Achieving and maintaining glycemic control is essential for reducing the risk of diabetes-associated microvascular complications (retinopathy, nephropathy, and neuropathy) and in many cases reducing the risk of macrovascular complications such as myocardial infarction (1–3).

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have each published similar patient-centered guidelines for type 2 diabetes management, although, in general, ADA takes a more conservative approach (4–7). Taking into account patient factors, ADA recommends a general glycemic target of an A1C value <7.0%, whereas AACE recommends an A1C value ≤6.5% (4,6). ADA

■ ABSTRACT

Background. Patients with type 2 diabetes require treatment intensification to maintain glycemic control. Clinician reluctance, patient injection fears, hypoglycemia, weight gain, or other objections may lead to clinical inertia, whereby therapy is not intensified and patients live with uncontrolled hyperglycemia and increased risk for complications. Initiation of injectable therapy with a glucagon-like peptide (GLP)-1 receptor agonist and/or basal insulin is a recommended option for patients with type 2 diabetes inadequately controlled on one or more oral agents.

Purpose. This article reviews clinical evidence and provides information on dosing and administration of iGlarLixi, a titratable fixed-ratio combination of insulin glargine and the GLP-1 receptor agonist lixisenatide that effectively lowers both fasting and postprandial glucose levels.

Findings. In phase 3 trials, iGlarLixi provided greater A1C reduction than insulin glargine or lixisenatide alone, without increased hypoglycemia risk compared with insulin glargine. iGlarLixi did not lead to weight gain versus insulin glargine and was associated with a lower frequency of gastrointestinal adverse effects than lixisenatide. iGlarLixi was recently approved by the U.S. Food and Drug Administration to improve glycemic control in adults with type 2 diabetes inadequately controlled on basal insulin (<60 units daily) or lixisenatide. iGlarLixi is administered by subcutaneous injection once daily, and the dose is titrated based on each patient’s insulin needs using a simple titration algorithm.

Conclusion. iGlarLixi offers an effective and well-tolerated treatment option for patients with type 2 diabetes requiring additional glycemic control, with comparable or improved safety outcomes than its separate components. Because of its simple regimen and low rate of adverse effects, iGlarLixi may improve adherence and, consequently, therapeutic outcomes.
reserves more (<6.5%) or less (<8.0%) stringent goals for specific patient groups, such as younger, newly diagnosed patients or older patients with multiple comorbidities, respectively (4,5).

All patients newly diagnosed with type 2 diabetes should receive counseling about lifestyle changes, such as improving nutrition and increasing physical activity and exercise. The majority of patients will begin therapy with metformin, unless contraindicated by comorbidity or intolerance. Patient response should be evaluated no later than 3 months after starting therapy, and, if the A1C goal has not been achieved, ADA and AACE guidelines recommend similar stepwise approaches. The general outline of these approaches is intensification to dual therapy with an additional class of oral agent, a glucagon-like peptide (GLP)-1 receptor agonist, or basal insulin for appropriate patients; further intensification to triple therapy with a third class of oral agent, a GLP-1 receptor agonist, or basal insulin; and further intensification to injectable therapy with basal insulin or a GLP-1 receptor agonist for patients not already using an injectable agent. Each step is reviewed after 3 months to determine treatment response (4,6). At any point in therapy, clinicians should consider combination injectable therapy with basal insulin plus a GLP-1 receptor agonist or prandial insulin when patients using basal insulin have achieved their target fasting plasma glucose (FPG) levels but A1C levels remain above target (4,6). In the past few years, there has been increasing interest in combining a GLP-1 receptor agonist with basal insulin, given the equal or slightly superior efficacy of this approach, with additional benefits of weight neutrality and less hypoglycemia than when adding prandial insulin (8-11). Despite existing guidelines, treatment intensification at each step is often delayed, leading to poor glycemic control (12,13). Delays longer than 7 years in treatment intensification with basal insulin have been reported in patients with type 2 diabetes uncontrolled on oral antidiabetes drugs (OADs) (12). Close to 50% of patients with type 2 diabetes treated in routine practice using any type of therapy do not maintain an A1C value <7.0%, and ~22% have an A1C value ≥8.0% (14).

Among patients using basal insulin, only ~30% reach their A1C targets, indicating a need for either improved titration or the addition of a prandial agent (14,15).

