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

Month/Year of Review: September 2014 **Date of Last Review:** May 2010
PDL Classes: Insulin **Source Document:** Provider Synergies

Current Status of PDL Class:

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

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

Previous Conclusions and Recommendation:

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

Conclusions and Recommendations:

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

Methods:

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

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

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

New Systematic Reviews:

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

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

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

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

Guidelines:

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

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

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

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

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

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

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

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

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

Recommended Care recommendations:

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

Limited Care recommendations:

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

Comprehensive Care recommendations:

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

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

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

New Formulations/Indications:
None

New FDA safety alerts:
None

New Trials:
A total of 1536 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, 20 relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 2 for the full abstracts.

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

Swinnen et al performed a study to determine whether insulin glargine was noninferior to insulin detemir in lowering A1c in patients with type 2 diabetes. Patients (n=973) were randomized to either glargine once daily or determir twice daily for six months. Patients were all insulin naïve but were allowed to be on oral agents during and prior to study initiation. The primary outcome was percent of patients to reach an A1c of $\leq$7%. Similar percentages of patients in both treatment groups reached the target A1c (27.5% of glargine and 25.6% of determir patients; $p=0.254$). Predetermined noninferiority margin was set at -7.68%; the difference between treatments was 1.85% (95% CI -3.78 to 7.48%), demonstrating noninferiority of glargine to detemir. Overall population improvements in A1c were also similar between treatments (1.46% A1c for glargine vs. 1.54% A1c for detemir; $p =0.149$). Significantly more detemir patients achieved an A1c $\leq$6.5% (22.7 vs. 16.5%; $p=0.017$). Incidence of hypoglycemia was similar between groups. Weight gain was higher in the glargine group: difference 0.77 kg, $p\leq0.001$. More patients on glargine than on detemir completed the

study (95.4 and 89.9%, respectively, p≤ 0.001). This was a fair quality study. Although an open label trial, study design methodology was well described and outcomes were well defined.[11]

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

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

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

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

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

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

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

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

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

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

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

Aschner et al conducted a study to compare the efficacy and safety of insulin glargine with sitagliptin a dipeptidyl peptidase-4 (DPP-4) inhibitor in patients with uncontrolled diabetes. Adults with type-2 diabetes (n=515) were randomized to either 24 weeks insulin glargine (titrated to attain a fasting blood glucose of 4.0 to 5.5 mmol/L) or 100 mg oral sitagliptin once daily. The primary outcome was change from baseline in mean A1c after 24 weeks. At study end, adjusted mean reduction in HbA1c was greater for patients on insulin glargine (n=227; –1.72%) than for those on sitagliptin (n=253; –1.13%) with a mean difference of –0.59%; 95% CI –0.77 to –0.42. The rate of all hypoglycemic episodes was greater with insulin glargine than with sitagliptin (4.21 vs. 0.50 events per patient-year; p<0·0001). Severe hypoglycemia occurred in only three (1%) patients on insulin glargine and one (<1%) on sitagliptin. This was a fair quality trial. Although it was an open label design and the treatments were from different classes, the trial method and materials were well defined; as were the trial outcomes and results.[22]

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

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

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

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

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

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

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

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

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

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

References

1. Swinnen SG, Simon AC, Holleman F, Hoekstra JB, Devries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2011;(7):CD006383. doi:10.1002/14651858.CD006383.pub2.

2. Rys P, Pankiewicz O, Łach K, Kwaskowski A, Skrzekowska-Baran I, Malecki MT. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: A systematic review. *Diabetes & Metabolism*. 2011;37(3):190-200. doi:10.1016/j.diabet.2010.12.003.

3. Szypowska A, Golicki D, Groele L, Pańkowska E. Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes: a systematic review and meta-analysis. *Pol Arch Med Wewn*. 2011;121(7-8):237-246.

4. Esposito K, Chiodini P, Capuano A, Petrizzo M, Improta MR, Giugliano D. Basal supplementation of insulin lispro protamine suspension versus insulin glargine and detemir for type 2 diabetes: meta-analysis of randomized controlled trials. *Diabetes Care*. 2012;35(12):2698-2705. doi:10.2337/dc12-0698.

