A
n estimated 30.3 million people in the United States, or 9.4% of the population, now have diabetes, with about 1 in 4 yet to be diagnosed. The numbers are significantly higher in the 65-years-and-older population, in which 25.2% have the disease.¹

The burden of diabetes can be difficult for patients and complex for the US health system. Direct medical costs for diabetes in 2012 were $176 billion, about $1 out of every $10 spent on healthcare in the United States.² Overall medical costs for those with diabetes are, on average, 2 to 3 times higher than for those without the disease, with more than half the cost attributable to the diabetes itself. People with diabetes also have higher rates of hospitalization and longer lengths of stay than those without, accounting for about a quarter of all US hospital inpatient costs. In addition, the cost of medications has risen substantially in recent years. Today, about a third of what the United States spends on medications can be attributed to diabetes.²

A substantial percentage of diabetes-related healthcare costs are the result of complications from the disease, which includes cardiovascular disease (CVD), chronic kidney disease (CKD), neuropathy, and diabetic retinopathy. Such complications account for 25% of emergency department visits and 45% of inpatient admissions.² Maintaining glycemic control, typically defined as a glycated hemoglobin (A1C) less than 7%, can significantly reduce the risk of these complications.³

Despite high spending and the availability of effective treatments, control of diabetes in this country remains poor. The most recent government figures show that while glycemic control has improved from 1999 through 2010, nearly half of US adults with diabetes still do not reach an A1C of less than 7%; about 20% do not have an A1C less than 8%. The percentages are even worse for patients on insulin therapy from 2007 to 2010: just 30% reached an A1C of less than 7% and just 64% reached less than 8%.⁴

Insulin Therapy

Traditionally, insulin therapy has been reserved as a third- or even fourth-line treatment for diabetes, used when all other options fail. However, given a greater understanding of the benefits of early

Diabetes, particularly type 2 diabetes (T2D), has become an epidemic in the United States, with a significant portion of patients unable to meet recommended glycemic targets. All individuals with type 1 diabetes (T1D) and a significant majority of those with T2D will ultimately require insulin therapy. However, there are several barriers to its use. The introduction of the new, ultra-long-acting basal insulins degludec and glargine U-300, and the single-injection combinations of insulin degludec/liraglutide and insulin glargine U-100/lixisenatide, offer options that may overcome several of those barriers, including the high risk of hypoglycemia, glycemic variability, and relatively short duration of action. This article spotlights the outcomes of the phase 3 clinical trials for these newer formulations, as well as more recent meta-analyses and real-world studies. It also highlights the implications for managed care plans as they move to add these insulins to their formularies.

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insulin initiation on beta-cell preservation and reduced microvascular complications, the most recent guidelines from the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) recommend earlier initiation for patients with hyperglycemia uncontrolled on other antidiabetic medications.1

As the first part of this supplement noted, there are numerous barriers to the early initiation of insulin. These include the strict timing required for insulin injections, patient fear of needles, the risk of hypoglycemia, and weight gain.5-8

Many of those fears are justified. While basal insulins detemir and glargine, with reduced frequency of injection and glucose monitoring, are usually the first option used when initiating insulin therapy, they have numerous limitations, including the risks of hypoglycemia, particularly nocturnal hypoglycemia, and weight gain; inter- and intra-individual variability; and the potential for twice-daily injections.9-13

The longer-acting basal insulins degludec and glargine U-300 require a once-daily injection, have a longer and more stable pharmacokinetic profile, exhibit lower within-subject variability, do not result in significant weight gain, and carry a lower risk of hypoglycemia. There is also less involvement with the hepatic or renal systems, and they can be combined with fast-acting insulin or a glucagon-like peptide-1 receptor agonist (GLP-1 RA) in a single injection.8,10 This improved clinical profile is leading diabetes experts to recommend the use of basal insulin much earlier in the disease state, with the addition of a GLP-1 RA (either separately or in a fixed dose) if basal insulin alone is insufficient to control A1C.14,15

This article highlights the efficacy and safety of insulins degludec and glargine U-300, as well as the combination insulin degludec/liraglutide U-100/3.6 mg/mL and glargine/lixisenatide U-100/33 mcg/mL, and discusses the managed care implications of these newer insulin formulations.

