 7.

OBJECTIVE: Therapeutic options are limited for diabetes patients with renal disease. This report presents 52-week results from a study assessing the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus (T2DM) and renal impairment. DESIGN: Double-blind study in patients stratified by baseline renal impairment (moderate, severe or end-stage renal disease [ESRD] on haemodialysis) randomised to saxagliptin 2.5 mg once daily or placebo added to other antidiabetic drugs in use at baseline, including insulin.PATIENTS: A total of 170 adults with glycated haemoglobin (HbA(1c)) 7-11% and creatinine clearance < 50 ml/min or ESRD were randomised and treated. Absolute changes in HbA(1c) and fasting plasma glucose (FPG) from baseline to week 52 were evaluated using analysis of covariance (ANCOVA) with last observation carried forward. Repeated-measures analyses were also performed. RESULTS: Adjusted mean decrease in HbA(1c) was greater with saxagliptin than placebo (difference, -0.73%, $p < 0.001$ [ANCOVA]). Reductions in adjusted mean HbA(1c) were numerically greater with saxagliptin than placebo in patients with renal impairment rated as moderate (-0.94% vs. 0.19% respectively) or severe (-0.81% vs. -0.49%), but similar to placebo for those with ESRD (-1.13% vs. -0.99%). Reductions in adjusted mean FPG were numerically greater with saxagliptin in patients with moderate or severe renal impairment. Saxagliptin was generally well tolerated; similar proportions of patients in the saxagliptin and placebo groups reported hypoglycaemic events (28% and 29% respectively). CONCLUSIONS: Saxagliptin 2.5 mg once daily offers sustained efficacy and good tolerability for patients with T2DM and renal impairment

3. Borges JL, Bilezikian JP, Jones-Leone AR, Acusta AP, Ambery PD, Nino AJ, Grosse M, Fitzpatrick LA, Cobitz AR. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naïve type 2 diabetes mellitus patients. Diabetes Obes Metab. 2011 Nov;13(11):1036-46. doi: 10.1111/j.1463-1326.2011.01461.x.

The purpose of this study was to evaluate if superior glycaemic control could be achieved with Avandamet® (rosiglitazone/metformin/AVM) compared with metformin (MET) monotherapy, and if glycaemic effects attained with AVM are durable over 18 months of treatment. Bone mineral density (BMD) and bone biomarkers were evaluated in a subgroup of patients. METHODS: This was a phase IV, randomized, double-blind, multi-centre study in 688, drug naïve, male and female patients who had an established clinical diagnosis of type 2 diabetes mellitus (T2DM). Patients were randomized in a 1 : 1 ratio either to AVM or MET.RESULTS: As initial therapy in patients with T2DM, AVM was superior to MET in achieving statistically significant reductions in glycated haemoglobin (HbA1c) ($p < 0.0001$) and fasting plasma glucose (FPG) ($p < 0.001$), with more patients reaching recommended HbA1c and FPG targets for intensive glycaemic control. The glycaemic effects attained with AVM compared to MET monotherapy were durable over 18 months of treatment. In the bone substudy, AVM was associated with a significantly lower BMD in comparison with MET at week 80 in the lumbar spine and total hip ($p < 0.0012$ and $p = 0.0005$, respectively). Between-treatment differences were not statistically significant for distal one-third of radius BMD, femoral neck BMD or total BMD. CONCLUSION: Superior glycaemic control was achieved with AVM compared with MET monotherapy. The superior glycaemic effects were shown to be durable over 18 months of treatment. AVM was associated with a significantly reduced BMD in comparison with MET at week 80 in the lumbar spine and total hip.

4. Göke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I; D1680C00001 Investigators. **Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial.** Int J Clin Pract. 2010 Nov;64(12):1619-31. doi: 10.1111/j.1742-1241.2010.02510.x. Epub 2010 Sep 16.

