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Insulin Drug Class Update

Date of Review: September 2017 **End Date of Literature Search:** June 2017

Current Status of PDL Class:
See **Appendix 1.**

Purpose of Review:
To evaluate new evidence for insulin products on the Preferred Drug List (PDL) and, if appropriate, update current recommendations for placement of specific insulin formulations on the Oregon Health Plan (OHP) PDL and update current clinical prior authorization (PA) criteria if appropriate.

Research Questions:
1. Is there any new comparative evidence for insulin treatments on surrogate efficacy endpoints (e.g., hemoglobin A1C [A1C] less than 7%) and long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. Is there any new comparative evidence for insulin treatments on harms outcomes (e.g., severe hypoglycemia, heart failure, diabetic ketoacidosis, pancreatitis, weight gain, etc.)?
3. Are there subpopulations of patients with diabetes mellitus for which specific insulin formulations may be more effective or associated with less harm?

Conclusions:
One high quality systematic review[1], four clinical practice guidelines[2–5], one new randomized clinical trial[6] (RCT) and one new formulation[7] were identified in this review. Subgroup analyses specific to Medicaid patients were not conducted; however, the evidence is applicable to Oregon's Medicaid patients. Several systematic reviews and meta-analyses were not included due to poor quality or because the evidence available for the analysis was of poor quality.[8–15]
CLINICAL EFFICACY
- There is insufficient comparative evidence in specific subgroup populations, and between insulins for clinically meaningful health outcomes. In addition, there is insufficient comparative evidence between different formulations of the same insulin (i.e., pens versus vials).
- There is low quality evidence in patients with type 1 diabetes mellitus (T1DM) of no difference in A1C lowering for the following comparisons: insulin degludec and insulin detemir; insulin glargine and insulin degludec; insulin detemir and insulin glargine; follow-on (F-O) insulin glargine (Basaglar) and insulin glargine U100 (Lantus); insulin glargine U100 and insulin glargine U300; fixed-dose combination product (FDCP) insulin degludec/aspart and insulin detemir.
- In patients with type 2 diabetes mellitus (T2DM), there is moderate quality evidence that daily insulin degludec and daily insulin glargine were similar in the number of patients achieving an A1C less than 7% (pooled risk ration [RR] 0.96; 95% CI, 0.90 to 1.03).[1] There was low quality evidence of no difference in A1C lowering in patients with T2DM between the following comparisons: insulin detemir and insulin glargine; F-O insulin glargine and insulin glargine U100; FDCP insulin degludec/aspart and insulin glargine U100.[1]

- A new 100 units/mL formulation of insulin glargine, Basaglar KwikPen, was found to be non-inferior to another formulation of insulin glargine 100u/mL (formulation not provided) when studied in patients with T1DM and T2DM (low quality evidence).[7] A 24-week randomized controlled trial (RCT) in patients with T1DM found Basaglar and a comparator insulin glargine 100u/mL formulation to lower A1C, -0.35% and -0.46%, respectively. In T2DM patients, Basaglar was non-inferior to a comparator insulin glargine 100u/mL formulation with A1C lowering of -1.3% in both groups.[7]
- In patients with T2DM at high risk for CV events, there was an 8.5% incidence of the first occurrence of an adjudicated major cardiovascular (CV) event (death from CV causes, nonfatal myocardial infarction [MI] or nonfatal stroke) in patients treated with insulin degludec versus 9.3% for insulin glargine (HR 0.91; 95% CI, 0.78 to 1.06; P<0.001 for noninferiority).[6]

SAFETY

- There is low quality evidence that insulin degludec has less risk of nocturnal hypoglycemia than insulin glargine U100 in patients with T1DM based on three studies (rate ratio 0.61; 95% CI, 0.46 to 0.82).[1,16–18] Due to reporting methods absolute risk reductions (ARR) could not be calculated for two of the three studies. In the third study, nocturnal hypoglycemia in patients with T1DM treated with insulin degludec was less than with insulin glargine at 52 weeks (ARR 2.0%/NNT 50).[16]
- Data from six studies found moderate quality evidence in patients with T2DM than insulin degludec had a reduced incidence of nocturnal hypoglycemia compared to insulin glargine (rate ratio 0.71; 95% CI, 0.59 to 0.85).[1] Results were statistically significant for two studies lasting 52 weeks and no differences were found in four studies lasting 26 weeks.[19–24] The two studies showing differences found a 1.4 -7% less risk of nocturnal hypoglycemia with insulin degludec compared to insulin glargine (NNT 14-71).[20,21]
- There is moderate quality evidence that severe hypoglycemia rates were not clinically different between basal insulin therapies.[3]
- Withdrawals due to adverse events were found to be higher, based on moderate quality evidence, in patients with T2DM treated with insulin detemir compared to insulin glargine U100 in trials lasting up to 52 weeks (RR 2.1; 95% CI, 1.4 to 3.3). In two of the six studies the withdrawal rates were statistically significantly higher with insulin detemir compared to insulin glargine resulting in an ARR of 3-4% and number needed to harm (NNH) of 25-33.[25,26]

Recommendations:

- No changes are recommended to the PDL based on new evidence.
- Remove requirement that patients must use 40 units or less per day of insulin to be candidates for an insulin pen. Removal of this restriction will allow patients who use large amounts of insulin to have access to concentrated insulin products (insulin glargine 300 units/mL [Toujeo], insulin lispro 200 units/mL [Humalog], insulin degludec [Tresiba] and combination products) as these products are not available in vials. This recommendation does not affect the PDL status of these insulin products.
- After executive session the committee voted to remove the PA requirement on insulin glargine (Lantus®) pens and insulin aspart (Novolog®) pens and require a trial of these products, in vial or pen formulation, before receiving other types of insulin pens.

Previous Conclusions and Recommendations:

- In adults with T1DM or T2DM, there is no difference between insulin detemir and glargine in absolute reduction of A1C or proportion with A1C of 7.0% or less between 12 to 52 weeks based on low quality evidence.
- In adults with T1DM or T2DM, there is no difference between insulin glargine U100 and U300 in absolute reduction in A1C or proportion with A1C of 7.0% or less between 4 to 6 months based on low to moderate quality evidence.