Insulin Degludec
Insulin degludec is an ultra–long-acting, once-daily insulin pen approved for use in adults, adolescents, and children with diabetes.16 Insulin degludec’s stable pharmacokinetic profile stems from the formation of multihexamers upon injection, resulting in a subcutaneous depot of insulin. This delays insulin absorption into the systemic circulation, while the insulin also binds to circulating albumin, resulting in a lengthened duration of action of more than 42 hours and a half-life of approximately 25 hours. Insulin degludec’s concentration does not vary once it reaches a steady-state concentration within 3 days of injection. In addition, its pharmacokinetics are similar even in individuals with renal and hepatic impairment, regardless of the degree of impairment.8 At the same time, this reduces glycemic variability, thus minimizing hypoglycemic and hyperglycemic excursions.17

Insulin degludec was evaluated in the BEGIN clinical trial program and an interim analysis of DEVOTE, which studied its cardiovascular (CV) safety. The BEGIN program was a series of nine 26- to 52-week, randomized, controlled, open-label, multicenter, treat-to-target trials in patients with T1D and T2D from more than 40 countries.12-25 Table 1 provides an overview of the trials.12,16-25

Three trials evaluated insulin degludec against insulin glargine in basal–bolus therapy in T1D and T2D, and 4 against glargine in basal–oral therapy in participants with T2D, for a total of 7 trials.12,16-25 A basal–oral trial in patients with T2D compared insulin degludec with sitagliptin, while another in patients with T1D compared it with insulin detemir.24,26

Patients with T2D had a baseline A1C of 7% to 10%, while those with T1D had a baseline of 10% or less. The trials excluded those with a history of recurrent severe hypoglycemia (more than 1 severe episode in the past 12 months) and allowed concomitant oral antidiabetic treatments. A severe hypoglycemic episode was defined as a symptomatic event that requires assistance from another individual to resolve the episode.

The 7 trials comparing insulin degludec with insulin glargine demonstrated noninferiority in A1C reductions. Rates of confirmed hypoglycemia, particularly nocturnal confirmed hypoglycemia, were either similar with the 2 insulins or significantly lower with insulin degludec.12,18-23

Meanwhile, a meta-analysis of those 7 trials found that patients treated with insulin degludec achieved similar or significantly better fasting blood glucose (FBG) and rates of hypoglycemia than those treated with glargine, even with lower mean total insulin doses. These results held across subgroups of patients with T1D, T2D who were insulin-naïve, and T2D who received basal–bolus therapy.17

A preplanned analysis of all 7 trials found significantly lower rates of overall confirmed hypoglycemia as well as nocturnal and severe episodes in insulin-naïve patients with T2D who received insulin degludec compared with insulin glargine (estimated rate ratio [RR], 0.83 [95% CI, 0.70-0.98]; RR, 0.64 [95% CI, 0.48-0.86], and RR, 0.14 [95% CI, 0.03-0.70], respectively).17 Rates of overall confirmed and nocturnal confirmed hypoglycemic episodes were significantly lower in the overall T2D population (overall confirmed RR, 0.83; 95% CI, 0.74-0.94; nocturnal confirmed RR, 0.68, 95% CI, 0.57-0.82), while rates of nocturnal confirmed episodes were lower in the T1D population only during the maintenance treatment period (RR, 0.75; 95% CI, 0.60-0.94). Overall reduction in hypoglycemic events in the 3 groups was lowest during the maintenance treatment.17