This article will provide information on the use of iGlarLixi, a new once-daily titratable fixed-ratio combination of basal insulin glargine, 100 units/mL, and lixisenatide, a short-acting GLP-1 receptor agonist, in the management of type 2 diabetes.

Rationale for Fixed-Ratio Combinations
A1C levels over time are influenced by daily fluctuations in basal and postprandial glucose (PPG) (16,17). The antihyperglycemic effect of most diabetes drugs, including basal insulin, is directed toward lowering basal hyperglycemia; exceptions include short-acting GLP-1 receptor agonists and prandial insulin (7).

iGlarLixi combines two different glucose-lowering agents with complementary mechanisms of action (18,19). Insulin glargine (Lantus, Sanofi-Aventis U.S.) is a long-acting basal insulin that targets FPG levels by mimicking physiologic insulin secretion to provide peakless insulin levels over a 24-hour period. Lixisenatide (Adlyxin, Sanofi-Aventis U.S.) is a once-daily GLP-1 receptor agonist that increases insulin levels and decreases glucagon secretion in a glucose-dependent manner, minimizing the risk of treatment-related hypoglycemia. Lixisenatide also slows gastric emptying, which reduces the rate at which postmeal glucose enters the circulation, thereby diminishing PPG excursions. Furthermore, lixisenatide demonstrated safety in patients with type 2 diabetes and a recent acute coronary syndrome in the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial (NCT01147250) (20). Lixisenatide was approved in the United States in July 2016 as an adjunct to diet and exercise for treatment of patients with type 2 diabetes (21).

In recommendations from ADA and the European Association for the Study of Diabetes and from AACE, a GLP-1 receptor agonist can be used early in treatment or as intensification of basal insulin therapy to provide additional prandial control, or basal insulin can be added to existing GLP-1 receptor agonist therapy as part of a stepwise approach (Figures 1 and 2) (4–6). In addition, the use of initial combination therapy with agents that correct specific pathophysiologic disturbances and that have complementary mechanisms of action is in agreement with the “pathophysiologic” approach for the management of type 2 diabetes (22). The development of the fixed-ratio combination of insulin glargine and lixisenatide follows a patient-centric treatment approach, since iGlarLixi provides several advantages over administering its component treatments separately. iGlarLixi offers simpler and more convenient treatment initiation, dosing schedules, and titration for health care professionals and patients. Furthermore, the combination mitigates the weight gain associated with insulin alone and is better tolerated than lixisenatide alone because of the relatively slow increase in GLP-1 receptor agonist dose in the fixed-ratio combination (23). This slower increase of GLP-1 receptor agonist dose reduces the risk of gastrointestinal adverse events such as vomiting, nausea, and diarrhea typically associated with GLP-1 receptor agonists, including lixisenatide (11,18,23). A simplified regimen may improve adherence by reducing the number of injections required compared with administering the components separately. Studies have shown that adherence decreases as treatment reg-
imens become more complicated and more injections are added (24–26). Furthermore, the expected reduction in gastrointestinal adverse events, a reduced risk of hypoglycemia, and weight neutrality are likely to have positive impacts on treatment adherence (25).

**Clinical Trials With iGlarLixi**

The efficacy and safety of iGlarLixi in the management of type 2 diabetes were evaluated in two multinational and multicenter phase 3 clinical trials that used open-label, randomized, parallel-group designs. LixiLan-O (NCT02058147) compared iGlarLixi with insulin glargine alone in patients already using basal insulin at screening with or without one to two OADs but who were not meeting glycemic goals (27). LixiLan-O was conducted in 23 countries including the United States, Canada, Chile, Mexico, South Africa, Australia, and 17 European countries, whereas LixiLan-L was conducted in 18 countries including the United States, Canada, Chile, Mexico, Australia, and 13 European countries.

LixiLan-O enrolled insulin-naïve patients with type 2 diabetes inadequately controlled on metformin alone or on metformin combined with a second OAD. After a 4-week run-in for metformin optimization, patients were randomly assigned to receive iGlarLixi (daily dose up to 60 units insulin glargine/20 μg lixisenatide), insulin glargine (up to 60 units/day), or lixisenatide (maintenance dose of 20 μg/day) while continuing therapy with metformin. Patients using iGlarLixi or insulin glargine titrated their drug to achieve fasting self-monitored plasma glucose levels of 80–100 mg/dL (23).

