



New Insulin/GLP-1RA Agents: Overview for the Pharmacist

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Learning Objectives

- Describe two novel diabetic agents that combine insulin and a GLP-1 Receptor Agonist
- Recognize clinical trials which define safety and efficacy of these agents
- Describe common side effects, drug interactions and precautions of each agent
- Identify how these agents may fit into existing guidelines and pharmacy practice

Abstract

Diabetes is a rapidly growing disease that is progressive in nature. Many medications are approved for the treatment of diabetes however, several novel agents show improved efficacy and safety over current therapies. In late 2016, two novel diabetic agents became available, insulin glargine and lixisenatide and insulin degludec and liraglutide. These medications combine basal insulin and a glucagon-like peptide-1 receptor agonist and were approved by the FDA to improve glycemic control in patients with Type 2 Diabetes Mellitus. Both products have shown benefits to patients during clinical trials. This review will discuss characteristics of each agent and where the use of these drugs may be implemented into current treatment guidelines.



Diabetes Mellitus (DM) is a common illness that affects more than 30 million Americans.¹ DM is rapidly increasing in prevalence in the United States and is expected to double by the year 2030. DM is currently the 7th leading cause of death.^{1,2} Diabetes Mellitus Type 2 (DMT2) accounts for 90-95% of all diagnosed cases in the United States.¹

It is no surprise that with the increasing prevalence and progressive nature of DMT2, that nearly 300 drug companies are involved with the development of new DMT2 drugs, and others are developing new delivery systems.³ Advances are continuously being made to treatment approaches.⁴ Diabetes treatment is ever evolving and it appears as though every year there are several new bottles on the shelf or new pens in the refrigerator. Pharmacists must not only be aware of these new drugs, but should feel confident in recommending or determining if these new drugs are appropriate in patient care.⁴

The combination of a basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1RA) is becoming more popular in practice because these pharmacologic actions complement each other.⁵ In late 2016, two new combination drugs were approved by the FDA for control of DMT2. Soliqua, a combination of insulin glargine and lixisenatide, and Xultophy, a combination of insulin degludec and liraglutide, contain both a basal insulin and GLP-1 receptor agonist. This article will review these two new insulin/GLP-1RA agents.

These products contain long-acting insulin analogs. Both insulin glargine and insulin degludec form multi-hexamers in the

subcutaneous tissue which slowly dissolves into monomers and are absorbed.⁶ This contributes to their long-acting activity.⁶ The purpose of these insulins is to mimic the natural basal insulin in the body and this can result in decreased fasting and postprandial blood glucose.⁶ GLP-1 receptor agonists, on the other hand, bind to several GLP-1 receptors in the body and enhance insulin secretion in a glucose dependent manner.⁶ This mechanism ultimately controls postprandial glucose secretion and increases satiety and promotes weight loss.⁶ According to the American Diabetes Association (ADA) guidelines, both insulin and GLP-1 agonists are currently considered second line in patients with DMT2 and are reserved for patients who did not respond to metformin monotherapy, or for those who present upon diagnosis with an A1c >9% along with metformin.⁷ These agents are also recommended for those who present upon diagnosis with an A1c >10% as part of combination insulin therapy.⁷ The combination of these drugs are only appropriate for use in patients with DMT2 due to its GLP-1 receptor agonist component.

Soliqua (insulin glargine and lixisenatide)

Soliqua was developed by Sanofi and approved in November 2016 to improve glycemic control in adults with DMT2 inadequately controlled on basal insulin or lixisenatide.⁸ Soliqua's efficacy was studied through the LixiLan-L and LixiLan-O clinical trials.^{9,10}

In the LixiLan-O trial, DMT2 patients who were inadequately controlled on metformin therapy were given either Lantus (insulin glargine) alone, Adlyxin



(lixisenatide) alone or Soliqua (in the trial referred to as iGlarLixi) as add-on to metformin.⁹ The objective was to evaluate the efficacy and safety of iGlarLixi compared to Lantus or Adlyxin in DMT2 patients inadequately controlled on metformin.⁹ The primary outcome was A1c change at 30 weeks. The results of the study showed that there were significant reductions in A1c when patients were given iGlarLixi versus Lantus or Adlyxin monocomponents ($P < 0.0001$).⁹ In addition, more patients on iGlarLixi reached goal A1c ($P < 0.0001$), had a decrease in mean body weight ($P < 0.0001$), and had improved postprandial glycemic control compared to the other groups (95% CI iGlarLixi versus iGlar -2.8 to -2.0, 95% CI iGlarLixi versus Lixi -1.6 to -0.6), while having similar rates of symptomatic hypoglycemia (iGlarLixi 26%, iGlar 24%, Lixi 6%).⁹