In the time insulin degludec has been approved, real-world studies have been published and presented. One, EU-TREAT, was a European, multicenter, real-world evidence study investigating the effect of switching to insulin degludec from any other basal insulin (primarily insulin glargine U-100) in people with T1D (n = 1717) and T2D (n = 833). Six months after switching, patients experienced a significant reduction in A1C (~0.2% for T1D and ~0.5% for T2D), results that were sustained at 12 months. Rates of overall
was also a significant reduction in fasting plasma glucose (FPG) in patients who were able to significantly reduce their total daily insulin dose (–4.9 units T1D; –2.5 T2D) at 6 months, which remained stable at 12 months.26

The DEVOTE Trial
The CV safety of insulin degludec was evaluated in DEVOTE, a double-blind, treat-to-target, event-driven outcomes trial. The trial
enrolled 7637 patients with T2D (85.2% had established CVD, CKD, or both) who were randomized to receive either insulin degludec U-100 or insulin glargine U-100 once daily between dinner and bedtime. The primary composite outcome in the time-to-event analysis was the first occurrence of a major CV event (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) with a prespecified noninferiority margin of 1.3. The secondary outcome was severe hypoglycemia.29

The primary outcome occurred in 8% (325) of patients in the insulin degludec group and 9.3% (356) in the insulin glargine group (hazard ratio [HR], 0.91; 95% CI, 0.78-1.06; P <.001 for noninferiority). At 24 months, the AIC was 7.5 ± 1.2% in each group, with a significantly lower mean fasting plasma glucose level in the insulin degludec group than in the insulin glargine group (128 ± 56 vs 136 ± 57 mg/dL; P <.001). The insulin degludec group experienced 40% fewer episodes of severe hypoglycemia compared with the insulin glargine group (RR, 0.60; P <.001 for superiority; odds ratio [OR], 0.73; P < .001 for superiority) with no difference in rates of other adverse events.29

**Insulin Glargine U-300**

Insulin glargine U-300 is another long-acting basal insulin analog pen. While it has the same molecule and metabolism as insulin glargine U-100, it delivers the same amount of insulin in just a third of the volume required. This reduced surface area results in a more prolonged and constant release of insulin into the bloodstream, with a steady state reached within 3 to 4 days of daily administration and a half-life of 19 hours. Insulin glargine U-100, in contrast, reaches a steady state after 2 to 4 days of once-daily administration and has a half-life of 12 hours. When converting from U-100 to U-300, the same number of insulin units can be used. However, when switching from U-300 to U-100, it is recommended to reduce the insulin unit by 20%.30,31

Insulin glargine U-300 was evaluated in the EDITION trials, a series of 6 international, randomized, open-label, active-control, treat-to-target, noninferiority phase 3a studies comparing insulin glargine U-300 with insulin glargine U-100. The studies included 792 participants with T1D and 2737 with T2D. The duration was 6 months, with a planned 6-month extension phase.32-38 Table 2 provides an overview of the trials.32

A patient-level meta-analysis of the efficacy and safety of insulin glargine U-300 in the EDITION 1, 2, and 3 trials (conducted in patients with T2D) found AIC reductions were better sustained over 12 months in the insulin glargine U-300 group than in those receiving insulin glargine U-100 (–0.10%; 95% CI, –0.18 to –0.02; P = .0174). There was also a significantly lower rate of nocturnal or severe hypoglycemia in the insulin glargine U-300 group (RR, 0.82; 95% CI, 0.67-0.99), although there was no significant difference in the annualized rate of confirmed or severe hypoglycemia at any time of day.39

A real-world, observational study found significantly lower rates of hypoglycemia with similar blood glucose control in patients with T2D who switched from another basal insulin (including insulin glargine U-100, insulin detemir, and insulin degludec U-100) to insulin glargine U-300. After 6 months, patients who switched experienced 33% fewer hypoglycemic events (event rate per 100 patient-months: 7.98 vs 5.32, respectively; P < .01) versus those who switched to other basal insulins, with no impact on AIC.40

A similar study in patients 65 years and older found those switching to insulin glargine U-300 were 57% less likely to experience hypoglycemia at 6 months (OR, 0.43; 95% CI, 0.307-0.607; P < .0001) than those who switched to another basal insulin (insulin glargine U-100, insulin detemir, or insulin degludec). There were no significant differences with glycemic control.41