Purpose: To assess the efficacy and safety of saxagliptin vs. glipizide as add-on therapy to metformin in patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone. METHODS: A total of 858 patients [age ≥ 18 years; glycated haemoglobin (HbA(1c)) > 6.5 - 10.0%; on stable metformin doses ≥ 1500 mg/day] were randomised 1 : 1 to saxagliptin 5 mg/day or glipizide up-titrated as needed from 5 to 20 mg/day for 52 weeks. The primary objective was to assess if the change from baseline HbA(1c) achieved with saxagliptin plus metformin was non-inferior to glipizide plus metformin. RESULTS: The per-protocol analysis demonstrated non-inferiority of saxagliptin vs. glipizide; adjusted mean changes from baseline HbA(1c) were -0.74% vs. -0.80%, respectively; the between-group difference was 0.06% (95% CI, -0.05% to 0.16%). Treatment with saxagliptin vs. glipizide was associated with a significantly smaller proportion of patients with hypoglycaemic events (3.0% vs. 36.3%; $p < 0.0001$) and a divergent impact on body weight (adjusted mean change from baseline -1.1 kg with saxagliptin vs. 1.1 kg with glipizide; $p < 0.0001$). There was a significantly smaller rise in HbA(1c) (%/week) from week 24 to 52 with saxagliptin vs. glipizide (0.001% vs. 0.004%; $p = 0.04$) indicating a sustained glycaemic effect beyond week 24. Excluding hypoglycaemic events, the proportion of patients experiencing adverse events (AEs) was similar (60.0% saxagliptin vs. 56.7% glipizide); treatment-related AEs were less common with saxagliptin vs. glipizide (9.8% vs. 31.2%), attributable to the higher frequency of hypoglycaemia in glipizide patients. Discontinuation rates resulting from AEs were similar (~4%). CONCLUSION: Saxagliptin plus metformin was well tolerated, provided a sustained HbA(1c) reduction over 52 weeks, and was non-inferior to glipizide plus metformin, with reduced body weight and a significantly lower risk of hypoglycaemia.

5. Reasner C, Olansky L, Seck TL, Williams-Herman DE, Chen M, Terranella L, Johnson-Levonas AO, Kaufman KD, Goldstein BJ. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2011 Jul;13(7):644-52. doi: 10.1111/j.1463-1326.2011.01390.x.

This study was conducted to compare the glycaemic efficacy and safety of initial combination therapy with the fixed-dose combination of sitagliptin and metformin versus metformin monotherapy in drug-naive patients with type 2 diabetes. METHODS: This double-blind study (18-week Phase A and 26-week Phase B) randomized 1250 drug-naïve patients with type 2 diabetes [mean baseline haemoglobin A1c (HbA1c) 9.9%] to sitagliptin/metformin 50/500 mg bid or metformin 500 mg bid (uptitrated over 4 weeks to achieve maximum doses of sitagliptin/metformin 50/1000 mg bid or metformin 1000 bid). Results of the primary efficacy endpoint (mean HbA1c reductions from baseline at the end of Phase A) are reported herein. RESULTS: At week 18, mean change from baseline HbA1c was -2.4% for sitagliptin/metformin FDC and -1.8% for metformin monotherapy ($p < 0.001$); more patients treated with sitagliptin/metformin FDC had an HbA1c value <7% ($p < 0.001$) versus metformin monotherapy. Changes in fasting plasma glucose were significantly greater with sitagliptin/metformin FDC (-3.8 mmol/l) versus metformin monotherapy (-3.0 mmol/l; $p < 0.001$). Homeostasis model assessment of β-cell function (HOMA-β) and fasting proinsulin/insulin ratio were significantly improved with sitagliptin/metformin FDC versus metformin monotherapy. Baseline body weight was reduced by 1.6 kg in each group. Both treatments were generally well tolerated with a low and similar incidence of hypoglycaemia. Abdominal pain (1.1 and 3.9%; $p = 0.002$) and diarrhoea (12.0 and 16.6%; $p = 0.021$) occurred significantly less with sitagliptin/metformin FDC versus metformin monotherapy; the incidence of nausea and vomiting was similar in both groups. CONCLUSION: Compared with metformin monotherapy, initial treatment with sitagliptin/metformin FDC provided superior glycaemic improvement with a similar degree of weight loss and lower incidences of abdominal pain and diarrhoea

6. Hollander PL, Li J, Frederich R, Allen E, Chen R; CV181013 Investigators. Safety and efficacy of saxagliptin added to thiazolidinedione over 76 weeks in patients with type 2 diabetes mellitus. Diab Vasc Dis Res. 2011 Apr;8(2):125-35.