IglarLixi resulted in a significantly (P<0.0001) greater reduction in A1C, compared with insulin glargine or lixisenatide, as well as significantly more patients achieving with 2-drug combination (order not meant to denote any specific preference - choice dependent on a variety of patient- & disease-specific factors):

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A1C <7.0% (73.7, 59.4, and 33.0%, respectively). Additional details and outcomes of this trial are summarized in Table 1. For patients on iGlarLixi, the lixisenatide component mitigated the potential for weight gain typically experienced with the introduction of insulin, and a statistically significant weight difference of 1.4 kg was seen between the iGlarLixi and insulin glargine arms at 30 weeks (\( P < 0.0001 \)) (23). Importantly, iGlarLixi combination therapy provided greater glycemic control than insulin glargine alone, without increasing hypoglycemia risk compared with insulin glargine. The incidence of gastrointestinal adverse events was lower in patients using iGlarLixi than in patients treated with lixisenatide alone; 9.6 and 3.2% of patients treated with iGlarLixi experienced nausea and vomiting, respectively, compared with 24.0 and 6.4% of patients treated with lixisenatide, respectively (Table 2) (23).

LixiLan-L enrolled patients with type 2 diabetes inadequately controlled on basal insulin with or without up to two OADs (27). After a 6-week run-in period during which insulin glargine was initiated or optimized, patients were randomly assigned to treatment with iGlarLixi (daily dose up to 60 units insulin glargine/20 μg lixisenatide) or insulin glargine (up to 60 units/day), with or without metformin. Details and clinical outcomes of this trial are summarized in Table 1.

Compared with insulin glargine, iGlarLixi resulted in a significantly greater (\( P < 0.0001 \)) reduction in A1C and significantly more patients achieving A1C <7.0% (55 vs. 30% of patients; \( P < 0.0001 \)). Body weight decreased in patients using iGlarLixi and increased in patients using insulin glargine, with a between-group difference of 1.4 kg at 30 weeks (\( P < 0.0001 \)). Use of iGlarLixi was not associated with increased risk for symptomatic hypoglycemia (plasma glucose ≤70 mg/dL) despite greater reductions in A1C than insulin glargine (27). The rates of nausea, vomiting, and diarrhea (Table 2) were lower than historically seen with lixisenatide alone, most likely due to the gradual increase of the lixisenatide dose, which follows in parallel to the insulin glargine titration (17,27).

The LixiLan-O and LixiLan-L trials combined showed that iGlarLixi provides superior A1C reduction compared with either of its individual
**Initiation and Titration of iGlarLixi**

iGlarLixi was recently approved by the U.S. Food and Drug Administration (FDA) for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes inadequately controlled on basal insulin (<60 units daily) or lixisenatide (21). In the United States, iGlarLixi is available in a 3:1 dosing ratio of 3 units insulin glargine to 1 μg lixisenatide per milliliter (29). iGlarLixi is self-administered once daily with 1 hour before the first meal of the day via subcutaneous injection, using a modified version of the established SoloSTAR pen currently used with insulin glargine (29). The injector contains 3 mL of prefilled and premixed insulin glargine and lixisenatide in a cartridge (Figure 3) and delivers insulin glargine/lixisenatide doses from 15 units/5 μg to 60 units/20 μg per injection. The insulin glargine dose is displayed in the selection window and titrated by insulin units according to the patient's needs, until target FPG is achieved. The lixisenatide dose changes with the insulin glargine dose in a titrable fixed-ratio dose up to a maximum of 20 μg per injection (Figure 3) (29). iGlarLixi initiation dosing of insulin glargine begins with 15 units insulin glargine in patients with type 2 diabetes inadequately controlled on <30 units of basal insulin or on lixisenatide or basal insulin alone. Titration from 15 units insulin glargine per injection to 60 units insulin glargine per injection is achieved in a titrable fixed-ratio dose up to a maximum of 20 μg per injection (Figure 3) (29). Initiation dosing of iGlarLixi for patients previously on basal insulin or on lixisenatide begins with 15 units insulin glargine per injection and titration from 15 units insulin glargine per injection to 60 units insulin glargine per injection is achieved in a titrable fixed-ratio dose up to a maximum of 20 μg per injection (Figure 3) (29).