The results of the TAKE CONTROL trial, a 24-week, open-label, 1:1 ratio, randomized, controlled, 2-arm, parallel-group, multicenter, multinational study, were announced in September 2017. They showed greater AIC control with no increased risk of hypoglycemia in patients taking insulin glargine U-300 with a simple dose, patient-driven titration compared with those whose dose titration was physician-driven.42 Nearly 68% of patients in the self-managed titration group reached the predefined blood glucose target without experiencing severe and/or confirmed hypoglycemia, compared with 58.4% in the physician-driven titration group (RR, 1.15; 95% CI, 1.02-1.30; P = .0187). Comparable proportions of patients in both groups (6.4% vs 6.3%), experienced at least 1 severe and/or confirmed hypoglycemic event. Full results will be presented in 2018.43

**Combination Products**

The 2018 ADA Standards of Medical Care in Diabetes recommends combination injectable therapy with a GLP-1 RA for patients with T2D receiving basal insulin who continue to have an uncontrolled AIC, despite an acceptable FPG or daily dose of basal insulin exceeding 0.5 units/kg. The addition of a GLP-1 RA is an alternative to adding a rapid-acting insulin injection or changing to twice- or three-times-daily premixed insulin.1

The individual pharmacologic actions of basal insulin and GLP-1 RAs complement each other. Basal insulin helps control fasting glucose, but it has limited effects on postprandial hyperglycemia. GLP-1 RAs decrease postprandial glucose excursions by inhibiting glucagon secretion and suppressing appetite, delaying gastric emptying. GLP-1 RAs also have an extremely low risk of hypoglycemia.44,45 Having a medication that addresses fasting and postprandial glucose is a useful tool for controlling a patient’s diabetes.

Administering separate injections each day for a basal insulin and a once- or twice-daily GLP-1 RA requires 2 or 3 daily injections, which may be perceived as a significant barrier.46 In late 2016, the FDA approved 2 fixed-dose basal insulin/GLP-1 RAs: insulin glargine U-100/lixisenatide (insulin glargine 100 units/mL and lixisenatide 33 mcg/mL) and insulin degludec/liraglutide (insulin degludec 100 units/mL and liraglutide 3.6 mg/mL).47
TABLE 2. Efficacy of Insulin Glargine 300 U/mL [Gla-300] in Clinical Studies

<table>
<thead>
<tr>
<th>Study treatment</th>
<th>EDITION 4 (T1D)</th>
<th>EDITION JP 1 (T1D, Japan)</th>
<th>EDITION 1 (T2D)</th>
<th>EDITION 2 (T2D)</th>
<th>EDITION 3 (T2D)</th>
<th>EDITION JP 2 (T2D, Japan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Adult T1D, A1c 7%-10%</td>
<td>Adult Japanese T1D, A1c 7%-10%</td>
<td>Adult T2D, A1c 7%-10%</td>
<td>Adult T2D, A1c 7%-10%</td>
<td>Adult T2D, A1c 7%-11%</td>
<td>Adult Japanese T2D, A1c 7%-10%</td>
</tr>
<tr>
<td>Study treatment</td>
<td>Gla-300 or Gla-100, plus previous treatment</td>
<td>Gla-300 or Gla-100, plus previous treatment</td>
<td>Gla-300 or Gla-100, plus previous treatment</td>
<td>Gla-300 or Gla-100, plus previous treatment</td>
<td>Gla-300 or Gla-100, plus previous treatment</td>
<td>Gla-300 or Gla-100, plus previous treatment</td>
</tr>
<tr>
<td>Mealtime insulin analog</td>
<td>Basal + mealtime insulin</td>
<td>Basal + mealtime insulin</td>
<td>Basal + mealtime insulin</td>
<td>Basal + mealtime insulin</td>
<td>Basal + mealtime insulin</td>
<td>Basal + mealtime insulin</td>
</tr>
<tr>
<td>Mealtime insulin analog ± metformin</td>
<td>Basal + mealtime insulin</td>
<td>Basal + mealtime insulin</td>
<td>Basal + mealtime insulin</td>
<td>Basal + mealtime insulin</td>
<td>Basal + mealtime insulin</td>
<td>Basal + mealtime insulin</td>
</tr>
<tr>
<td>OADs (SU discontinued)</td>
<td>Insulin-naive therapy</td>
<td>OADs (SU discontinued)</td>
<td>Insulin-naive + noninsulin therapy</td>
<td>OADs (SU discontinued)</td>
<td>Insulin-naive + noninsulin therapy</td>
<td>OADs (SU discontinued)</td>
</tr>
<tr>
<td>OADs (SU continued with dose adjustments)</td>
<td>Basal insulin ± OADs</td>
<td>OADs (SU continued with dose adjustments)</td>
<td>Basal insulin ± OADs</td>
<td>OADs (SU continued with dose adjustments)</td>
<td>Basal insulin ± OADs</td>
<td>OADs (SU continued with dose adjustments)</td>
</tr>
</tbody>
</table>