5. Department of Veteran Affairs. VA/DOD Clinical Practice Guideline for the Management of Diabetes Mellitus (DM). *http://www.healthquality.va.gov/guidelines/cd/diabetes/*. 2010. Available at: http://www.healthquality.va.gov/guidelines/CD/diabetes/DM2010_FUL-v4e.pdf. Accessed June 30, 2014.

6. American Diabetes Association. Standards of Medical Care in Diabetes--2014. *Diabetes Care*. 2014;37(Supplement_1):S14-S80. doi:10.2337/dc14-S014.

7. Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract*. 2011;17 Suppl 2:1-53.

8. International Diabetes Federation. International Diabetes Federation 2012 Clinical Guidelines Task Force Global Guideline for Type 2 Diabetes. *www.idf.org*. 2012. Available at: http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf. Accessed June 30, 2014.

9. Press Announcements > FDA approves Afrezza to treat diabetes. *www.fda.gov*. 2014. Available at: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm403122.htm. Accessed June 30, 2014.

10. Forst T, Larbig M, Hohberg C, et al. Adding insulin glargine vs. NPH insulin to metformin results in a more efficient postprandial beta-cell protection in individuals with type 2 diabetes. *Diabetes Obes Metab*. 2010;12(5):437-441. doi:10.1111/j.1463-1326.2010.01209.x.

11. Swinnen SG, Dain M-P, Aronson R, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes Care*. 2010;33(6):1176-1178. doi:10.2337/dc09-2294.

12. Chacra AR, Kipnes M, Ilag LL, Sarwat S, Giaconia J, Chan J. Comparison of insulin lispro protamine suspension and insulin detemir in basal-bolus therapy in patients with Type 1 diabetes. *Diabetic Medicine*. 2010;27(5):563-569. doi:10.1111/j.1464-5491.2010.02986.x.

13. Fogelfeld L, Dharmalingam M, Robling K, Jones C, Swanson D, Jacober S. A randomized, treat-to-target trial comparing insulin lispro protamine suspension and insulin detemir in insulin-naive patients with Type 2 diabetes. *Diabetic Medicine*. 2010;27(2):181-188. doi:10.1111/j.1464-5491.2009.02899.x.

14. Strojek K, Shi C, Carey MA, Jacober SJ. Addition of insulin lispro protamine suspension or insulin glargine to oral type 2 diabetes regimens: a randomized trial. *Diabetes Obes Metab*. 2010;12(10):916-922. doi:10.1111/j.1463-1326.2010.01257.x.

15. Philotheou A, Arslanian S, Blatniczky L, Peterkova V, Souhami E, Danne T. Comparable efficacy and safety of insulin glulisine and insulin lispro when given as part of a Basal-bolus insulin regimen in a 26-week trial in pediatric patients with type 1 diabetes. *Diabetes Technol Ther*. 2011;13(3):327-334. doi:10.1089/dia.2010.0072.

16. Hsia SH. Insulin glargine compared to NPH among insulin-naïve, U.S. inner city, ethnic minority type 2 diabetic patients. *Diabetes Res Clin Pract*. 2011;91(3):293-299. doi:10.1016/j.diabres.2010.11.028.

17. Van Bon AC, Bode BW, Sert-Langeron C, DeVries JH, Charpentier G. Insulin Glulisine Compared to Insulin Aspart and to Insulin Lispro Administered by Continuous Subcutaneous Insulin Infusion in Patients with Type 1 Diabetes: A Randomized Controlled Trial. *Diabetes Technology & Therapeutics*. 2011;13(6):607-614. doi:10.1089/dia.2010.0224.

18. Sourij H, Schmoelzer I, de Campo A, et al. Non-glycemic effects of insulin therapy: a comparison between insulin aspart and regular human insulin during two consecutive meals in patients with type 2 diabetes. *European Journal of Endocrinology*. 2011;165(2):269-274. doi:10.1530/EJE-11-0061.