- There is low quality evidence that there are no differences in rates of severe hypoglycemia or serious adverse events between insulin detemir and glargine in adults enrolled in studies up to 1 year in length; however, there may be increased risk of drug discontinuation with insulin detemir due to adverse events (pooled RR 2.1; 95% CI, 1.4 to 3.3).
- In adults with T1DM or T2DM, glargine concentration (U100 vs. U300) did not affect rates of severe hypoglycemia or serious adverse events based on low quality evidence in studies up to 6 months in length. However, there is moderate quality evidence that rates of nocturnal hypoglycemia may be less with U300 in adults with T2DM, but not T1DM, over 6 months (38% vs. 51%; pooled RR 0.75; 95% CI, 0.67 to 0.84; I^2=0%).
- In adults with T1DM and T2DM, insulin degludec was found to be non-inferior to insulin glargine U100, insulin detemir and sitagliptin based on moderate evidence. Risk of hypoglycemia was found to be less with insulin degludec compared to insulin glargine in patients with T1DM and T2DM; however, differences were small suggesting additional long-term evidence is needed to clarify clinical significance.
- Make insulin glargine U300 and insulin degludec non-preferred and subject to current PA criteria for insulin pens.

Background:

More than 29 million people in the United States are thought to be living with diabetes.[27] In Oregon, it is estimated that 287,000 adults have diabetes, in which 38,000 are thought to be OHP members. There are over 7,000 patients in the Oregon Medicaid fee-for-service population alone that have T2DM and almost 1,000 have T1DM.[28] Caring for patients with diabetes enrolled in OHP accounted for $106 million in direct medical claims for diabetes and diabetes-related complications in 2012. The overall cost to the state is estimated at $3 billion a year.[28]

Insulin is used to mimic endogenous insulin release in patients with T1DM and is often necessary to obtain glucose targets in patients with T2DM. Adjustments in insulin doses are made to obtain target fasting and prandial glucose levels while minimizing the risk of hypoglycemia. Insulins are categorized by onset and duration of action. Most T1DM patients use multiple daily injections of basal and prandial insulins. Patients with T2DM who require insulin therapy are usually initiated on a basal insulin product. Basal insulins include NPH and recombinant analog formulations glargine, detemir, and degludec. Prandial insulins include formulations of regular insulin, and recombinant analogs lispro, aspart and glulisine. Evidence suggests no clinical differences in A1C lowering between the different basal insulins products in patients with T1DM or T2DM.[3] Hemoglobin A1C lowering has been shown to be similar between the different prandial insulins. Common insulin adverse reactions are hypoglycemia, injection site reactions, and weight gain. Basal insulin analogs and rapid-acting insulin analogs may have a reduced risk of hypoglycemia.[5]

Clinically meaningful outcomes in patients with diabetes include microvascular (i.e., retinopathy, nephropathy, neuropathy) and macrovascular complications (i.e., stroke, myocardial infarction), mortality, and severe hypoglycemia. Because hyperglycemia is associated with increased microvascular complications and possibly macrovascular outcomes, A1C changes are often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies.[4] The Diabetes Control and Complication Trial (DCCT), which was a large prospective trial in patients with T1DM, provided evidence that intensive insulin therapy led to improved glucose control and reductions in microvascular outcomes.[29] A study in T2DM patients reiterated the DCCT findings, that maintenance of glucose lowering targets minimized microvascular complications in this population.[30] Due to the increased risk of CV disease in patients with diabetes, the effect of insulin on CV outcomes is of high importance. Evidence has shown that intensive glucose control produced a trend towards less risk of CV events in patients with T1DM.[29] In patients with T2DM intensive glucose control reduced CV outcomes based on the United Kingdom Prospective Diabetes Study (UKPDS) study; however, this was not shown in subsequent studies (Action to Control Cardiovascular Risk in Diabetes [ACCORD], The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE] and Veterans Affairs Diabetes Trial [VADT]]).[4] There is a paucity of evidence on the risk or benefit of insulin use on CV outcomes in patients with diabetes from RCTs specifically designed to assess CV events. One study compared insulin glargine to standard of care and n-3 fatty acids or placebo in patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. The study

found similar rates of CV outcomes (nonfatal MI, nonfatal stroke, or death from CV causes) in both groups: 2.94 and 2.85 per 100 person-years in patients with a median follow-up of 6.2 years (HR 1.02; 95% CI, 0.94 to 1.11).[31]

Utilization:
The highest insulin utilization is for the preferred product insulin glargine (Lantus) with 43% of the insulin market share. For short-acting insulin, insulin lispro (16%) and insulin apart (18%) have the highest utilization. The number of non-preferred insulins prescription claims comprises 7% of insulin utilization and 49% of net costs for the class. Overall preferred insulin products account for 51% of the insulin class costs. The concentrated insulin products account for 4% of the market share and 17% of the net costs for the class.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer for new drug approval included in this review, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Systematic Reviews:

DERP – Long-Acting Insulins for Type 1 and Type 2 Diabetes
The Drug Effectiveness Review Project (DERP) released a report on long-acting insulins used for the treatment of T1DM and T2DM in adults and children in May of 2017.[1] The review included the following: insulin glargine U100 or U300 (Basaglar U100, Lantus U100, Toujeo U300), insulin detemir (Levemir), insulin degludec (Tresiba), insulin degludec/insulin aspart (Ryzodeg 70/30) and insulin glargine biosimilar, which they describe as F-O glargine (Basaglar). Sixty-one studies comparing insulin products were included in the review with a search date lasting till November 2016. Efficacy and harms data was insufficient for long-acting insulin use in children with diabetes.

Insulin Degludec and Insulin Detemir
Type 1 Diabetes

- There is low quality evidence of no difference in glycemic control between insulin degludec and insulin detemir in children and adolescents or adults with T1DM based on two fair-quality trials. There was insufficient evidence available to evaluate differences in risk of nocturnal or severe hypoglycemia.[1]

Insulin Degludec versus Insulin Glargine U100

Type 1 Diabetes

- Insulin degludec and insulin glargine demonstrated similar A1C lowering in patients with T1DM based on three fair to good quality trials lasting up to 52 weeks (low strength of evidence).
- Nocturnal hypoglycemia was lower with insulin degludec than insulin glargine U100 with a pooled rate ratio of 0.61 (95% CI, 0.46 to 0.82; I^2 = 55%) based on low quality evidence.[1] Data from one of the original trials that lasted 52 weeks found nocturnal hypoglycemia occurred in 72% of insulin degludec treated patients and 74% of glargine treated patients (ARR 2.0%/NNT 50; P=0.021).[16] In a second study the incidence of nocturnal hypoglycemia was 5.1 events per patient/year with insulin degludec compared to 12.3 events per patient/year with insulin glargine (p<0.01).[17] In a third study, the incidence of nocturnal hypoglycemia was 3 events/patient for insulin degludec compared to 4.5 events/patient for insulin glargine when patients were treatment for 24 weeks (p=0.001).[18] Data was insufficient to compare outcomes of severe hypoglycemia or withdrawals due to adverse events.