**Sample size**
- Gla-300, n = 274
- Gla-100, n = 275
- Gla-300, n = 121
- Gla-100, n = 122
- Gla-300, n = 404
- Gla-100, n = 403
- Gla-300, n = 435
- Gla-100, n = 438
- Gla-300, n = 122
- Gla-100, n = 121

**A1C (%) baseline mean**
- 8.1
- 8.1
- 8.2
- 8.2
- 8.5
- 8

**Mean A1C change from baseline,**
- Gla-300, –0.4
- Gla-100, –0.3
- Gla-300, –0.83
- Gla-100, –0.83
- Gla-300, –0.57
- Gla-100, –0.56
- Gla-300, –1.43
- Gla-100, –1.46
- Gla-300, –0.45
- Gla-100, –0.55
- Gla-300, –0.55

**Laboratory-measured FPG (mmol/L) mean change from baseline**
- Gla-300, –0.95
- Gla-100, –1.14
- Gla-300, –1.29
- Gla-100, –1.38
- Gla-300, –1.14
- Gla-100, –1.06
- Gla-300, –3.41
- Gla-100, –3.80
- Gla-300, –0.45
- Gla-100, –0.45

**Weight (kg): mean weight change from baseline**
- Gla-300, 0.1
- Gla-100, 0.4
- Gla-300, 0.9
- Gla-100, 0.9
- Gla-300, 0.08
- Gla-100, 0.66
- Gla-300, 0.49
- Gla-100, 0.71
- Gla-300, 0.62
- Gla-100, 0.37

**Insulin dose: basal insulin dose at month 6 (U/kg/day unless otherwise indicated)**
- Gla-300, 0.47
- Gla-100, 0.40
- Gla-300, 0.97
- Gla-100, 0.88
- Gla-300, 0.92
- Gla-100, 0.62
- Gla-300, 0.35
- Gla-100, 0.34
- Gla-100, 0.33

**Mealtime insulin dose at month 6 (U/kg/day)**
- Gla-300, 0.34
- Gla-100, 0.44
- Gla-300, 0.55
- Gla-100, 0.55

**Additional**

Insulin degludec/liraglutide was evaluated in the 12-week DUAL I and DUAL II studies. The former compared the combination to monotherapy with insulin degludec or liraglutide in 1663 adults; the latter compared the combination to insulin degludec alone titrated to a maximum of 50 units in 413 adults. Primary end points included reductions in A1C and FPG, proportion of patients achieving A1C less than 7%, and proportion of patients reaching the A1C target without hypoglycemia and/or weight gain.46-47