19. Koivisto V, Cleall S, Pontiroli AE, Giugliano D. Comparison of insulin lispro protamine suspension versus insulin glargine once daily in basal-bolus therapies with insulin lispro in type 2 diabetes patients: a prospective randomized open-label trial. *Diabetes Obes Metab*. 2011;13(12):1149-1157. doi:10.1111/j.1463-1326.2011.01484.x.

20. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Insulin analogues in children with Type 1 diabetes: a 52-week randomized clinical trial. *Diabetic Medicine*. 2013;30(2):216-225. doi:10.1111/dme.12041.

21. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus. *Pediatr Diabetes*. 2011;12(7):632-641. doi:10.1111/j.1399-5448.2010.00750.x.

22. Aschner P, Chan J, Owens DR, et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. *The Lancet*. 2012;379(9833):2262-2269. doi:10.1016/S0140-6736(12)60439-5.

23. Inagaki N, Atsumi Y, Oura T, Saito H, Imaoka T. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. *Clin Ther*. 2012;34(9):1892-1908.e1. doi:10.1016/j.clinthera.2012.07.007.

24. Mathiesen ER, Hod M, Ivanisevic M, et al. Maternal Efficacy and Safety Outcomes in a Randomized, Controlled Trial Comparing Insulin Detemir With NPH Insulin in 310 Pregnant Women With Type 1 Diabetes. *Diabetes Care*. 2012;35(10):2012-2017. doi:10.2337/dc11-2264.

25. Hickman M, McBride R, Boggess K, Strauss R. Metformin Compared with Insulin in the Treatment of Pregnant Women with Overt Diabetes: A Randomized Controlled Trial. *American Journal of Perinatology*. 2012;30(06):483-490. doi:10.1055/s-0032-1326994.

26. Davies M, Heller S, Sreenan S, et al. Once-Weekly Exenatide Versus Once- or Twice-Daily Insulin Detemir: Randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. *Diabetes Care*. 2013;36(5):1368-1376. doi:10.2337/dc12-1333.

27. Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Francisco RPV. Randomized trial of metformin vs insulin in the management of gestational diabetes. *American Journal of Obstetrics and Gynecology*. 2013;209(1):34.e1-34.e7. doi:10.1016/j.ajog.2013.03.022.

28. Karagianni P, Polyzos S, Kartali N, Zografou I, Sambanis C. Comparative efficacy of exenatide versus insulin glargine on glycemic control in type 2 diabetes mellitus patients inadequately treated with metformin monotherapy. *Advances in Medical Sciences*. 2013;58(1):38-43. doi:10.2478/v10039-012-0078-7.

29. Meneghini L, Kesavadev J, Demissie M, Nazeri A, Hollander P. Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013;15(8):729-736. doi:10.1111/dom.12083.

Appendix 1: Prior Authorization Criteria

Insulins

Goal(s):

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

Initiative:

- Initiative

Length of Authorization:

Up to 12 months

Requires PA: Non-Preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code	
2. Is this an OHP covered diagnosis?	Yes: Go to #3	No: Pass to RPh; Deny, (Not covered by the OHP)
3. Is the request for an Insulin Pen or Cartridge?	Yes: Go to #4	No: Go to #5
4. Is the insulin being administered by the patient or a non-professional caregiver AND any of the following criteria apply: • Does the patient have physical dexterity problems/vision impairment • Comprehension related issues • Dosing errors with use of vials • The patient is on a low dose of insulin (≤40 units/day) • Is the request for a child < 18 years old? •	Yes: Go to #5	No: Pass to RPh; go to #6

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. • Yes: Inform provider of covered alternatives in class. www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml. For insulin pens approve for 1 year (other preferred products covered without a PA) • No: Approve for 1 year		
6. RPh only • Requests for insulin pens and cartridges on a client-specific basis • Refer to the PDL for the preferred pens. AND/OR • If the above criteria are met and the request is NOT for convenience issues alone then approve insulin pen or cartridge use.		

P&T / DUR Action: 9/16/10 (KS)
Revision(s): 12/16/10
Initiated: 1/1/11