**TABLE 1. Clinical Outcomes in Phase 3 Clinical Trials of iGlarLixi for Patients With Type 2 Diabetes**

| Treatment Arm | n   | A1C, Screening (%) | A1C, Baseline (%) | ΔA1C, Baseline to Week 30 (%) | FPG, Baseline (mg/dL) | ΔFPG, Baseline to Week 30 (mg/dL) | 2-h PPG, Baseline (mg/dL) | Δ2-h PPG, Baseline to Week 30 (mg/dL) | Body Weight, Baseline (kg) | ΔBody Weight, Baseline to Week 30 (kg) | Documented Symptomatic Hypoglycemia* (%/EPY) | Patients Achieving A1C <7.0% at Week 30 (%) | Patients Achieving A1C <7.0% Without Weight Gain at Week 30 (%) | Patients Achieving A1C <7.0%, No Weight Gain, and No Documented Symptomatic Hypoglycemia at Week 30 (%) |
|---------------|-----|-------------------|------------------|-----------------------------|----------------------|---------------------------------|------------------------|----------------------------------|-------------------|----------------------------------|----------------------------------------|----------------------------------|--------------------------------------------|--------------------------------------------------|
| LixiLan-O (23), insulin-naive patients | iGlarLixi | 468 | 8.2 | 8.1 | −1.6†‡ | 178.0 | −62.4† | 273.7 | −102.4 | 89.4 | −0.3† | 25.6/1.4 | 73.7†‡ | 43.2† | 31.8† |
| LixiLan-O (23), insulin-naive patients | iGlar | 466 | 8.2 | 8.1 | −1.3 | 175.7 | −59.0 | 263.2 | −59.6 | 89.8 | +1.1 | 23.6/1.2 | 59.4 | 25.1 | 18.9 |
| Lixisenatide | 233 | 8.3 | 8.1 | −0.9 | 176.4 | −27.0 | 265.2 | −82.6 | 90.8 | −2.3 | 64/0.3 | 33.0 | 27.9 | 26.2 |
| LixiLan-L (27), patients previously on basal insulin | iGlarLixi | 366 | 8.5 | 8.1 | −1.1† | 132.0 | −6.3 | 267.6 | −85.1 | 87.8 | −0.7† | 40/3.0 | 54.9† | 34.2† | 19.9† |
| LixiLan-L (27), patients previously on basal insulin | iGlar | 365 | 8.5 | 8.1 | −0.6 | 131.9 | −8.3 | 269.7 | −25.1 | 87.1 | −0.7 | 42.5/4.2 | 29.6 | 13.4 | 9.0 |

*Plasma glucose ≤70 mg/dL. †P <0.0001 vs. iGlar; ‡P <0.0001 vs. lixisenatide.
iGlarLixi (with 5 μg lixisenatide) and is titrated to achieve target FPG, as with insulin glargine alone. In individuals receiving basal insulin doses of 30–60 units, the starting iGlarLixi dose would be 30 units. Once initiated, the dose of iGlarLixi should be titrated weekly in 2- to 4-unit intervals, either upward or downward, based on a patient’s metabolic needs, blood glucose monitoring results, and glycemic control goal (Table 3) (29). Clinicians should inform patients switching from basal insulin that an initial, transient rise in FPG levels might be seen, with no apparent impact on A1C levels, since they will be initiating iGlarLixi at a lower insulin dose (back-titration). FPG levels are expected to come back down once iGlarLixi has been titrated to achieve glycemic goals. It may be helpful for clinicians to let patients know their anticipated final dose, explaining that they are not failing when they move away from the starting dose, since that is part of the normal treatment pattern (30). The average dose from the LixiLan clinical trials was 40 units in insulin-naive patients and 47 units in insulin-experienced patients (23,27).

The flexibility in dosing provided by the pen means that patients are able to titrate their dose depending on their own personal needs. The pen has a range on the dial that is blacked out to prevent dosing below the appropriate range (i.e., 3–14 units) and is locked at the top dose. The pen works with all needles compatible with SoloSTAR. Storage conditions for iGlarLixi pens are summarized in Table 4 (29).