An analysis of the 2 trials found that patients receiving the combination had a lower mean A1C overall, with a greater percentage reaching target at weeks 8 and 12. At week 12, in a combination of degludec U-100 and liraglutide versus degludec U-100, the estimated A1C change was −0.53% (95% CI, −0.63 to −0.44). Additionally
at week 12, in a combination of degludec U-100 and liraglutide versus liraglutide, the estimated A1C change was −0.43% (CI, −0.53 to −0.33). A higher percentage of patients in the combination group also reached their target A1C without hypoglycemia or hypoglycemia plus weight gain versus insulin degludec alone, but not versus liraglutide alone. Mean FPG was also lower in the combination group, with a higher proportion achieving their target FPG in weeks 4 to 12 than participants in any of the monotherapy groups. Finally, there was a lower mean weight gain from weeks 4 to 12 in the combination group versus the other groups. At week 12, patients taking the combination of degludec U-100 and liraglutide versus degludec U-100 had an estimated weight difference of −1.41 kg (95% CI, −1.72 to −1.10). Additionally, at week 12, patients taking the combination of degludec U-100 and liraglutide versus liraglutide had an estimated weight difference of 1.73 kg (95% CI, 1.42–2.04). Hypoglycemia occurred infrequently in all groups.48

**Insulin Glargine/Lixisenatide**

The safety and efficacy of insulin glargine/lixisenatide U-100/33 mcg/mL was evaluated in more than 1900 people with T2D during two 30-week clinical studies: LixiLan-L and LixiLan-O. LixiLan-L was an insulin intensification trial comparing the fixed combination to insulin glargine U-100 in a population with a mean baseline A1C of 8.1%. LixiLan-O compared the fixed combination to once-daily insulin U-100 or once-daily lixisenatide in a population with a mean baseline A1C of 8.5%.49,50

In LixiLan-L, 55% of participants receiving the combination obtained an A1C of less than 7% at 30 weeks compared with 30% of those receiving insulin glargine alone. Both groups experienced similar rates of hypoglycemia, with the most frequently reported adverse event in the combination group being nausea (10.4%). Overall, 2.7% (n = 10) of participants in the combination group discontinued due to adverse events (4 were due to nausea). In the insulin glargine group, 0.8% (n = 3) discontinued due to unreported adverse events (AEs).49

In the LixiLan-O trial, 74% of participants reached a target A1C of less than 7% with the combination compared with 59% on insulin glargine alone and 33% on lixisenatide alone (P < .0001 for all). AEs were similar to those seen in LixiLan-L, with similar rates of severe hypoglycemia.10

**Novel Insulins and Managed Care**

The cost of insulin has increased exponentially in recent years. One study reported a 3-fold increase between 2002 and 2013. Insulin costs increased from $231.48 per member per year (PMPY) (95% CI, $190.40–$272.55) in 2002 to $736.09 PMPY (95% CI, $639.72–$832.47) in 2013, even as the cost of other diabetes-related medications stayed flat or fell (Figure).51

In 2016, pharmacy benefit manager (PBM) Prime Therapeutics released a study showing a 50% increased use of insulin by its members and an 80% increase in the cost of insulin between 2011 and June 2015. Insulin, the study found, now accounted for $1 of every $20 paid for all drugs in the pharmacy benefit.52 Another PBM, Express Scripts, reported spending $77.50 PMPY in 2015 on diabetes drugs compared with the second highest spending category, pain/inflammation, at $40.65 PMPY. The increase was primarily driven by the cost of insulins.51

While still expensive, the pricing difference between the new and old generation basal insulins is minimal, thus improving their utility.5 Novel Insulins and Managed Care

**Cost-Effectiveness of Insulin Degludec U-100**

One model assessed the budget impact of switching from insulin glargine 100 to insulin degludec in all US commercially insured patients with TID and T2D on basal–bolus therapy and patients

### TABLE 3. Cost of Ultra–Long-Acting Basal Insulins

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Average Wholesale Price per 1000 Units</th>
<th>Median National Average Drug Acquisition Cost per 1000 Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin degludec</td>
<td>$355</td>
<td>$285</td>
</tr>
<tr>
<td>Insulin glargine U-100</td>
<td>$298</td>
<td>$239</td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td>$203</td>
<td>$239</td>
</tr>
<tr>
<td>Insulin glargine biosimilar</td>
<td>$736</td>
<td>$203</td>
</tr>
<tr>
<td>Insulin degludec/liraglutide prefilled pen</td>
<td>$508</td>
<td>$404</td>
</tr>
</tbody>
</table>

NA indicates not available.

