

Transitioning to Fixed-Ratio Combination Therapy: Five Frequently Asked Questions Health Care Providers Should Anticipate From Their Patients

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A patient who is overweight with type 2 diabetes and takes multiple oral anti-hyperglycemic agents has been informed that the current treatment plan is not providing adequate glycemic control and that adding insulin therapy is recommended. However, the patient is concerned about insulin causing weight gain or leading to hypoglycemia and is looking for a treatment that will avoid or reduce these issues. Taking all of these considerations into account, the health care provider recommends that the patient start insulin and a glucagon-like peptide 1 (GLP-1) receptor agonist given as fixed-ratio combination (FRC) therapy administered with a prefilled pen device that allows for both basal insulin and a GLP-1 receptor agonist to be delivered in a single daily injection.

Basal insulin and GLP-1 receptor agonists have different but complementary modes of action. Basal insulin predominantly regulates blood glucose between widely spaced meals and overnight (1) through the movement of glucose from blood into certain cells of the body (including skeletal muscle) and the suppression of hepatic glucose production (2); GLP-1 receptor agonists affect glucose control through glucose-dependent insulin secretion, slowing gastric emptying, inducing satiety, and suppressing excess postprandial glucagon release (3). FRC therapies that contain both a basal insulin and a GLP-1 receptor agonist have been shown to improve glycemic control with a risk of hypoglycemia that is

similar to that associated with the use of basal insulin alone (4,5). In addition, FRC therapies have been shown to mitigate insulin-induced weight gain and to reduce the likelihood of the gastrointestinal (GI) adverse events that are associated with the use of GLP-1 receptor agonists. This effect is the result of slower up-titration of the GLP-1 receptor agonist component of an FRC compared with the titration schedule recommended when a GLP-1 receptor agonist is used alone (6–8).

Two titratable FRC therapies have been approved by the U.S. Food and Drug Administration: iGlarLixi, a combination of the long-acting analog insulin glargine (100 units/mL) and the GLP-1 receptor agonist lixisenatide (33 µg/mL) (9), and IDegLira, a combination of the long-acting analog insulin degludec (100 units/mL) and the GLP-1 receptor agonist liraglutide (3.6 mg/mL) (10). In the United States, both iGlarLixi and IDegLira are approved for people with type 2 diabetes “as an adjunct to diet and exercise” (9,10). However, IDegLira is not recommended as a first-line therapy for patients with diabetes that is inadequately controlled with diet and exercise (10).

Individuals for whom FRC therapy is being considered as a treatment option may have questions and concerns regarding these novel formulations. In this article, we discuss five common questions that patients have about FRCs and provide information

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TABLE 1. Who Are Good Candidates for Transitioning to FRC Therapy?

✓	Patients with insufficient glycemic control on diet and exercise, oral antihyperglycemic agents, basal insulin, or a GLP-1 receptor agonist
✓	Patients with insulin requirements within the available range of FRC dosing
✓	Patients requiring a ratio of insulin to GLP-1 receptor agonist that is compatible with the available FRC medications
✓	Patients who prefer a single daily injection to multiple daily injections
✓	Patients who are concerned about weight gain
✓	Patients with concerns about the risk of hypoglycemia with increasing insulin dosage
✓	Patients who are already taking a GLP-1 receptor agonist and would like to reduce associated GI adverse events

that may help health care providers (HCPs) address these inquiries.

1. "Is an FRC therapy right for me?"

To address this question, it is helpful for HCPs to be familiar with the advantages and disadvantages of this therapeutic option. In clinical trials, FRC therapies led to greater reductions in A1C than their individual components—basal insulin or a GLP-1 receptor agonist—when used alone (4,5,11). Other advantages of FRC therapies over insulin alone include their ability to reduce A1C without increasing the risk of hypoglycemia and their ability to mitigate insulin-associated weight gain. In addition, compared with GLP-1 receptor agonist therapy alone, FRC therapies are less likely to cause GI adverse events (4–7,11–13). FRC therapies also have the advantage of only requiring a single daily injection rather than the multiple daily injections required if an individual separately administers basal insulin and a once- or twice-daily GLP-1 receptor agonist.

One key differentiator between the two available FRC therapies is based on the properties of the GLP-1 receptor agonist component in each combination. Liraglutide (a component of IDegLira) has been shown to reduce fasting plasma glucose more than lixisenatide (a component of iGlarLixi), whereas lixisenatide has been found to reduce postprandial plasma glucose more than liraglutide (14). However, the degree of A1C

reduction between the two FRCs is similar.