Type 2 Diabetes

- Six (n= 4,434) trials provided moderate-strength evidence that there was no difference in glycemic efficacy between insulin degludec and insulin glargine based on the number of patients achieving an A1C less than 7% (RR 0.96; 95% CI, 0.90 to 1.03; I^2= 0%) and the number of patients meeting this A1C goal with no episodes of confirmed hypoglycemia (RR 1.0; 95% CI, 0.88 to 1.1; I^2=17%).[1]
- Low-strength evidence found insulin degludec given three times weekly had less glucose lowering efficacy than insulin glargine U100 given daily. Fewer patients in the insulin degludec group achieved an A1C less than 7% compared to insulin degludec, 47% versus 56%, respectively (ARR 0.09; RR 0.84; 95% CI, 0.74 to 0.95; I^2=0%).[1] Nocturnal hypoglycemia was more common in patients treated with insulin degludec 3 times weekly (given before breakfast) compared to daily insulin glargine based on low-strength evidence (rate ratio 2.1; 95% CI, 1.1 to 4.2).[1] Insulin degludec is only approved for daily use.
- There was no difference between daily insulin degludec and daily insulin glargine in the number of patients with severe hypoglycemia. Moderate-strength evidence found fewer episodes of nocturnal hypoglycemia with daily insulin degludec compared to daily insulin glargine U100 based on evidence from six trials (rate ratio 0.71; 95% CI, 0.59 to 0.85; I^2=0%).[1] Two studies, lasting 52 weeks, found statistically significantly less nocturnal hypoglycemia with insulin degludec compared to insulin glargine. In one study insulin degludec was found to have a 40% incidence of nocturnal hypoglycemia compared to 47% in the insulin glargine group (ARR 7%/NNT 14; P=0.0399).[20] In the second study the incidence of nocturnal hypoglycemia was 13.8% for insulin degludec compared to 15.2% for insulin glargine (ARR 1.4%/NNT 71: P=0.038).[21] There were no statistically significant differences found in nocturnal hypoglycemia rates between insulin degludec and insulin glargine in studies lasting 26 weeks.
- There was no difference in withdrawal rates due to adverse events in comparisons of daily insulin degludec and daily insulin glargine.

Insulin Detemir versus Insulin Glargine

Type 1 Diabetes

- No difference in A1C or plasma glucose was found between insulin detemir and insulin glargine U100 based on low-strength evidence from two studies lasting 26 or 52 weeks.[1] Low-strength evidence found no difference in severe hypoglycemia or withdrawals related to adverse events between insulin detemir and insulin glargine based on two RCTs and two observational studies.
- Rates of severe hypoglycemia and withdrawal rates between insulin detemir and insulin glargine were found to be similar based on low-strength of evidence.[1]

Type 2 Diabetes

- In patients with T2DM, there was no difference in A1C reduction or achievement in A1C goals between insulin detemir and insulin glargine U100 based on low-strength of evidence.[1] Low-strength of evidence from four cohort studies found of no difference in risk of cancer between insulin detemir and insulin glargine when compared to no insulin exposure.
- Severe and nocturnal hypoglycemia rates were similar between insulin detemir and insulin glargine U100 based on low-strength of evidence.
- Patients treated with insulin detemir had significantly more withdrawal rates due to adverse events compared to insulin glargine U100 (RR 2.1; 95% CI, 1.4 to 3.3; I^2=0%) based on moderate-strength of evidence (6 studies).[1,25,26,32–35] The withdrawal rates due to adverse events was consistently higher in all six studies and statistically significant in two studies (ARR 3-4%/NNT 25-33).[25,26]

F-O Glargine vs. Glargine U100

Type 1 Diabetes

- Hemoglobin A1C lowering was similar between F-O glargine and glargine U100 in patients with T1DM based on low-strength of evidence. Evidence was insufficient to determine risk differences between F-O glargine and glargine U100 for severe hypoglycemia, nocturnal hypoglycemia and withdrawals due to adverse events.

Type 2 Diabetes

- F-O glargine was similar to glargine U100 in A1C lowering in patients with T2DM based on low-strength of evidence. Evidence was insufficient for comparisons of nocturnal hypoglycemia, severe hypoglycemia or withdrawals due to adverse events between the two products.[1]

Insulin Glargine U300 vs. Insulin Glargine U100

Type 1 Diabetes

- Hemoglobin A1C lowering was similar between insulin glargine U300 and insulin glargine U100 based on low-strength of evidence from four trials.[1] Severe hypoglycemia and withdrawals due to adverse events were not different between the groups. There was moderate strength of evidence that there was no difference in the risk of nocturnal hypoglycemia between insulin glargine U300 and insulin glargine U100 (RR 0.91; 95% CI, 0.80 to 1.05; I^2=39.1%).[1]

Type 2 Diabetes

- Low-strength of evidence from seven observational trials found the incidence of severe hypoglycemia was 5.4% with insulin glargine administered via a pen compared to 7.5% with insulin glargine administered via vial and syringe (RR 0.72; 95% CI, 0.65 to 0.79; I^2=0%).[1]

Fixed-dose Combination Products (FDCP) Degludec/Aspart vs. Detemir

Type 1 Diabetes

- Low-strength of evidence found similar A1C lowering between the FDCP insulin degludec/aspart and insulin detemir based on one study. Evidence was insufficient to determine differences for severe or nocturnal hypoglycemia or withdrawals due to adverse events for this comparison.[1]

Fixed-dose Combination Products (FDCP) Degludec/Aspart vs. Glargine

Type 2 Diabetes

- Hemoglobin A1C reductions were similar between insulin degludec/aspart and insulin glargine based on one trial providing low-strength of evidence. Insufficient evidence prevented comparative risk of episodes of nocturnal hypoglycemia, severe hypoglycemia and withdrawals due to adverse events.[1]

New Guidelines:

NICE – Diabetes in Children and Young People

In a 2015 update, National Institute for Health and Care Excellence (NICE) provided guidance for the management of children and young people with T1DM and T2DM.[2] The recommended target to minimize complications is an A1C is 6.5% or less. The use of multiple daily basal-bolus insulin regimens are recommended for all T1DM patients. If multiple daily injections are not feasible, then continuous subcutaneous insulin infusion is recommended. NICE recommends the use of metformin monotherapy for children and young people with T2DM. No other treatments were mentioned for the management of T2DM in children and young people.