To assess the long-term efficacy and safety of saxagliptin in patients with type 2 diabetes mellitus inadequately controlled with thiazolidinedione monotherapy, 565 patients were randomised to saxagliptin (2.5 mg or 5 mg) or placebo added to thiazolidinedione over 76 weeks (24-week short-term + 52-week long-term extension period) in this phase 3, double-blind, placebo-controlled trial; 360 patients completed the study. At 76 weeks, adjusted mean changes from baseline HbA(1C) (repeated measures model; 95% CI) for saxagliptin 2.5 mg, 5 mg, and placebo were -0.59% (-0.75, -0.43), -1.09% (-1.26, -0.93), and -0.20% (-0.39, -0.01), respectively (post hoc and nominal $p=0.0019$ and $p<0.0001$ for saxagliptin 2.5 mg and 5 mg vs. placebo, respectively). Adverse event frequency was similar between groups. Confirmed hypoglycaemic events were 1.0% and 0% vs. 0.5% for saxagliptin 2.5 mg and 5 mg vs. placebo, respectively. Results should be interpreted with caution given the proportion of patients who discontinued or required glycaemic rescue therapy during the 76-week course of study. Saxagliptin added to thiazolidinedione provided sustained incremental efficacy vs. placebo with little hypoglycaemia for up to 76 weeks and was generally well tolerated.

7. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin–treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2011;154

Objective: To test whether twice-daily exenatide injections reduce $HbA_1(c)$ levels more than placebo in people receiving insulin glargine. DESIGN: Parallel, randomized, placebo-controlled trial, blocked and stratified by $HbA_1(c)$ level at site,performed from October 2008 to January 2010. Participants, investigators, and personnel conducting the study were masked to treatment assignments. (ClinicalTrials.gov registration number: NCT00765817) Adults with type 2 diabetes and an $HbA_1(c)$ level of 7.1% to 10.5% who were receiving insulin glargine alone or in combination with metformin or pioglitazone (or both agents). Assignment by a centralized, computer-generated, random-sequence interactive voice-response system to exenatide, 10 µg twice daily, or placebo for 30 weeks. The primary outcome was change in $HbA_1(c)$ level. Secondary outcomes included the percentage of participants with $HbA_1(c)$ values of 7.0% or less and 6.5% or less, 7-point self-monitored glucose profiles, body weight, waist circumference, insulin dose, hypoglycemia, and adverse events. RESULTS: 112 of 138 exenatide recipients and 101 of 123 placebo recipients completed the study.

The HbA_1(c) level decreased by 1.74% with exenatide and 1.04% with placebo (between-group difference, -0.69% [95% CI, -0.93% to -0.46%]; P < 0.001). Weight decreased by 1.8 kg with exenatide and increased by 1.0 kg with placebo (between-group difference, -2.7 kg [CI, -3.7 to -1.7]). Average increases in insulin dosage with exenatide and placebo were 13 U/d and 20 U/d. The estimated rate of minor hypoglycemia was similar between groups. Thirteen exenatide recipients and 1 placebo recipient discontinued the study because of adverse events (P < 0.010); rates of nausea (41% vs. 8%), diarrhea (18% vs. 8%), vomiting (18% vs. 4%), headache (14% vs. 4%), and constipation (10% vs. 2%) were higher with exenatide than with placebo. CONCLUSION: Adding twice-daily exenatide injections improved glycemic control without increased hypoglycemia or weight gain in participants with uncontrolled type 2 diabetes who were receiving insulin glargine treatment. Adverse events of exenatide included nausea, diarrhea, vomiting, headache, and constipation.