For both available FRC therapies, contraindications include hypersensitivity or allergy to either of their components; they are also not recommended for patients with gastroparesis. In addition, as with liraglutide when given alone, IDegLira is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2 (10).

In some other cases, FRC therapy might not be suitable for consideration as a treatment option. Examples of this would be a patient who requires more than the maximum dose of insulin that the pens provide (50 units for IDegLira and 60 units for iGlarLixi) or less than the recommended starting dose (16 units for IDegLira and 15 units for iGlarLixi) and a patient who requires a different ratio of insulin to GLP-1 receptor agonist (6,9,10).

Characteristics of patients who may benefit from FRC therapy are summarized in Table 1.

2. "How do I use the pen and where should I store it?"

FRC medications are provided to patients as prefilled disposable pens that contain a fixed ratio of a basal insulin and a GLP-1 receptor agonist. FRC pens are easy to use, and illustrated step-by-step instructions are provided in the patient information leaflet included with each medication. Patients and HCPs may find that FRC pens

have a similar look and feel to insulin pens. Instructions are similar for iGlarLixi and IDegLira and include removing the cap, attaching a new needle, selecting the correct dose using the dose indicator dial, injecting, and preparing the pen for storage (9,10). When prescribing an FRC product, HCPs should demonstrate the correct way to use the pen and address any questions patients might have. Further information can be found on the respective product websites, and additional support is available from the product manufacturers, if needed.

Both IDegLira and iGlarLixi should be stored in a refrigerator at between 2 and 8°C (35.6 and 46.4°F) until first use. It is important that the medications not be allowed to freeze or be subjected to extreme heat; any frozen medication or medication that may have been exposed to extreme heat should be discarded (9,10). Advise patients not to store the pens overly close to the freezer section in their refrigerator and not to leave them in their vehicle.

After their first use, iGlarLixi pens can be kept at room temperature for up to 28 days, and IDegLira pens can be kept either at room temperature or in the refrigerator for up to 21 days (9,10). When using a new pen, it is recommended that the pen be left at room temperature for at least 1 hour before use to make injections more comfortable (9).

The pen needle should be removed and safely discarded directly after each use, and a new needle should be

inserted immediately before administration of the next dose. This step prevents contamination and leakage of the pens, helps to ensure accurate dosing, and avoids dulling of the needles from repeated use, with attendant skin damage.

3. "When should I take my medication?"

Both iGlarLixi and IDegLira are administered as once-daily subcutaneous injections. iGlarLixi should be taken within 1 hour before the first meal of the day because of its rapid on–rapid off pharmacokinetic/pharmacodynamic profile and lixisenatide’s slowing of gastric emptying (4,5,11,15). IDegLira can be taken at any time of the day and does not have to be taken at a specific time relative to meals (9,10); however, it is advised that the same time be chosen each day to minimize the risk of patients forgetting a dose or inadvertently double-dosing (9,10). Patients should not take extra or increased doses to make up for any missed doses. If they miss a dose, then they should take the next dose on the next day, as they would normally.

4. "How do I titrate my medication?"

FRC doses are titrated according to the insulin component of the medication, which is visible in the pen’s dose window. As the insulin dose is increased, the GLP-1 receptor agonist dose will also increase at a fixed ratio.

For iGlarLixi, the U.S. prescribing information (9) notes that:

- For patients naive to basal insulin or to a GLP-1 receptor agonist, currently on <30 units of basal insulin, or on a GLP-1 receptor agonist and not taking insulin, the recommended starting dose is 15 units once daily.
- For patients whose glycemia is inadequately controlled on 30–60 units of basal insulin with or without a separate GLP-1 receptor agonist, the recommended starting dose is 30 units once daily.

For IDegLira, the U.S. prescribing information (10) notes that:

- For patients naive to basal insulin or a GLP-1 receptor agonist, the recommended starting dose is 10 units once daily.
- For patients currently on basal insulin or a GLP-1 receptor agonist, the recommended starting dose is 16 units once daily.

For both iGlarLixi and IDegLira, previously used GLP-1 receptor agonist and basal insulin therapies should be discontinued at the time of switching to the FRC therapy. Because FRC product labeling differs from one country to another, prescribers will need to determine what the label indications and dosing recommendations are for the country in which they practice.