When starting iGlarLixi, clinicians should also provide information on the scope and duration of expected adverse events. Across clinical trials with iGlarLixi, the adverse events seen were predominantly gastro-

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**TABLE 3.** iGlarLixi SoloSTAR pen device and dose delivery of insulin glargine (units) and lixisenatide (μg) ranging from 15 units insulin glargine/5 μg lixisenatide to 60 units insulin glargine/20 μg lixisenatide.

| SOLIQUA 100/33 (dose window display)* | Insulin glargine component dose | Lixisenatide component dose | Comment |
|----------------------------------------|---------------------------------|-----------------------------|---------|
| 2                                      | –                               | –                           | Safety test dose – not for injection |
| 15                                     | 15 units                        | 5 mcg                       | Recommended starting dosage for patients previously treated with lixisenatide or less than 30 units of basal insulin |
| 16                                     | 16 units                        | 5.3 mcg                     |         |
| 17                                     | 17 units                        | 5.7 mcg                     |         |
| 18                                     | 18 units                        | 6 mcg                       |         |
| 19                                     | 19 units                        | 6.3 mcg                     |         |
| 20                                     | 20 units                        | 6.7 mcg                     |         |
| 21                                     | 21 units                        | 7 mcg                       |         |
| 22                                     | 22 units                        | 7.3 mcg                     |         |
| 23                                     | 23 units                        | 7.7 mcg                     |         |
| 24                                     | 24 units                        | 8 mcg                       |         |
| 25                                     | 25 units                        | 8.3 mcg                     |         |
| 26                                     | 26 units                        | 8.7 mcg                     |         |
| 27                                     | 27 units                        | 9 mcg                       |         |
| 28                                     | 28 units                        | 9.3 mcg                     |         |
| 29                                     | 29 units                        | 9.7 mcg                     |         |
| 30                                     | 30 units                        | 10 mcg                      | Recommended starting dosage for patients previously treated with 30 to 60 units of basal insulin |
| 31                                     | 31 units                        | 10.3 mcg                    |         |
| 32                                     | 32 units                        | 10.7 mcg                    |         |
| 33                                     | 33 units                        | 11 mcg                      |         |
| 34                                     | 34 units                        | 11.3 mcg                    |         |
| 35                                     | 35 units                        | 11.7 mcg                    |         |
| 36                                     | 36 units                        | 12 mcg                      |         |
| 37                                     | 37 units                        | 12.3 mcg                    |         |
| 38                                     | 38 units                        | 12.7 mcg                    |         |
| 39                                     | 39 units                        | 13 mcg                      |         |
| 40                                     | 40 units                        | 13.3 mcg                    |         |
| 41                                     | 41 units                        | 13.7 mcg                    |         |
| 42                                     | 42 units                        | 14 mcg                      |         |
| 43                                     | 43 units                        | 14.3 mcg                    |         |
| 44                                     | 44 units                        | 14.7 mcg                    |         |
| 45                                     | 45 units                        | 15 mcg                      |         |
| 46                                     | 46 units                        | 15.3 mcg                    |         |
| 47                                     | 47 units                        | 15.7 mcg                    |         |
| 48                                     | 48 units                        | 16 mcg                      |         |
| 49                                     | 49 units                        | 16.3 mcg                    |         |
| 50                                     | 50 units                        | 16.7 mcg                    |         |
| 51                                     | 51 units                        | 17 mcg                      |         |
| 52                                     | 52 units                        | 17.3 mcg                    |         |
| 53                                     | 53 units                        | 17.7 mcg                    |         |
| 54                                     | 54 units                        | 18 mcg                      |         |
| 55                                     | 55 units                        | 18.3 mcg                    |         |
| 56                                     | 56 units                        | 18.7 mcg                    |         |
| 57                                     | 57 units                        | 19 mcg                      |         |
| 58                                     | 58 units                        | 19.3 mcg                    |         |
| 59                                     | 59 units                        | 19.7 mcg                    |         |
| 60                                     | 60 units                        | 20 mcg                      | Maximum daily dosage |

*The dose window on the SOLIQUA 100/33 pen displays numbers for the even units and displays lines for the odd units.
intestinal in nature (Table 2) and generally transient, with a greater incidence during the initial 8-week titration period. Strategies used for minimizing gastrointestinal adverse events when initiating GLP-1 receptor agonists are also appropriate for iGlarLixi, such as the suggestion that patients eat slowly and stop eating when they feel full and that GLP-1 receptor agonist administration should be avoided before a large or high-fat meal (31,32). Advising patients of the nature and duration of adverse events, as well as giving them strategies to minimize possible adverse events, may reassure patients when or if the events arise, and this step may help to prevent patients from stopping therapy. Despite greater A1C reductions with iGlarLixi, the risk of hypoglycemia was not increased compared with insulin glargine. However, hypoglycemia may still be experienced because of the insulin component of iGlarLixi, and it is therefore necessary to provide patients with the appropriate strategies to avoid it or treat it.