**FIGURE.** Increases in Cost of Insulin Between 2002 and 2013 Relative to Other Antidiabetic Drugs

![Diagram](https://via.placeholder.com/150)
with T2D on basal–oral therapy. The study found an annual cost savings of $357.13 per patient per year (PPPY) for those with T1D, a reduction driven primarily by reduced insulin usage.\textsuperscript{54} The study found a cost increase of $1420 PPPY among patients with T2D on basal–bolus therapy, driven by the higher dose of insulin degludec required.\textsuperscript{54} A cost savings of $1206.61 PPPY among patients with T2D on basal–oral therapy was driven primarily by reductions in the cost of treating severe hypoglycemic episodes.

Overall, insulin degludec demonstrated cost savings of $240 million per year, or 3.5%, compared with insulin glargine U-100. However, as the authors noted, the study was based only on a model and may not translate into real-world savings.\textsuperscript{54}

Several cost-effectiveness studies conducted in Europe, where the products have been available longer, have been published. A prospective, real-world, observational study of 476 patients in Sweden who switched to insulin degludec from other basal insulins (nearly all analogs) found life expectancy gains and lower estimated direct lifetime healthcare costs of SEK 22,757 (US$2841). This resulted in the dominance of insulin degludec in the incremental cost-effectiveness ratio (ICER).\textsuperscript{55}

A scenario analysis comparing insulin degludec with insulin glargine U-300 also demonstrated the dominance of insulin degludec in patients with T1D and T2D basal-only therapy, with annual per-patient costs £53.36 (US$74.70) lower in T1D, and £52.12 (US$72.97) lower in T2D. The cost difference was driven primarily by the lower insulin degludec dose required for patients with T2D on basal–bolus. The ICER per incremental quality-adjusted life-year (QALY) gained with insulin degludec versus insulin glargine U-300 was estimated at £17,918 (US$25,084), even without considering any hypoglycemia benefit (Table 4).\textsuperscript{56}

### Cost-Effectiveness of Insulin Glargine U-300

A cost-utility evaluation of insulin glargine U-300 versus insulin glargine U-100 in patients with T2D from the perspective of the Spanish National Health System found insulin glargine U-300 with an ICER of €5294 (US$6510) per QALY, making it cost-effective given the €30,000 (US$36,891) per QALY threshold for Spain (typically $50,000 for the United States). The cost-effectiveness was driven by lower hypoglycemia rates and dosing flexibility.\textsuperscript{57}

### Cost-Effectiveness of Combination Therapies

An analysis from the Swedish Institute for Health Economics used a 40-year time frame and a societal perspective to assess the cost-effectiveness of the combination insulin degludec/liraglutide pen compared with 6 potential intensification treatment options for patients with T2D whose conditions remained uncontrolled on basal insulin alone. The analysis found that the combination was cost-effective at SEK 70,000 (US$8740)-per-QALY. It had an ICER against intensified basal insulin of SEK 28,000 (US$3496) per QALY; SEK 70,000 (US$8740) per QALY versus neutral protamine Hagedorn (NPH) insulin; and SEK 60,000 (US$7491) per QALY versus NPH insulin plus liraglutide. Differences in A1C reductions due to efficacy and response over time drove the results.\textsuperscript{58}

### Table 4. Total Costs Per Patient and Incremental Cost-Effectiveness: Insulin Degludec Versus Insulin Glargine U100\textsuperscript{56}