NICE – Type 1 Diabetes in Adults

NICE guidance was issued on management of adults with T1DM.[3] Twenty-eight studies were identified that compared the following long-acting insulins: insulin glargine, insulin detemir, insulin degludec and NPH insulin. Twenty-six studies were identified that compared rapid-acting insulins. Evidence for insulin aspart, lispro, glulisine, and regular insulin were identified. Evidence graded as low or very low quality was not included. After review of the evidence, nine recommendations were made for managing adults with T1DM (Table 1).

Table 1. NICE Recommendations for Adults with T1DM[3]

1. Offer multiple daily injection basal-bolus regimens, rather than twice-daily mixed insulin regimens.
2. Newly diagnosed adults should not be offered non-basal-bolus insulin regimens (i.e., twice-daily mixed, basal only or bolus only).
3. Offer insulin detemir given twice daily as basal insulin therapy.
4. If twice daily injections are not desired, offer once daily insulin glargine or once daily insulin detemir.
5. Offer rapid-acting insulin analogs injected before meals rather than regular insulin.
6. Do not use rapid-acting insulins after meals on a routine basis.
7. Consider twice-daily regular mixed insulin regimens if a multiple daily injection of basal-bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen.
8. Consider a twice-daily analogs mixed insulin regimen if use of twice-daily regular insulin causes hypoglycemia that affects quality of life.
9. Consider the addition of metformin to insulin therapy in patients with a BMI of 25 kg/m^2 or more who wish to minimize insulin doses.

Review of the Evidence

Long-Acting Insulins

NICE found moderate quality evidence of no clinically significant differences between insulin glargine and insulin degludec for changes in A1C, weight, quality of life and nocturnal hypoglycemia.[3] In studies with less than or equal to 6 months follow-up, the mean difference in A1C was only -0.13% (-0.25 to- 0.01%) favoring insulin degludec. Studies with greater than 6 months follow-up there was no clinically meaningful difference in A1C.[3] Body weight gain was 0.2 kg (0.51 to 0.91 kg) higher with insulin degludec compared to insulin glargine. Depending on the study duration nocturnal hypoglycemia was either more common or less common with insulin degludec compared to insulin glargine. In trials 6 months or less degludec was found to have 7 more nocturnal hypoglycemia episodes (87 fewer to 109 more), per 1000 people, than insulin glargine and in studies of more than 6 months duration insulin degludec had 7 less hypoglycemia episodes (80 fewer to 80 more), per 1000 people, than insulin glargine.[3]

In comparisons between insulin detemir and insulin glargine, there was moderate quality evidence of more injection site reactions with insulin detemir (66 more per 1000 patients).[3] No clinically important differences were found between insulin detemir and insulin glargine for outcomes of A1C, severe hypoglycemia and body weight gain. A comparison between insulin detemir and NPH found 40 fewer nocturnal hypoglycemia events (per 1000 patients treated) with insulin detemir based on moderate quality of evidence and trials lasting greater than 6 months.[3]

In patients with T1DM, NPH and insulin glargine had similar rates of severe hypoglycemia based on high quality evidence and similar rates of nocturnal hypoglycemia based on moderate quality evidence.[3] No clinically meaningful differences in weight changes were found between insulin glargine and NPH based on moderate quality evidence. For the outcomes of severe hypoglycemia, adverse events and severe adverse events, insulin detemir and insulin degludec were found to be clinically similar (0 events for each outcome in both groups) based on moderate quality evidence. A study of insulin detemir dosed once daily versus twice daily found no clinical difference between the dosing regimens on A1C changes or hypoglycemia rates based on high quality evidence. In addition, no clinically meaningful differences were found for NPH dosed once daily compared to twice daily. Meta-analysis of A1C data and risk for severe hypoglycemia between long-acting basal insulin analogs and NPH do not show clinically meaningful differences in A1C and imprecise results for severe hypoglycemia (Table 2).[3]

Table 2. Comparison of Long-Acting Insulins based on Meta-analysis data.[3]

Insulin	Mean Change (95% CrI)	A1C Lowering Compared to NPH (twice daily) (95% CrI)	Severe Hypoglycemia†
NPH (twice daily)	-0.32 (-0.49 to -0.15)	NA	
Insulin detemir (once or twice-daily)	-0.53 (-0.92 to -0.11)	-0.21 (-0.57 to 0.17)	NR
Insulin detemir (twice-daily)	-0.48 (-0.69 to -0.29)	-0.16 (-0.27 to -0.05)[a]	OR 0.92 (95% CI, 0.63 to 1.43)
Insulin glargine (once-daily)	-0.42 (-0.71 to -0.13)	-0.10 (-0.34 to 0.14)	OR 0.99 (95% CI, 0.02 to 47.97)*
Insulin detemir (once-daily)	-0.40 (-0.66 to -0.13)	-0.08 (-0.27 to 0.13)	OR 0.95 (95% CI, 0.01 to 57.39)*
Insulin degludec (once-daily)	-0.35 (-0.68 to -0.02)	-0.03 (-0.31 to 0.26)	OR 1.02 (95% CI, 0.01 to 52.8)*
NPH (once-daily)	-0.28 (-0.61 to 0.06)	0.04 (-0.25 to 0.33)	OR 0.85 (95% CI, 0.01 to 45.68)*

[a] Results were statistically significant (p-value not provided)
* Results should be interpreted with caution due to wide confidence intervals which suggests uncertainty in the results.
† No comparisons were statistically significant.
Abbreviations: CI = confidence interval; OR = odds ratio; NPH = neutral protamine Hagedorn; NR = not reported