In the LixiLan-L trial, DMT2 patients who were inadequately controlled on Lantus (insulin glargine) were randomized and given either Lantus (insulin glargine) alone or Soliqua (in the trial referred to as iGlarLixi).¹⁰ The objective was to evaluate the efficacy and safety of iGlarLixi compared with Lantus in DMT2 patients who were inadequately controlled on Lantus.¹⁰ The primary outcome was A1c change at 30 weeks.¹⁰ The results of the study showed that there were significant reductions in A1c from baseline when patients were given iGlarLixi versus Lantus ($P < 0.0001$).¹⁰ In addition, patients on iGlarLixi had a decrease in mean body weight, while those on Lantus had an increase in mean body weight (both $P < 0.0001$).¹⁰ Symptoms of hypoglycemia

were comparable between groups (iGlarLixi 40%, iGlar 42.5%).¹⁰

From these two studies, it was concluded that the expected reduction in A1c for patients was 1.09-2.41% in 30 weeks.⁹⁻¹¹

Soliqua 100/33 unit-mcg/mL (100 units of insulin glargine and 33 mcg of lixisenatide per mL) is available in a pen and delivers doses from 15-60 units of insulin in a single injection.⁸ The injections can be delivered subcutaneously into the thigh, upper arm, or abdomen. Before initiating Soliqua, lixisenatide or basal insulin therapies should be discontinued.⁸ Dosing should be based on prior glucose lowering therapy.^{8,12} In patients who have previously been inadequately controlled on lixisenatide, or those patients currently on less than 30 units of basal insulin, Soliqua 15 units should be initiated.^{9,12} However, in patients who have previously been inadequately controlled on 30-60 units of basal insulin, Soliqua 30 units should be initiated.^{8,12} Maximum daily dosage is 60 units per day.^{8,12} Manufacturer labeling recommends titrating the dose of Soliqua by 2-4 units per week dependent on the patient's metabolic needs.^{8,12} This medication should be taken in the morning.¹²

There are no dosage adjustments specified in the manufacturer labeling for mild to moderate renal impairment, however patients should be monitored carefully as studies have shown lixisenatide concentrations are increased in patients with renal impairment.^{8,12} The half-life of Soliqua was found to be 3 hours, and the clearance of Soliqua is 35L/h.⁸ Soliqua is not recommended in patients with end stage renal disease.¹² Dosage adjustments are not





specified in the package insert for hepatic impairment, however due to the pharmacokinetic principles of both insulin glargine and lixisenitide, it is unlikely Soliqua will be affected by hepatic impairment.^{8,12}

After administration of Soliqua, insulin glargine showed no pronounced peak.⁸ Lixisenatide reached a peak concentration at 2.5-3 hours after administration.⁸ While there was a small decrease observed in concentration of lixisenitide between combination Soliqua and lixisenitide alone, this difference was not considered clinically relevant.⁸

Like many injectable glucose-lowering agents (i.e. Lantus, Victoza), Soliqua pens should be stored in the refrigerator prior to initial use and stored at room temperature after first use.¹² The pen may be used for up to 14 days following first use.¹²

The most common side effects of Soliqua include hypoglycemia, headache, nausea, diarrhea and hypersensitivity reactions.^{8,12} The chances of hypoglycemia are increased when a patient is taking Soliqua in combination with other glucose-lowering agents. In addition, drugs that mask or enhance the signs and symptoms of hypoglycemia, like beta blockers and some antibiotics (e.g. quinolones and sulfmethoxazole) should be avoided.¹² If a patient has pancreatitis, or expected pancreatitis, Soliqua should be discontinued immediately.⁸ Lixisenatide slows gastric emptying and therefore this product should not be used in patients with gastroparesis.^{8,12} The delayed gastric emptying may affect absorption of oral medications. As a result, oral contraceptives and antibiotics should be

taken at least 1 hour before or 11 hours after administration of Soliqua.⁸ This can be problematic as patients must take this medication in the morning, so it is important to counsel patients on why this is necessary.⁸ In addition, patients on oral medications with narrow therapeutic indexes, such as warfarin or digoxin, should receive careful clinical monitoring.⁸ Soliqua has not been extensively studied in pregnancy; however, based on animal studies there may be risks to the fetus from exposure to lixisenatide.^{8,12} Therefore, this medication is not recommended in pregnancy.