<table>
<thead>
<tr>
<th>Costs in US$/Year</th>
<th>T1D Basal-Only Therapy</th>
<th>T2D Basal–Bolus Therapy</th>
<th>T1D Basal-Only Therapy</th>
<th>T2D Basal–Bolus Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>779.97</td>
<td>834.66</td>
<td>740.31</td>
<td>732.54</td>
</tr>
<tr>
<td>Pen needles</td>
<td>198.50</td>
<td>198.50</td>
<td>49.62</td>
<td>49.62</td>
</tr>
<tr>
<td>Hypoglycemic events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsevere daytime events</td>
<td>95.47</td>
<td>95.47</td>
<td>17.06</td>
<td>17.06</td>
</tr>
<tr>
<td>Nonsevere nocturnal events</td>
<td>15.14</td>
<td>18.26</td>
<td>5.73</td>
<td>8.96</td>
</tr>
<tr>
<td>Severe events</td>
<td>776.38</td>
<td>776.38</td>
<td>8.13</td>
<td>58.06</td>
</tr>
<tr>
<td>Total costs</td>
<td>1865.46</td>
<td>1923.27</td>
<td>820.87</td>
<td>866.25</td>
</tr>
<tr>
<td>Incremental QALYs (IDeg-IGlar U100)</td>
<td>0.0044</td>
<td>0.0073</td>
<td>0.0084</td>
<td></td>
</tr>
<tr>
<td>ICER (cost/QALY)</td>
<td>Dominant</td>
<td>Dominant</td>
<td>22,411.24</td>
<td></td>
</tr>
</tbody>
</table>

ICER indicates incremental cost-effectiveness ratio; IDeg, insulin degludec; IGlar, insulin glargine; QALYs, quality-adjusted life-years; T1D, type 1 diabetes; T2D, type 2 diabetes; US$, US dollars.

Another analysis, this one from the United Kingdom, reached similar conclusions on the cost-effectiveness of the insulin degludec/liraglutide combination. This analysis found that the combination was more effective and less costly than basal insulin (U-100 insulin glargine or insulin detemir) plus liraglutide, and basal–bolus therapy (U-100 glargine and insulin aspart). Additionally, it was concluded that the combination was highly cost-effective compared with up-titrated insulin glargine U-100, with an ICER of £6090 (US$8525) per QALY gained.

Payer Considerations
The lower doses required of the insulin and GLP-1 RA combinations versus individual administration, and the improved adverse event profile of either used alone, should be considered in any cost/benefit analysis, managed care experts note. While there are published studies evaluating adherence, the ability to move from 2 to 1 daily with combination injections is expected to have a positive impact.

The cost of insulin affects not just payers, but also patients, given the high percentage of Americans now covered by high-deductible plans. About half of commercially insured Americans today have a single-person deductible of at least $1000, and a third have deductibles of at least $2000. Thus, they may pay a considerable portion of their insulin before first-dollar pharmacy coverage begins. Indeed, the media has begun reporting on the challenges patients face in paying for insulin.

When evaluating the newer insulins for formulary placement, payers should consider multiple factors: safety, efficacy, cost, and existing formulation options. Newer insulin therapies will also provide opportunities to track adherence and outcomes. As with many chronic disease states, adherence will be essential to ensure promising outcomes for patients. Thus, once-daily combination products, as well as flexible insulin dosing, will encourage compliance for these products. Another factor that payers must consider is patient population. Diabetes is prevalent, and insulin and GLP-1 RAs are recommended earlier in patient therapy, thus usage of these medications will increase.

Conclusions
As noted in the first part of this supplement, there are numerous patient and provider barriers to the use of insulin, despite national recommendations to begin insulin earlier in the disease state. The approach to patients with diabetes should take patient-specific factors into consideration, as a one-size-fits-all approach is not supported within the guidelines.

Insulin degludec and insulin glargine U-300, with their more stable pharmacokinetic/pharmacodynamic profiles, flexible dosing, reduced risk of hypoglycemia, and lower likelihood of weight gain, may help overcome those barriers. The availability of single-injection insulin/GLP-1 RAs offers another option to clinicians seeking to individualize diabetes treatment for their patients and improve adherence as well as clinical outcomes. Ensuring that these new options are financially accessible to patients requires that plans carefully evaluate the economic considerations, taking into account the cost of complications related to poor glycemic control.

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REFERENCES