Drug Use Research & Management Program
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Month/Year of Review: April 2012
PDL Class: DM - Insulin

Date of Last Review: September 2010
Source Document: Provider Synergies

Current Preferred Agents:

Short-Acting
Human insulin regular (Humulin® R)
Human insulin regular (Novolin® R)

Rapid-Acting
Insulin aspart (Novolog®)
Insulin lispro (Humalog®)

Rapid/Intermediate-Acting Combination
Insulin aspart 70/30 (Novolog® Mix)
Insulin lispro 50/50, 75/25 (Humalog® Mix)

Intermediate-Acting
Human insulin NPH (Humulin® N)
Human insulin NPH (Novolin® N)

Long-Acting
Insulin glargine (Lantus®)

Current Non-Preferred Agents:

Rapid-Acting
Insulin glulisine (Apidra® and Apidra Solostar®)

Long-Acting
Insulin detemir (Levemir®)

Previous Recommendations:

1. Evidence does not support a difference in efficacy/effectiveness
2. Evidence does not support a difference in harms or adverse events
3. Insulin aspart and lispro are both listed as Pregnancy Category B while insulin determir, glargine, and glulisine are listed as Pregnancy Category C
4. Recommend inclusion of at least one agent from each subgroup: Short acting, rapid acting, rapid/intermediate acting combination products, intermediate acting, long acting

PA Criteria/QL: Clinical criteria to approve insulin pens/cartridges. Requests for PA for school-aged children should be reviewed on a client specific basis.

Methods:

A MEDLINE OVID search was conducted using all included drugs in subjects with diabetes and limits for humans, English language, and controlled clinical trials or meta-analysis from September 2010 to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, 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 Trials:

A total of 318 citations resulted and after review for inclusions, five potentially relevant clinical trials were identified and brief details are described in table 1.

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Thalange , 2011[1] RCT, open-label	Detemir vs. NPH + insulin aspart with meals and snacks	Aged 2-16 yr with type 1 diabetes (n=348)	HbA1c at week 52	Mean HbA1c was similar between groups at baseline (8.2 vs. 8.1%), and changed little over 1 yr (8.1 vs. 8.3%).
Swinnen, 2010[2] Non-inferiority, open-label, RCT	Insulin glargine once daily vs. insulin detemir twice daily	Insulin-naïve type 2 diabetic patients on stable oral drugs, HbA1c 7.5-10% N=973	Percentage of patients reaching A1C <7% without symptomatic hypoglycemia @24 weeks	<u>% reaching A1C<%</u> Glargine: 27.5% Detemir: 25.6% difference: 1.85% [95% CI 3.78 to7.48%] *7 patients on glargine and 22 on detemir dropped out of the study due to adverse events (P < 0.005)
Fogelfeld, 2010[3] RCT, open-label, non-inferiority	Insulin lispro vs. insulin detemir	Insulin-naïve, type 2 diabetes, on ≥2 oral diabetic meds, HbA1c 7.5-10% N=442	Change from baseline in HbA1c (non-inferiority margin of 0.4%) @ week 24	<u>Change from baseline in HbA1c</u> Lispro: -1.47 ± 1.01% Detemir: -1.24 ± 1.11% LS difference: -0.21% [95% CI -0.39 to -0.03%]
Hsia, 2011[4] RCT, open-label	Bedtime NPH vs. bedtime glargine vs. morning glargine N=85	Adults with type 2 diabetes, HbA1c 7.5-12% despite treatment with oral medications, from inner city population	Between-group difference in the change of HbA1c from baseline.	<u>Change from baseline in HbA1c</u> NPH: -1.4 ± 1.7% Glar(PM): -1.3 ± 1.2% Glar (AM): -1.9 ± 1.4% differences between groups = -0.06%; 95% CI (-0.24 to 0.12), confirming noninferiority
Philotheou, 2011[5] RCT, open-label	Insulin glulisine vs. insulin lispro	4-17 years old, type 1 diabetes, HbA1c 6.0-11% (n=572)	Non-inferiority of glulisine to lispro in HbA1c at 26 week	<u>Change from baseline in HbA1c</u> Glulisine: +0.1 ± 0.08% Lispro: +0.16 ± 0.07% Glar (AM): -1.9 ± 1.4% • differences between groups = NS
HbA1c = hemoglobin A1c, NPH = neutral protamine Hagedorn, RCT = randomized controlled trial, NS = nonsignificant				