Rapid-Acting Insulins

Evidence evaluating insulin lispro and insulin glulisine found no clinically meaningful differences for the outcomes of A1C (MD 0.01% lower with lispro), severe hypoglycemia (MD 0), hypoglycemia (MD 0.07 [episodes/patient-month] higher with lispro in studies ≤ 6 months and MD 0.01[episodes/patient-month) lower with lispro in studies lasting > 6 months), and nocturnal hypoglycemia (MD 0.2 episodes lower with lispro) based on moderate quality evidence.[3] Moderate quality evidence found conflicting results for quality of life assessments in studies comparing insulin aspart to regular human insulin dependent upon type of assessment used. The investigators found moderate quality evidence of no clinically significant differences between insulin glulisine and regular insulin for A1C (MD 0.03% lower with glulisine), severe hypoglycemia (MD 0.08 [episodes/patient-month) lower with insulin glulisine), hypoglycemia (16 more events per 1000

for insulin glulisine), and nocturnal hypoglycemia (MD 0).[3] There was no clinical difference in A1C lowering between Insulin lispro and regular insulin (MD of 0.03% favoring insulin lispro), severe hypoglycemia or nocturnal hypoglycemia. A reduction in nocturnal hypoglycemia was found with insulin aspart compared to regular insulin with a MD -1.1 (episodes/month) in studies of 6 months or less. There were no clinically meaningful differences between insulin lispro and insulin glulisine for outcomes of A1C, hypoglycemia (severe, minor, and nocturnal) or injection site reactions.[3]

Studies that compared pramlintide with insulin to insulin alone in T1DM found less risk of severe hypoglycemia and weight gain with the combination regimen but also increased risk of nausea, vomiting and anorexia based on moderate quality of evidence.[3] Studies of adjunctive metformin added to insulin therapy in patients with T1DM found moderate to high quality evidence that the addition of metformin reduces the dose of insulin required to maintain glucose control. No differences between adjunctive metformin and insulin versus insulin alone were found in outcomes of A1C, hypoglycemia, weight change or gastrointestinal (GI) discomfort. One study found no benefit on A1C, dose of insulin or weight change when liraglutide was added to insulin in patients with T1DM.[3]

NICE – Type 2 Diabetes in Adults

NICE updated several recommendations to its 2015 guidance on the management of T2DM.[36] Recommendations include a target A1C of 7.0% or less for most patients. If target A1C is not met with diet, lifestyle and adherence reinforcement, drug treatment should be considered. Insulin is usually recommended after failure of optimization of oral antidiabetic therapies and in patients with symptoms of hyperglycemia.

In patients who are candidates for insulin, metformin therapy should be continued unless contraindicated or not tolerated. NPH insulin is recommended with or without short-acting insulin; however, this practice is less common in the United States (US). Insulin detemir or insulin glargine is recommended in patients who require assistance in insulin administration, experience lifestyle altering hypoglycemia, or the patient would require NPH and additional oral antidiabetic treatments.[36] Pre-mixed (biphasic) insulin analogues are recommended if injecting immediately before a meal, hypoglycemia is an issue or postprandial hyperglycemia is a concern. Patients who start on NPH insulin may need to be switched to insulin detemir or insulin glargine if target A1C levels are not reached due to hypoglycemia, or if the patient experiences significant hypoglycemia, has problems operating the NPH insulin device (not available in the US), or who require assistance in insulin administration.

The American Diabetes Association – Standards of Medical Care 2017

The ADA updates their standards of care in diabetes on an annual basis.[4] The 2017 standards contain comprehensive recommendations for managing all aspects of patients with diabetes. ADA makes recommendations based on review and grading of the evidence. Recommendations are given a rating ranging of A, B, C and E (Table 3). Statement of extensive literature search is included but specific methods are not described. Updates pertaining to the pharmacology of T1DM and treatment goals are included in this review.

Table 3. ADA Evidence-grading System.[4]

Leve of Evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered
B	Supportive evidence from well-conducted cohort studies
C	Supportive evidence from poorly controlled or uncontrolled studies
E	Expert consensus or clinical experience

Hemoglobin A1C goals – A goal of less than 7% is recommended for most patients based on level A evidence.[4] A lower goal of less than 6.5% may be appropriate for those that are candidates for more intensive management without experiencing significant hypoglycemia (level C evidence). Patients with limited life expectancy, history of severe hypoglycemia and advanced complications may be more appropriately managed with a higher goal of less than 8% (level B evidence).[4]

Pharmacological Management of T1DM – ADA recommends that most patients with T1DM should be managed with multiple daily injections of prandial and basal insulin or continuous subcutaneous insulin infusion (Level A evidence).[4] In an effort to minimize hypoglycemia, most patients should use rapid-acting insulin analogs (Level A evidence).

AACE/ACE Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm

An updated consensus statement was released by the AACE/ACE in 2017.[5] Recommendations are based on evaluation and rating of the evidence. The AACE/ACE also include a subjective factor impact and two-thirds "expert consensus" in the overall recommendation grade, which may permit risk of bias in their final recommendations. Several authors have associations with industry that can also influence recommendations. The strength of the recommendations were provided in a visual format but were not assigned a GRADE recommendation which can also limit interpretation of the recommendations.

Target A1C values of 6.5% or less are recommended for patients with T2DM if they can be reached safely and affordably.[5] Recommendations from the AACE/ACE are based on entry level A1C (level of A1C at time of diagnosis).[5] Basal insulin is recommended, in patients with an A1C of ≥ 7.5%, in dual therapy and triple therapy regimens, as an option with metformin. A basal insulin is recommended in patients already on dual therapy with an A1C of 8% or higher and/or patients with a long history of diabetes who may not be able to reach glucose lowering targets with a third oral agent. A GLP-1 RA can also be tried but most likely the patient will still require insulin to control hyperglycemia.[5] Though efficacy of NPH and basal insulin analogs has been shown to be similar, basal insulin analogs are recommended due to reduced risk of hypoglycemia. Patients may require rapid-acting insulin to cover postprandial hyperglycemia in T2DM patients. In this scenario, rapid-acting insulin analogs are recommended over regular insulin because they have reduced risk of hypoglycemia.[4]

Safety Alerts:

No new safety alerts identified.

New Formulations:

A new formulation of insulin glargine, called Basaglar, was approved to improve glycemic control in adult and pediatric patients with T1DM and in adults with T2DM.[7] Basaglar is a long-acting insulin to be injected once daily at a dose based on individual patient needs. Basaglar is available in a 100 units/mL KwikPen device. Approval of Basaglar was partially based on clinical efficacy and safety data from studies of another insulin glargine product that was not specifically named. Two additional studies compared Basaglar to another type of insulin glargine 100u/mL (exact formulation not stated). An open-label study in adult patients with T1DM compared Basaglar to insulin glargine 100u/mL, both in combination with mealtime insulin lispro. Patients (n=535) were a mean age of 41 years, had a 16-year history of T1DM and baseline A1C of 7.7%. After 24-weeks, Basaglar was non-inferior to insulin glargine 100u/mL with an A1C decreases of -0.35% and -0.46%, respectively.[7] A second double-blind, 24-week study compared Basaglar to another insulin glargine product 100u/mL in patients with T2DM also taking at least 2 oral antidiabetic medications. The mean age was 59 years and the baseline A1C was 8.33%. Basaglar was non-inferior to the other insulin glargine 100u/mL formulation with both groups achieving an A1C reduction of -1.3%.[7]

Randomized Controlled Trials:

One thousand 95 potentially relevant clinical trials were evaluated from the literature search. After further review, only 1 trial was included (**Table 4**). Trials were excluded because they offered no new additional information from sources already included in the review. The remaining trials are briefly described in the table below. The full abstracts are included in Appendix 2.

