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Drug Use Research & Management Program
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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 1).

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% <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 7.5% to 11% in pretreated patients and 7% to 10% in treatment-naïve patients. <u>Exclusion:</u> 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	<u>Adjusted mean change from baseline A1C</u>: 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 <u>Adjusted Mean Weight Gain:</u> Pio + L: 2.3kg Pio + P: 1.2Kg Difference: 1.1kg 95% CI 0.2 to 2.0 P=0.014	NA	<u>Hypoglycemia:</u> P io + L: 5 (2%) Pio + P: 0 (0%) <u>Discontinuation due to AE</u>: 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	<u>Adjusted mean change from baseline A1C</u>: L (333): -0.44	NA	<u>Hypoglycemia:</u> 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%).

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APPENDIX 1:

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 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.

Appendix 3: Quality Assessment and evidence grading methods:

The methodology and tools described below is the standard approach that will be used by OSU staff to review drugs for the Oregon Health Authority Pharmacy and Therapeutics (P&T) Committee. These methods and tools were developed by the Oregon Evidence-based Practice Center Drug Effectiveness Review Project (DERP) and used in their systematic review process. The full Review Methods for the DERP can be found on their website at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm. These methods will evolve to best fit the needs of the P&T Committee and to stay current with the standards of evidence review and principles of best evidence.

Quality Assessment

Trials included in reviews for drugs will be assessed for internal validity using the quality assessment tool below. Each trial will subsequently be rated as Good, Fair, or Poor. Studies rated as good meet all the criteria and studies that have a fatal flaw are rated poor quality. The remainder will be rated in the Fair category.

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Clinically important differences
• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.
• No	Criteria not reported or description of enrolled patients only.
5. Were outcome assessors blinded to treatment allocation?	

6. Was the care provider blinded? **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), nonadherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
• Unclear	Insufficient information provided to determine the level of attrition

Grading the strength of the evidence:
The evidence will be graded as high, moderate, low or insufficient and use an approach also accepted by the Evidence-based Practice Center Program. A comprehensive evaluation will assess the major domains including are risk of bias, consistency, directness, and precision of the evidence. After assessing each of the domains for the group of studies, an overall assessment is made for each measured outcome being assessed for benefit and harm. When there is no evidence available or the evidence is too limited or too indirect to make conclusions, the evidence will be described as insufficient. The following table provides the definitions adopted by the Evidence-based Practice Center for these terms.

Strength of Evidence Grades and Definitions[1]:

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

References:
Oregon Evidence-Based Practice Center. Drug Effectiveness Review Project: Systematic Review Methods and Procedures. Available at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/upload/DERP_METHODS_WEB_Final_January-2011-2.pdf