Systematic Reviews:

A Cochrane review from 2011 evaluated the comparative efficacy of insulin detemir and insulin glargine in the treatment of type 2 diabetes and identified four randomized trials directly comparing determir to glargine lasting 24 to 52 weeks. [6] Overall, risk of bias in the trials was high, mainly because all trials were open-label and neither participants nor study personnel were blinded. For the majority of efficacy outcomes, there was statistical heterogeneity between the studies. Overall, there was low quality evidence that there was no significant difference in efficacy in terms of change in HbA1c or hypoglycemic events. The mean difference in the endpoint of HBA1c between the agents was not statistically different (0.08%; 95% CI -.10 to 0.27). The percentage of patients achieving good glycemic control at study endpoint was similar between the two insulins (RR 0.96; 95%CI 0.81 to 1.14). There was also low quality evidence that there was no difference in safety between the two insulins. There was no difference in the relative risk of having at least once hypoglycemic event (RR 0.98; 95% CI 0.92 to 1.05), without evidence for statistically heterogeneity. There was high quality evidence that there was a difference in weight gain. Insulin detemir was associated with a statistically significant less weight gain than insulin glargine (mean difference of 0.91kg; 95% CI -1.21 to -0.61). There was insufficient evidence to make conclusions regarding quality of life, cost effectiveness, or mortality. To achieve the same glycemic control, it

was found that insulin detemir was often injected twice daily in a higher dose but with less weight gain, while insulin glargine was only injected once daily.

New drugs:
None

New FDA Indications:
In May 2011, the FDA approved insulin lispro (Humalog) use in a continuous insulin infusion pump in the pediatric population.

New FDA safety alerts:
None

Guidelines:
The American Association of Clinical Endocrinologists (AACE) 2011 Diabetes Care Plan Guidelines state that insulin is required in all patients with type 1 diabetes, and it should be considered for patients with type 2 diabetes, when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.[7] When insulin therapy is indicated in patients with type 2 diabetes, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and determir are preferred over intermediate-acting NPH because they are associated with less hypoglycemia. Short- or rapid-acting insulin may considered if postprandial hyperglycemia is present; rapid-acting insulin analogues being the prefer agent of the two because they have a more rapid onset and offset of action and are associated with less hypoglycemia. Premixed insulin analogue therapy may be appropriate for patients in whom adherence to a drug regimen is problematic; although, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared with basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.[7]

According to the AACE, the preferred treatment for postprandial hyperglycemia in pregnant women is regular or rapid-acting insulin analogues. Basal insulin can be controlled with the use of rapid-acting insulin via infusion pump therapy or long-acting insulin.[7]

Recommendations:

- No further research or review needed at this time.

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Hepatitis B Antivirals PA Criteria

Month/Year of Review: February 2012
Last Oregon Review: September 2010 (Provider Synergies)

The Oregon Health Resources Commission reviewed this class of agents for Chronic Hepatitis B (CHB) for addition to the Oregon PDL last September. The full source document can be found on the HRC website: http://www.oregon.gov/OHA/pharmacy/therapeutics/docs/ps-2009-11-hep-b.pdf.

Previous Recommendations:

1. Evidence does not support a difference in efficacy/effectiveness
2. Evidence does not support a difference in harms/adverse events
3. Recommend including this class on the PDL and consider including entecavir (Baraclude) and tenefovir disoproxil fumarate (Viread)
4. Recommend establishing PA criteria for non-preferred products

Summary:
There are currently five oral nucleoside/nucleotide analogues (NA) available: lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir disoproxil fumarate. The long term clinical goals of antiviral therapy in CHB include reducing the development of cirrhosis, hepatocellular carcinoma, and death. There is moderate evidence suggesting that all of the NA have positive effects on one or more intermediate biomarkers associated with CHB including suppression of Hepatitis B Virus (HBV) DNA, normalization of serum alanine aminotransferase (ALT), hepatitis B e antigen (HBeAg) loss or seroconversion, and hematologic response of improved necroinflammatory and fibrosis scores but no one treatment has shown to improve all biomarkers and there remains controversy over how these intermediate outcomes are related and if they predict clinical long term outcomes. The high-quality systematic review prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Minnesota Evidence-based Practice center concluded that observational studies suggest that male gender, coinfection with Hepatitis C, D, or HIV, increased HBV DNA, and cirrhosis were associated with an increased risk of hepatocellular carcinoma and death.[1] Although, there is limited direct evidence that any anti-HBV therapies have a beneficial impact on these clinical outcomes, there is growing evidence that prolonged and effective suppression of HBV DNA can decrease the risk of cirrhosis and hepatocellular carcinoma. This supports the current trend to use long term antiviral therapy. [2]