For optimal control of blood glucose, FRC medications require titration toward a desired blood glucose target. Starting at the recom-

mended dose, the FRC dose should be titrated upward or downward until the target blood glucose level is achieved. It is recommended that iGlarLixi be adjusted by 2–4 units each week, and IDegLira should be adjusted by 2 units every 3–4 days. The dose required to achieve target blood glucose control will vary depending on patients’ weight, degree of insulin resistance, and other individual factors (Table 2). When prescribing an FRC medication, it is important to remind patients that the starting dose is typically insufficient for controlling their blood glucose, and that they will likely need to titrate the dose upward (as instructed) to achieve a sufficient glucose-lowering effect. Providing such advice will help avoid patient misconceptions about whether the medication is actually working. It is also important to maintain regular contact with the patient (e.g., via phone, electronic health record, or office visit) to provide ongoing mentoring, feedback, and encouragement.

In the event of hypoglycemia, the dose of iGlarLixi or IDegLira can be progressively down-titrated as needed to avoid hypoglycemia; however, in the case of iGlarLixi, it cannot be dosed to deliver <15 units, and alternative treatment would be indicated if a dose of <15 units is required. Patients and HCPs should be aware that additional upward or downward titration of an FRC medication may be needed in the event of changes in physical activity or meal patterns, in

TABLE 2. Titration of IDegLira and iGlarLixi

FRC Therapy	Frequency	Recommended Dose Range, units	Self-Monitored Blood Glucose Level	Titration, units
IDegLira	Every 3–4 days	10–50	Above target range	+2*
			Within target range	0*
			Below target range	–2*
iGlarLixi	Weekly	15–60	Above target range	+2 to +4†
			Within target range	0†
			Below target range	–2 to –4†

*1 unit IDegLira contains 1 unit insulin degludec and 0.036 mg liraglutide.

†1 unit iGlarLixi contains 1 unit insulin glargine and 0.33 µg lixisenatide.

cases of renal or hepatic dysfunction or acute illness, and if other antihyperglycemic medication is added to or withdrawn from a patient's treatment regimen. To help with educating patients about FRC dose titration, tutorial videos are available on the product websites.

5. "What are the potential adverse effects associated with FRC therapies?"

FRC therapies have been shown to be weight neutral or to cause weight loss compared with basal insulin alone because of the weight-reducing effect of the GLP-1 receptor agonist component (4,5,11,12). Transitioning to FRC therapy from basal insulin does not increase the risk of hypoglycemia (4,5,11,12), and, for IDegLira, a lower incidence of hypoglycemia has been reported compared with insulin degludec or insulin glargine alone in uncapped doses (16).

Although the use of GLP-1 receptor agonists alone results in GI adverse events, including nausea, vomiting, and diarrhea, in ~37% of patients, its administration as a component of an FRC reduces the risk of experiencing these events by ~50% (5). The difference in frequency of GI adverse events—especially during the up-titration period—is thought to be explained by the smaller incremental dose increase of the GLP-1 receptor agonist component when it is administered as part of an FRC compared with the larger incremental dose increase of the GLP-1 receptor agonist that is typically recommended when used as a stand-alone therapy (4,5,13). GI adverse events tend to be mild to moderate and occur mainly in the first 8 weeks of treatment. In clinical trials of FRC therapies, very few patients (0–1.5%) permanently discontinued treatment because of adverse GI events (4,5,11).

Other reported adverse events of FRC therapy include nasopharyngitis, headache, and upper respiratory tract infection (9,10); however, causation has not yet been established.

Summary

The FRC therapies iGlarLixi and IDegLira can help patients achieve glycemic goals with similar rates of hypoglycemia and reductions in insulin-induced weight gain and GLP-1 receptor agonist–induced GI adverse events. Additionally, FRC therapies give patients the option of combining insulin therapy with a GLP-1 receptor agonist in a once-daily injection instead of administering multiple daily injections. This reduction in injection burden may be more acceptable to patients and may improve both treatment adherence and persistence. HCPs are vital in providing essential support and information to ensure patients' safe and efficaciously transition to FRC therapy.

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Author Contributions

All authors have written, reviewed, edited, and provided final approval of this manuscript. I.B. is the guarantor of this work and, as such, takes responsibility for the integrity and accuracy of the review.

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