### Specific Safety Concerns for GLP-1 Receptor Agonist Therapy

Despite reassurances from both the FDA and the European Medicines Agency (33), the possible association between incretin therapy and acute pancreatitis and/or pancreatic cancer remains controversial. Several recent analyses have added to data showing no increase in risk of acute pancreatitis associated with the use of GLP-1 receptor agonists in patients with type 2 diabetes, including a large population-based study (34), a meta-analysis of long-term clinical trial data (35), and long-term cardiovascular outcome trials (36–38), whereas others have continued to suggest a link (39). Similarly, although no association was found with pancreatic cancer in the majority of recent studies (36,38,40,41), an increase in cases was reported with liraglutide in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) cardiovascular outcomes study (13 in the liraglutide group [n = 4,668] vs. 5 in the placebo group [n = 4,672]) (37). In pooled data from clinical trials of lixisenatide, there were 21 cases (0.3%) of pancreatitis among patients treated with lixisenatide compared with 14 cases (0.2%) in patients treated with a comparator (incidence rate of 0.21 vs. 0.17 per 100 patient-years) (29,42). In the ELIXA trial, the incidence of both pancreatitis and pancreatic cancer was lower for lixisenatide (n = 3,031) compared with placebo (n = 3,032) (5 vs. 8 patients and 3 vs. 9 patients, re-

### TABLE 2. Gastrointestinal Adverse Events in Clinical Trials of iGlarLixi

| Condition                  | LixiLan-O (23) | LixiLan-L (27) |
|----------------------------|---------------|---------------|
|                            | iGlarLixi     | iGlar         | Lixisenatide  | iGlarLixi | iGlar     |
| n                          | 468           | 466           | 233          | 366       | 365       |
| Nausea, n (%)              |               |               |              |           |           |
| Discontinuation due to nausea | 45 (9.6)     | 17 (3.6)      | 56 (24.0)    | 38 (10.4) | 2 (0.5)   |
| Vomiting, n (%)            |               |               |              |           |           |
| Discontinuation due to vomiting | 2 (0.4)      | 0 (0.0)       | 6 (2.6)      | 4 (1.1)   | 0 (0.0)   |
| Diarrhea, n (%)            |               |               |              |           |           |
| Discontinuation due to diarrhea | 42 (9.0)     | 20 (4.3)      | 21 (9.0)     | 16 (4.4)  | 10 (2.7)  |

iGlar, insulin glargine.

### TABLE 3. Insulin Glargine Dose Adjustments for Patients During Titration of iGlarLixi, Using the Median Level of the Past 3 Days of Fasting SMPG Values

| Fasting SMPG (mg/dL) | Adjust iGlar Units |
|---------------------|-------------------|
| >140                | +4                |
| ≤140                | +2                |
| <80                 | No change         |

iGlar, insulin glargine; SMPG, self-monitored plasma glucose.

### TABLE 4. Storing iGlarLixi SoloSTAR Pens

| Condition                  | Unopened SoloSTAR Pen                                      | Opened SoloSTAR Pen                                      |
|----------------------------|------------------------------------------------------------|----------------------------------------------------------|
| Storage conditions         | Can be refrigerated until expiration date printed on label  | Do not refrigerate an opened pen                          |
|                            | Do not freeze                                             | Keep out of direct heat                                   |
| Storage temperature        | Store pen in the refrigerator, with cap on and in the original box, at temperature between 2°C and 8°C | Keep at room temperature, below 30°C                      |
| Expiration                 | Discard after expiration date has passed                   | Discard 14 days after opening                             |
Fixed-ratio combinations of basal insulin and GLP-1 receptor agonists are suitable for use in a range of patients with type 2 diabetes. The FDA recently approved the use of iGlarLixi to improve glycemic control in adults with type 2 diabetes inadequately controlled on basal insulin (<60 units daily) or lixisenatide. The efficacy and safety of iGlarLixi was demonstrated in the LixiLan-O and LixiLan-L trials conducted in insulin-naïve and insulin-experienced patients with type 2 diabetes, respectively (23,27). In LixiLan-O, patients had inadequate glycemic control on metformin with or without a second OAD; addition of iGlarLixi to metformin resulted in a substantial number of patients achieving A1C <7.0% in a safe and well-tolerated manner (23). In LixiLan-L, patients inadequately controlled on basal insulin, with or without metformin, derived additional benefit and glycemic control with iGlarLixi (27). In both LixiLan trials, patients achieved greater reductions in A1C with iGlarLixi than with insulin glargine alone or lixisenatide alone, without increased hypoglycemic risk.