Table 4. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Marso, et al[6] (DEVOTE)	1. Insulin Degludec* 2. Insulin Glargine U100* * Treat-to-target	Patients (n=7637) with T2DM at high risk of CV disease, chronic kidney disease or both	First occurrence of an adjudicated major CV event (death from CV causes, non-fatal MI or nonfatal stroke)	Insulin Degludec: 325 (8.5%) Insulin Glargine: 356 (9.3%) HR 0.91; 95% CI 0.78 to 1.06 P <0.001 for noninferiority
Lane, et al[ł37] (SWITCH 1)	1. Insulin Degludec* 2. Insulin Glargine U100* * Treat-to-target	Patients (n=501) with T1DM and at least 1 risk factor for hypoglycemia 16-week titration and 16-week maintenance	Rate of overall severe or blood glucose-confirmed (less than 56 mg/dL) symptomatic hypoglycemia episodes during the maintenance period	Insulin Degludec: 323 Insulin Glargine: 337 HR 0.89; 95% CI 0.85 to 0.94 P <0.001 for noninferiority and superiority
Wysham, et al[ł38] (SWITCH 2)	1. Insulin Degludec* 2. Insulin Glargine U100* * Treat-to-target	Patients (n=721) with T2DM and at least 1 risk factor for hypoglycemia and previously treated with basal insulin with or without oral antidiabetic drugs	Rate of overall severe or blood glucose-confirmed (less than 56 mg/dL) symptomatic hypoglycemia episodes during the maintenance period	Insulin Degludec: 353 Insulin Glargine: 496 HR 0.70; 95% CI 0.61 to 0.80 P <0.001 for superiority

Abbreviations: CV= cardiovascular; MI = myocardial infarction; RCT = randomized clinical trial; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

Key: ł = study was published after search date, material verbally presented

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Appendix 1: Current Status of PDL Class.

Insulins (long-acting insulins bolded)

ROUTE	FORMULATION	BRAND	GENERIC	PDL	PA
SUB-Q	**VIAL**	**LANTUS**	**INSULIN GLARGINE,HUM.REC.ANLOG**	**Y**	Y
SUB-Q	**INSULN PEN**	**LANTUS SOLOSTAR**	**INSULIN GLARGINE,HUM.REC.ANLOG**	**Y**	Y
SUB-Q	**INSULN PEN**	**LEVEMIR FLEXTOUCH**	**INSULIN DETEMIR**	**Y**	Y
SUB-Q	CARTRIDGE	NOVOLOG	INSULIN ASPART	Y	Y
SUB-Q	INSULN PEN	HUMULIN 70/30 KWIKPEN	INSULIN NPH HUM/REG INSULIN HM	Y	Y
SUB-Q	INSULN PEN	NOVOLOG FLEXPEN	INSULIN ASPART	Y	Y
SUB-Q	INSULN PEN	NOVOLOG MIX 70-30 FLEXPEN	INSULIN ASPART PROTAM & ASPART	Y	Y
SUB-Q	VIAL	HUMALOG	INSULIN LISPRO	Y	
SUB-Q	VIAL	HUMALOG MIX 50-50	INSULIN NPL/INSULIN LISPRO	Y	
SUB-Q	VIAL	HUMALOG MIX 75-25	INSULIN NPL/INSULIN LISPRO	Y	
SUB-Q	VIAL	HUMULIN 70-30	INSULIN NPH HUM/REG INSULIN HM	Y	
SUB-Q	VIAL	HUMULIN N	INSULIN NPH HUMAN ISOPHANE	Y	
SUB-Q	VIAL	HUMULIN R U-500	INSULIN REGULAR, HUMAN	Y	
SUB-Q	VIAL	NOVOLIN 70-30	INSULIN NPH HUM/REG INSULIN HM	Y	
SUB-Q	VIAL	NOVOLIN N	INSULIN NPH HUMAN ISOPHANE	Y	
SUB-Q	VIAL	NOVOLOG	INSULIN ASPART	Y	
SUB-Q	VIAL	NOVOLOG MIX 70-30	INSULIN ASPART PROTAM & ASPART	Y	
INJECTION	VIAL	HUMULIN R	INSULIN REGULAR, HUMAN	Y	
INJECTION	VIAL	NOVOLIN R	INSULIN REGULAR, HUMAN	Y	
SUB-Q	**INSULN PEN**	**TOUJEO SOLOSTAR**	**INSULIN GLARGINE,HUM.REC.ANLOG**	**N**	Y
SUB-Q	**VIAL**	**LEVEMIR**	**INSULIN DETEMIR**	**N**	
SUB-Q	**INSULIN PEN**	**BASAGLAR KWIKPEN**	**INSULIN GLARGINE**	**N**	
SUB-Q	**INSULIN PEN**	**TRESIBA FLEXTOUCH**	**INSULIN DEGLUDEC**	**N**	
SUB-Q	**INSULIN PEN**	**RYZODEG FLEXTOUCH**	**INSULIN DEGLUDEC/ASPART**	**N**	
INHALATION	CART W/DEV	AFREZZA	INSULIN REGULAR, HUMAN	N	
SUB-Q	CARTRIDGE	HUMALOG	INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	APIDRA SOLOSTAR	INSULIN GLULISINE	N	Y
SUB-Q	INSULN PEN	HUMALOG KWIKPEN	INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	HUMALOG MIX 50-50 KWIKPEN	INSULIN NPL/INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	HUMALOG MIX 75-25 KWIKPEN	INSULIN NPL/INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	HUMULIN N KWIKPEN	INSULIN NPH HUMAN ISOPHANE	N	Y
SUB-Q	VIAL	APIDRA	INSULIN GLULISINE	N	

Appendix 2: Abstracts of Comparative Clinical Trials

Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes.

Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr PM, Lange M, Brown-Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB; DEVOTE Study Group.