In addition to comparative efficacy evaluated in the Provider Synergies review,[3] randomized controlled trials demonstrated that tenofovir treatment resulted in statistically significant improvements in Hepatitis B viral suppression compared to adefovir in both HBeAg+ (76% vs. 13%, RR 5.8, 95% CI 3.35,9.73) and HBeAg- patients (93% vs. 63%, RR 1.5, 95% CI 1.28, 1.69).[4] It was also reviewed and recommended by the Canadian Agency for Drugs and

Technologies in Health (CADTH) as well as recommended in current treatment guidelines.[5] Guidelines from the Association for the Study of Liver (EASL), the American Association for the Study of Liver Disease (AASLD), the National Institute of Health (NIH), and a panel of US expert hepatologists have all published guidelines or consensus statements for the management of CHB. These all recommend peginterferon alfa, entecavir, and tenofovir as preferred first-line drugs for CHB based largely on efficacy and a lower risk of the development of drug resistance.[6–8] While these newer antiviral agents have the potential for prolonged effective viral suppression, more studies on the safety profiles and efficacy on long term use of these newer agents are needed. Future clinical trials should incorporate long term outcomes to align treatment with the surrogate markers and whether these markers reflect important clinical outcomes.

Other Considerations:

- Lamivudine has the most robust long term safety data and still has a place in therapy in those with favorable parameters and low risk of resistance. It can also be recommended in clinical situations which a finite prophylaxis course is needed.
- Combination therapy with NA has not has not proven to be superior to monotherapy in inducing a higher rate of sustained response.

Recommendations:

Consider establishing prior authorization criteria for the non-preferred agents in this class to promote the use of the preferred and recommended products when feasible.

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Suggested PA Criteria

Hepatitis B Antivirals

Goal(s):

- **Cover hepatitis B agents according to OHP guidelines. Cover preferred products when feasible for covered diagnosis.**
- **Preferred products are selected based on evidence based reviews.**

Length of Authorization: Up to 1 year. Quantity limited to a 30 day supply per dispensing.

Pediatric age restrictions:

A. lamivudine (Epivir HBV)-2 years and up
B. adefovir dipivoxil (Hepsera)-12-17 years
C. entecavir (Baraclude)-16 years and up
D. telbivudine (Tyzeka)-safety and effectiveness not approved in pediatrics

Covered Alternatives that do not require a PA: See PDL list at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	Yes: Go to #3.	No: Pass to RPh, Deny for OHP Coverage.
3. Is the request for treatment of Chronic Hepatitis B?	Yes: Go to #4	No: Pass to RPh, Deny for Appropriateness
4. Is this a continuation of current therapy (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims. ***If request is for Pegasys, refer to PA criteria "Pegylated Interferon and Ribavirin."***	Yes: Go to Renewal Criteria	No: Go to #5
5. Has the client tried and is intolerant to, resistant to, or has a contraindication to the preferred products?	Yes: Document intolerance or contraindication. Approve requested treatment for 6 months with monthly quantity limit of 30 days supply.	No: Go to #6
6. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness &	Yes: Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.	No: Approve requested treatment for 6 months with monthly quantity limit of 30 days supply.

safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.		

Renewal Criteria		
1. Is client compliant with requested treatment? (see refill history).	Yes: Go to 2.	No: Deny. Forward to RPH for provider consult.
2. Is HBV DNA undetectable?	Yes: Approve for up to 1 year with monthly quantity limit of 30 days supply	No: Deny. Forward to RPH for provider consult.