Since Soliqua contains an insulin analog, patients should be counseled about usual insulin precautions, in particular hypoglycemia.¹²⁻¹³ Patients should also be counselled on how to administer Soliqua and be encouraged to never reuse needles.^{8,12-13}

Summary:

Use: To improve glycemic control in DMT2 patients who are inadequately controlled on basal insulin or lixisenitide.

Dose: 15-60 units subcutaneously once each morning at least 1 hour prior to first meal of the day. Maximum daily dose is 60 units. No dosing adjustments specified for renal or hepatic impairment.

% A1c Reduction: 1.09% to 2.41% after 30 weeks.

Important Considerations: Soliqua should be administered one hour prior to food. Keep Soliqua pens in the fridge prior to initial use. Soliqua should not be used in ESRD or in patients with pancreatitis or gastroparesis. Special precautions must be taken when a patient is receiving oral antibiotics, contraceptives or drugs with a



narrow therapeutic index due to delayed gastric emptying. There is insufficient data to determine if Soliqua is safe in pregnancy. Hypoglycemia is the most common adverse reaction and patients should be counselled on these signs and symptoms.

Xultophy (insulin degludec and liraglutide)

Xultophy was developed by Novo Nordisk and approved for use in November 2016 to improve glycemic control in DMT2 for patients who are inadequately controlled on basal insulin or liraglutide alone. Xultophy's efficacy was studied in a total of 1,393 patients in three different randomized, open-label trials over twenty-six weeks in the DUAL program (including DUAL-II, DUAL-III, and DUAL-V trials). The combination of basal insulin and GLP-1RA provides convenient administration of both products in a single, once-daily injection.¹⁴

In the DUAL-II trial, DMT2 patients who were inadequately controlled on metformin therapy were given either Tresiba (insulin degludec) alone or Xultophy (in the trial referred to as iDegLira).¹⁵ The objective of this study was to evaluate the efficacy and safety of iDegLira compared to Tresiba.⁹ The primary outcome was A1c change at 26 weeks. The results of the study showed that there were significant reductions in A1c when patients were given iDegLira versus Tresiba alone ($P < 0.001$).¹⁵ In addition, more patients on iDegLira had a decrease in mean body weight ($P < 0.001$) while having similar rates of symptomatic hypoglycemia (iDegLira 24% iDeg 25%).¹⁵

In the DUAL-III trial, DMT2 patients who were inadequately controlled on metformin and liraglutide, or metformin and exenatide therapy were randomized and

given either their previous GLP-1RA treatment and dose or Xultophy (called iDegLira).¹⁶ The objective of this study was to evaluate the efficacy and safety of iDegLira compared with GLP1-RAs in DMT2 patients who were inadequately controlled on liraglutide or exenatide.¹⁰ The primary outcome was A1c change at 26 weeks.¹⁰ The results of the study showed that there were significant reductions in A1c from baseline when patients were given iDegLira versus GLP-1RA therapy alone ($P < 0.001$).¹⁶ In addition, patients on iDegLira were more likely to reach their goal A1c than those with GLP-1RA alone ($P < 0.001$).¹⁶ Symptoms of hypoglycemia were higher in the iDegLira group ($P < 0.001$).¹⁶

In the DUAL-V trial, DMT2 patients who were inadequately controlled on metformin and Lantus (insulin glargine) therapy were randomized and given either Lantus (insulin glargine) or Xultophy (iDegLira).¹⁷ The primary outcome was A1c change at 26 weeks.¹⁷ The results of the study showed that there were significant reductions in A1c from baseline when patients were given iDegLira versus Lantus ($P < 0.001$).¹⁷ In addition, patients on iDegLira had a decrease in mean body weight, while those on Lantus had an increase in mean body weight ($P < 0.001$).¹⁷ Significantly fewer hypoglycemic events were reported in the iDegLira group ($P < 0.001$).¹⁷ From these studies, it was concluded that the expected reduction in A1c for patients is 1.3-1.9% over 26 weeks.¹⁵⁻¹⁷

Xultophy 100/3.6 units-mg/mL (100 units of insulin glargine and 3.6 mg of liraglutide per mL) is available in a pen and





can deliver doses from 10 to 50 units of insulin per injection. The injections can be delivered subcutaneously into the thigh, upper arm, or abdomen. Xultophy should be injected the same time daily and can be given with or without food. The maximum daily dose is 50 units of Xultophy (50 units insulin degludec and 1.8 mg of liraglutide). The initial starting dose is recommended at 16 units. Xultophy can be titrated up 2 units every 3-4 days as needed based upon blood glucose, metabolic needs, and glycemic control. If patients require doses that are frequently under 16 units, alternative therapy should be considered. At this time, there is no known information on renal or hepatic impairment dosage adjustments.¹⁴

Like many injectable glucose-lowering agents, Xultophy pens should be stored in the refrigerator prior to initial use and stored at room temperature after first use.¹²

Xultophy reaches steady state in approximately 48-72 hours after consistent daily administration. Protein binding is approximately 99% bound to plasma proteins.