Background: Degludec is an ultralong-acting, once-daily basal insulin that is approved for use in adults, adolescents, and children with diabetes. Previous open-label studies have shown lower day-to-day variability in the glucose-lowering effect and lower rates of hypoglycemia among patients who received degludec than among those who received basal insulin glargine. However, data are lacking on the cardiovascular safety of degludec. Methods: We randomly assigned 7637 patients with type 2 diabetes to receive either insulin degludec (3818 patients) or insulin glargine U100 (3819 patients) once daily between dinner and bedtime in a double-blind, treat-to-target, event-driven cardiovascular outcomes trial. The primary composite outcome in the time-to-event analysis was the first occurrence of an adjudicated major cardiovascular event (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) with a prespecified noninferiority margin of 1.3. Adjudicated severe hypoglycemia, as defined by the American Diabetes Association, was the prespecified, multiplicity-adjusted secondary outcome. Results: Of the patients who underwent randomization, 6509 (85.2%) had established cardiovascular disease, chronic kidney disease, or both. At baseline, the mean age was 65.0 years, the mean duration of diabetes was 16.4 years, and the mean (±SD) glycated hemoglobin level was 8.4±1.7%; 83.9% of the patients were receiving insulin. The primary outcome occurred in 325 patients (8.5%) in the degludec group and in 356 (9.3%) in the glargine group (hazard ratio, 0.91; 95% confidence interval, 0.78 to 1.06; P<0.001 for noninferiority). At 24 months, the mean glycated hemoglobin level was 7.5±1.2% in each group, whereas the mean fasting plasma glucose level was significantly lower in the degludec group than in the glargine group (128±56 vs. 136±57 mg per deciliter, P<0.001). Prespecified adjudicated severe hypoglycemia occurred in 187 patients (4.9%) in the degludec group and in 252 (6.6%) in the glargine group, for an absolute difference of 1.7 percentage points (rate ratio, 0.60; P<0.001 for superiority; odds ratio, 0.73; P<0.001 for superiority). Rates of adverse events did not differ between the two groups. Conclusions: Among patients with type 2 diabetes at high risk for cardiovascular events, degludec was noninferior to glargine with respect to the incidence of major cardiovascular events. (Funded by Novo Nordisk and others; DEVOTE ClinicalTrials.gov number, NCT01959529 .).

Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial.

Lane W, Bailey TS, Gerety G, Gumprecht J, Philis-Tsimikas A, Hansen CT, Nielsen TSS, Warren M; Group Information; SWITCH 1.

Importance: Hypoglycemia, common in patients with type 1 diabetes, is a major barrier to achieving good glycemic control. Severe hypoglycemia can lead to coma or death. Objective: To determine whether insulin degludec is noninferior or superior to insulin glargine U100 in reducing the rate of symptomatic hypoglycemic episodes.Design, Setting, And Participants: Double-blind, randomized, crossover noninferiority trial involving 501 adults with at least 1 hypoglycemia risk factor treated at 84 US and 6 Polish centers (January 2014-January 12, 2016) for two 32-week treatment periods, each with a 16-week titration and a 16-week maintenance period. Interventions: Patients were randomized 1:1 to receive once-daily insulin degludec followed by insulin glargine U100 (n = 249) or to receive insulin glargine U100 followed by insulin degludec (n = 252) and randomized 1:1 to morning or evening dosing within each treatment sequence. Main Outcomes And Measures: The primary end point was the rate of overall severe or blood glucose-confirmed (<56 mg/dL) symptomatic hypoglycemic episodes during the maintenance period. Secondary end points included the rate of nocturnal symptomatic hypoglycemic episodes and proportion of patients with severe hypoglycemia during the maintenance period. The noninferiority criterion for the primary end point and for the secondary end point of nocturnal hypoglycemia was defined as an upper limit of the 2-sided 95% CI for a rate ratio of 1.10 or lower; if noninferiority was established, 2-sided statistical testing for superiority was conducted. Results: Of the 501 patients randomized (mean age, 45.9 years; 53.7% men), 395 (78.8%) completed the trial. During the maintenance period, the rates of overall symptomatic hypoglycemia were 2200.9 episodes per 100 person-years' exposure (PYE) in the insulin degludec group vs

2462.7 episodes per 100 PYE in the insulin glargine U100 group for a rate ratio (RR) of 0.89 (95% CI, 0.85-0.94; P < .001 for noninferiority; P < .001 for superiority; rate difference, -130.31 episodes per 100 PYE; 95% CI, -193.5 to -67.16). The rates of nocturnal symptomatic hypoglycemia were 277.1 per 100 PYE in the insulin degludec group vs 428.6 episodes per 100 PYE in the insulin glargine U100 group, for an RR of 0.64 (95% CI, 0.56-0.73; P < .001 for noninferiority; P < .001 for superiority; rate difference, -61.94 episodes per 100 PYE; 95% CI, -83.85 to -40.03). A lower proportion of patients in the insulin degludec than in the insulin glargine U100 group experienced severe hypoglycemia during the maintenance period (10.3%, 95% CI, 7.3%-13.3% vs 17.1%, 95% CI, 13.4%-20.8%, respectively; McNemar P = .002; risk difference, -6.8%; 95% CI, -10.8% to -2.7%). Conclusions And Relevance: Among patients with type 1 diabetes and at least 1 risk factor for hypoglycemia, 32 weeks' treatment with insulin degludec vs insulin glargine U100 resulted in a reduced rate of overall symptomatic hypoglycemic episodes.

Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial.
Wysham C1, Bhargava A2, Chaykin L3, de la Rosa R4, Handelsman Y5, Troelsen LN6, Kvist K7, Norwood P8.