In the United States, the SoloSTAR pen approved for iGlarLixi administration delivers insulin glargine/lixisenatide doses from 15 unit/5 μg to 60 units/20 μg per injection. Because this therapy is a combination, iGlarLixi will only require a single copay, not two, as it would be required with individual therapies.

Any patient requiring additional control of PPG while using basal insulin is likely to derive benefit from a combination that contains one component that predominantly targets postprandial hyperglycemia; options for these patients generally include addition of one (basal-plus) or more (basal-bolus) injections of prandial insulin (depending on patient needs) or a GLP-1 receptor agonist, including a GLP-1 receptor agonist such as lixisenatide (4–6). Basal-plus and basal-bolus regimens are associated with increased risk of hypoglycemia versus basal insulin alone, as well as the potential for weight gain and a requirement for additional daily injections (11,17). iGlarLixi offers the benefit of two complementary medications delivered by a single daily injection, allowing a less complex and more convenient dosing schedule and easier titration than if the components were administered separately, which has the potential to improve treatment adherence (24,25).

The GLP-1 receptor agonist/basal insulin combination of iGlarLixi may provide benefit for patients who eat one large meal per day. These patients, for example, senior citizens receiving meals from a “Meals on Wheels” program, could potentially inject iGlarLixi before their midday meal. Although the prescribing information states that iGlarLixi should be injected within 1 hour before the first meal of the day (29), the extended coverage may mean that this approach would provide glycemic benefit while they have snacks or a light meal in the evening. Many patients fear hypoglycemia or weight gain, which are known to be common barriers to basal insulin initiation and intensification (25). Such patients may be more receptive to iGlarLixi because of its demonstrated low risk of hypoglycemia and weight neutrality. Although data from the LixiLan-O and LixiLan-L trials showed that patients treated with iGlarLixi or insulin glargine were receiving similar insulin glargine doses at the end of study, personal preliminary real-world observations suggest that patients transitioning to iGlarLixi from previous basal insulin treatment may require smaller doses of insulin glargine. If this is indeed the case, these lower insulin glargine doses could help facilitate weight loss and reduce hypoglycemia. In addition, this reduced insulin glargine requirement would allow patients currently on doses of insulin glargine >60 units to consider using iGlarLixi, since the final insulin dose would be less because of the glycemic benefit of lixisenatide in the combination. Because the addition of lixisenatide to insulin glargine...
is weight neutral or has weight loss potential, another group of patients who potentially could benefit from iGlarLixi versus other options is patients who are afraid of weight gain and require treatment intensification. Furthermore, the low risk of hypoglycemia with iGlarLixi, compared with basal-prandial insulin therapy, may also benefit patients who are at a greater risk of hypoglycemia, such as senior citizens. Additional patient populations who may benefit from treatment with iGlarLixi, or circumstances in which its use may be appropriate, are not limited to those discussed above, since they are only a small cross-section of patients who may benefit.

Conclusion
Clinicians, nurse practitioners, physician's assistants, and diabetes educators who manage patients with type 2 diabetes are well acquainted with basal insulin initiation as a vital part of diabetes care. iGlarLixi is a titratable fixed-ratio combination of two agents with complementary mechanisms of action, insulin glargine and lixisenatide, which target FPG and PPG, respectively. In the United States, iGlarLixi was recently approved in a 3:1 dosing ratio of insulin glargine and lixisenatide, respectively, and is administered once daily with a prefilled SoloSTAR pen in doses ranging from 15 to 60 units insulin glargine with each injection. iGlarLixi is appropriate for adults with type 2 diabetes inadequately controlled on basal insulin (<60 units daily) or lixisenatide. Clinical studies have shown that iGlarLixi provides superior glycemic control compared with insulin glargine or lixisenatide alone, without increased risk of hypoglycemia compared with insulin glargine. Furthermore, iGlarLixi mitigates the weight gain associated with insulin therapy alone and the gastrointestinal adverse events associated with GLP-1 receptor agonists, including lixisenatide. Importantly, the simple, once-daily dosing regimen and titration based on basal insulin needs, along with a reduced risk of hypoglycemia and weight gain, may improve patient adherence and therefore further improve glycemic control.

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Duality of Interest
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Author Contributions
Both of the authors researched data, contributed to discussion, and reviewed and edited the manuscript. D.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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