Side effects that were most commonly reported were hypoglycemia, nasopharyngitis, headache, nausea, diarrhea, increased lipase enzymes, and upper respiratory tract infections. Hypoglycemia remains the most common adverse reaction in patients using insulin products. There were no significant differences found in the occurrence of hypoglycemia in patients using Xultophy and comparator medications.¹⁵⁻¹⁶ Major precautions include pancreatitis, hypoglycemia, acute kidney injury, hypersensitivity and allergic reactions, and hypokalemia. A black box

warning for Xultophy is the risk of thyroid C-cell tumors. Xultophy can only be used in pregnancy when the benefit outweighs the risk to the fetus.¹⁴

Since Xultophy contains an insulin analog, patients should be counselled about usual insulin precautions, in particular, hypoglycemia. Patients should also be counseled on how to administer Xultophy and encouraged to never reuse needles.¹⁴



Knowledge Check: True or False?
Both Soliqua and Xultophy have a black box warning for thyroid C-cell tumors.

Answer: False, only Xultophy

Summary:

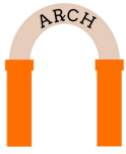
Use: To improve glycemic control in DMT2 patients who are inadequately controlled on basal insulin or liraglutide

Dose: Starting dose is 16 units subcutaneously once daily. Maximum daily dose is 50 units.

% A1c Reduction: 1.3-1.9% after 26 weeks

Important Considerations: Xultophy can be administered with or without food, as long as it is given the same time daily to help control blood glucose effectively. The pens should be stored in the refrigerator until they are ready for use, and can be stored at room temperature for 21 days once out of the fridge. Hypoglycemia is the main adverse reaction to this medication. There is a black box warning for thyroid C cell tumors.





Discussion

While Soliqua and Xultophy have different active ingredients, both agents appeared to be effective and may decrease a patient's A1c by roughly 1-2%.^{9,10,15-17} Many of the agents adverse events overlap due to the inclusion of similar drug classes.^{12,18} Upon literature search, no head-to-head trials of these agents have been found. Therefore, clinical judgment should be used when choosing one agent over the other based upon what is known for each drug individually. This decision should look closely at patient specific factors. For example, a patient who would like to take their insulin/GLP1-RA at night and/or without regard to meals may benefit from choosing Xultophy over Soliqua. However, a patient with family history of thyroid tumors may benefit from Soliqua instead of Xultophy.

Both classes of drugs are considered second line agents in the treatment of DMT2 (metformin is first-line).⁷ Particularly, these combination products fit well into the guidelines as options in patients who have been inadequately controlled on metformin in addition to, either a basal insulin or a GLP-1RA alone.⁷

Combinations of basal insulin and GLP-1RAs have shown promising results while limiting episodes of hypoglycemia.^{5,9,10,15-17} Patients may enjoy limiting their injections to once daily and potentially losing weight. These agents are convenient due to the fact that patients only have to carry one pen with them instead of two. There is potential for less confusion about "which-pen-is-which" or what drug they have already administered. In theory,

this added convenience might improve patient adherence and ultimately help forgetful patients better control their diabetes.

A shortcoming with these agents is in patients who require very high doses of basal insulin to control their blood sugars. Furthermore, while some patients appreciate only needing one injection per day, this may make little difference to patients who are on bolus (mealtime) insulin. Cost is also a considerable factor in choosing these agents, and it is possible not all insurances may cover the combination of these products.

Conclusion

Diabetes is a rapidly growing disease in the United States. Many new drugs are coming to market, and pharmacists must stay up to date on the newest products in order to properly make recommendations for optimal patient care. Soliqua and Xultophy were approved in late 2016 for the use in DMT2 patients for improved glycemic control. Both of these drugs are combinations of basal insulin and different GLP-1 receptor agonists. The medications have fixed ratios of basal insulin to the GLP-1 receptor agonist. Both agents show promising results in the reduction of A1c. The combination of two of these agents may potentially help improve compliance. Patient specific factors should be considered in determining whether these agents are appropriate in the treatment of DMT2. Overall, these drugs may be effective in certain patients to help achieve better glycemic control.





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