Importance: Hypoglycemia, a serious risk for insulin-treated patients with type 2 diabetes, negatively affects glycemic control. Objective: To test whether treatment with basal insulin degludec is associated with a lower rate of hypoglycemia compared with insulin glargine U100 in patients with type 2 diabetes. Design, Setting, And Participants: Randomized, double-blind, treat-to-target crossover trial including two 32-week treatment periods, each with a 16-week titration period and a 16-week maintenance period. The trial was conducted at 152 US centers between January 2014 and December 2015 in 721 adults with type 2 diabetes and at least 1 hypoglycemia risk factor who were previously treated with basal insulin with or without oral antidiabetic drugs. Interventions: Patients were randomized 1:1 to receive once-daily insulin degludec followed by insulin glargine U100 (n = 361) or to receive insulin glargine U100 followed by insulin degludec (n = 360) and randomized 1:1 to morning or evening dosing within each treatment sequence. Main Outcomes And Measures: The primary end point was the rate of overall symptomatic hypoglycemic episodes (severe or blood glucose confirmed [<56 mg/dL]) during the maintenance period. Secondary end points were the rate of nocturnal symptomatic hypoglycemic episodes (severe or blood glucose confirmed, occurring between 12:01 am and 5:59 am) and the proportion of patients with severe hypoglycemia during the maintenance period. Results: Of the 721 patients randomized (mean [SD] age, 61.4 [10.5] years; 53.1% male), 580 (80.4%) completed the trial. During the maintenance period, the rates of overall symptomatic hypoglycemia for insulin degludec vs insulin glargine U100 were 185.6 vs 265.4 episodes per 100 patient-years of exposure (PYE) (rate ratio = 0.70 [95% CI, 0.61-0.80]; P < .001; difference, -23.66 episodes/100 PYE [95% CI, -33.98 to -13.33]), and the proportions of patients with hypoglycemic episodes were 22.5% vs 31.6% (difference, -9.1% [95% CI, -13.1% to -5.0%]). The rates of nocturnal symptomatic hypoglycemia with insulin degludec vs insulin glargine U100 were 55.2 vs 93.6 episodes/100 PYE (rate ratio = 0.58 [95% CI, 0.46-0.74]; P < .001; difference, -7.41 episodes/100 PYE [95% CI, -11.98 to -2.85]), and the proportions of patients with hypoglycemic episodes were 9.7% vs 14.7% (difference, -5.1% [95% CI, -8.1% to -2.0%]). The proportions of patients experiencing severe hypoglycemia during the maintenance period were 1.6% (95% CI, 0.6%-2.7%) for insulin degludec vs 2.4% (95% CI, 1.1%-3.7%) for insulin glargine U100 (McNemar P = .35; risk difference, -0.8% [95% CI, -2.2% to 0.5%]). Statistically significant reductions in overall and nocturnal symptomatic hypoglycemia for insulin degludec vs insulin glargine U100 were also seen for the full treatment period. Conclusions And Relevance: Among patients with type 2 diabetes treated with insulin and with at least 1 hypoglycemia risk factor, 32 weeks' treatment with insulin degludec vs insulin glargine U100 resulted in a reduced rate of overall symptomatic hypoglycemia.

Appendix 3: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BASAGLAR safely and effectively. See full prescribing information for BASAGLAR

BASAGLAR (insulin glargine injection), for subcutaneous use
Initial U.S. Approval: 2000

---------- INDICATIONS AND USAGE ----------

BASAGLAR® is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. (1)

Limitations of Use:
Not recommended for treating diabetic ketoacidosis. (1)

----------DOSAGE AND ADMINISTRATION----------

- Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use. (2.2, 2.3, 2.4)
- Administer subcutaneously once daily at any time of day, but at the same time every day. (2.2)
- Rotate injection sites to reduce the risk of lipodystrophy. (2.1)
- Closely monitor glucose when converting to BASAGLAR and during initial weeks thereafter. (2.2)
- Do not dilute or mix with any other insulin or solution. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 units/mL (U-100) in 3 mL prefilled BASAGLAR® KwikPen® delivery device. (3)

---------- CONTRAINDICATIONS ----------

- During episodes of hypoglycemia. (4)
- Hypersensitivity to BASAGLAR or one of its excipients. (4)

----------WARNINGS AND PRECAUTIONS ----------

- *Never share* a BASAGLAR KwikPen between patients, even if the needle is changed. (5.1)
- *Hyper- or hypoglycemia with changes in insulin regimen:* Carry out under close medical supervision. (5.2)
- *Hypoglycemia:* May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal or hepatic impairment and hypoglycemia unawareness. (5.3, 6.1)
- *Medication Errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4)
- *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue BASAGLAR, monitor and treat if indicated. (5.5, 6.1)
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. (5.6)
- *Fluid retention and heart failure with concomitant use of thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.7)

----------ADVERSE REACTIONS ----------

Adverse reactions commonly associated with insulin glargine products (5% or greater incidence) are:

- Hypoglycemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, rash, edema, and weight gain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- *Drugs that affect glucose metabolism:* Adjustment of insulin dosage may be needed; closely monitor blood glucose. (7)
- *Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Signs and symptoms of hypoglycemia may be reduced or absent. (7)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2015

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to June Week 2 2017
Search Strategy:

#	Searches	Results
1	Insulin Glargine/	1411
2	Insulin Aspart/	575
3	insulin NPH.mp. or Insulin, Isophane/	742
4	Insulin Detemir/	482
5	Insulin Lispro/	783
6	Insulin/ad [Administration & Dosage]	10799
7	insulin glulisine.mp.	187
8	1 or 2 or 3 or 4 or 5 or 6 or 7	12780
9	limit 8 to (english language and humans and yr="2015 -Current")	1106
10	limit 9 to (clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or systematic reviews)	94

Appendix 5: Prior Authorization Criteria

Insulins

Goal:

- Restrict certain insulin products to specific patient populations to ensure appropriate use.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred insulin vials
- All pre-filled insulin pens, cartridges and syringes with the exception of insulin glargine (Lantus SoloSTAR®) or insulin aspart (Novolog Flexpen®)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is the request for an insulin pen or cartridge?	**Yes:** Go to #4	**No:** Go to #7
4. Is the request for either a short-acting or a long-acting insulin pen or cartridge?	**Yes:** Go to #5	**No:** Got to #6
5. Has the patient tried and failed or have contraindications to either: • insulin aspart (Novolog®) if the request is for short-acting insulin OR • insulin glargine (Lantus®) if the request is for long-acting insulin?	**Yes:** Go to #6	**No:** Pass to RPh; deny and recommend a trial of insulin glargine(Lantus SoloSTAR®) or insulin aspart (Novolog Flexpen®)
6. Will the insulin be administered by the patient or a non-professional caregiver **AND** do any of the following criteria apply: • The patient has physical dexterity problems/vision impairment • The patient is unable to comprehend basic administration instructions • The patient has a history of dosing errors with use of vials • The patient is a child less than 18 years of age?	**Yes:** Go to #7	**No:** Pass to RPh; deny for medical appropriateness
7. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives	**No:** Approve for up to 12 months

P&T / DUR Review: *9/17 (KS), 3/16; 11/15; 9/10*
Implementation: *10/15/17; 10/13/16; 1/1/11*