

10-12-2017

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Recommended Citation

Lewis J. New therapies for patients with type 2 diabetes. *Pharmacy Times*.

[https://www.pharmacytimes.com/publications/supplementals/2017/](https://www.pharmacytimes.com/publications/supplementals/2017/diabetessupplementseptember2017/new-therapies-for-patients-with-type-2-diabetes)

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Pharmacy Times

New Therapies for Patients With Type 2 Diabetes

2017-10-12 20:00:00

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Diabetes mellitus is a growing health problem in the United States. According to a recent CDC report, as of 2015, 30.3 million Americans (9.4% of the US population) have diabetes. Of these, 90% to 95% are diagnosed with type 2 diabetes (T2D). This number will likely continue to grow, because an estimated 84.1 million Americans have pre-diabetes, putting them at increased risk of T2D development.¹ The manufacturers of the novel combination therapies that enter the market each year hope to simplify medication regimens for patients with T2D and to improve their adherence. Select combination products that were approved in the last few years for T2D are listed in Table 1.²⁻⁹

TABLE 1. SELECTED COMBINATION PRODUCTS FOR T2D, APPROVED 2015-2017²⁻⁹

Generic name (brand)	FDA approval date	Dosage form/route	Drug classes
dapagliflozin/saxagliptin (Qtern)	2017	Tablet/oral	SGLT-2 inhibitor; DPP-4 inhibitor
canagliflozin/metformin (Invokamet XR)	2016	Tablet/oral	SGLT-2 inhibitor; biguanide
linagliptin/metformin (Jentadueto XR)	2016	Tablet/oral	DPP-4 inhibitor; biguanide
insulin glargine/lixisenatide (Soliqua)	2016	3-mL pre-filled pen/SC injection	Basal insulin; GLP-1 RA
Insulin degludec/liraglutide (Xultophy)	2016	3-mL pre-filled pen/SC injection	Basal insulin; GLP-1 RA
empagliflozin/metformin (Synjardy XR)	2015	Tablet/oral	SGLT-2 inhibitor; biguanide
empagliflozin and linagliptin (Glyxambi)	2015	Tablet/oral	SGLT-2 inhibitor; DPP-4 inhibitor
empagliflozin/metformin (Synjardy)	2015	Tablet/oral	SGLT-2 inhibitor; biguanide

DPP-4 indicates dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SC, subcutaneous; SGLT-2: sodium-glucose co-transporter 2; T2D, type 2 diabetes.

Many patients with T2D will require insulin therapy; however, these patients are also likely to develop insulin resistance over time. Due to insulin resistance and decreased endogenous insulin secretion, patients may require higher insulin doses and an increased number of insulin injections.¹⁰ As the needed insulin dosage increases, so, typically, does the volume of injected insulin. Because larger volumes of insulin can lead to painful injections and unpredictable insulin absorption,¹⁰ concentrated insulins have become more prominent in clinical practice. Several different insulin formulations have become available in the last few years. Two new insulin/glucagon-like peptide-1 receptor agonist (GLP-1 RA) combination products have also recently entered the market.

INSULIN

Four different concentrated insulins are currently indicated for patients with T2D. These concentrated insulins are available in the pen formulation, apart from Humulin R U-500, which is also available in the vial formulation (Table 2¹¹⁻¹⁶). Each pen delivers the desired insulin dose

in a smaller volume, which negates the need for dose conversions. For example, if a patient is instructed to inject 15 units of concentrated insulin, they should be advised to dial the pen to 15 units.

TABLE 2. DOSAGE FORMULATIONS OF SELECTED INSULIN PRODUCTS¹¹⁻¹⁶

Insulin Generic Name (Brand)	Pen Formulation	Insulin Dose Capacity per Pen	Maximum Single-Dose Delivery for Pen	Available in Vial?
degludec U-100 (Tresiba Flex-Touch)	100 units/mL (3-mL pen)	300 units	80 units	No
degludec U-200 (Tresiba Flex-Touch)	200 units/mL (3-mL pen)	600 units	160 units	No
glargine U-100 (Lantus SoloSTAR)	100 units/mL (3-mL pen)	300 units	80 units	Yes
glargine U-300 (Toujeo SoloSTAR)	300 units/mL (1.5-mL pen)	450 units	80 units	No
lispro U-100 (Humalog KwikPen)	100 units/mL (3-mL pen)	300 units	60 units	Yes
lispro U-200 (Humalog KwikPen)	200 units/mL (3-mL pen)	600 units	60 units	No

Humulin R U-500 in the vial formulation has been available since the 1950s. The U-500 regular insulin is 5 times more concentrated than insulin U-100. To avoid the risk of a dose conversion error for patients taking insulin U-500, many health care practices dispensed tuberculin syringes instead of insulin U-100 syringes; patients were at risk for administering the incorrect dosage.¹⁷ As a solution, a dedicated syringe for the administration of Humulin R U-500 insulin was approved by the FDA in July 2016; currently, this is the only device approved for use with a U-500 insulin vial.¹⁸ The U-500 insulin syringe is available by prescription only.

In 2016, Humulin R U-500 KwikPen was approved for patients with diabetes who inject more than 200 units of insulin per day.¹⁹ Each pen holds 1500 units, dials in 5-unit increments, and does not need dose conversions.¹⁹ The U-500 KwikPen comes in a distinctive aqua color and up to 300 units can be injected at a time. Humulin R U-500 has a longer duration of action than regular insulin U-100, and it may be used without basal insulin.¹⁰ Improvements in glycemic control have been observed when patients made the switch from U-100 insulin products to U-500 regular insulin.^{10,19,20} Although the risk for hypoglycemia does not appear to increase after switching from U-100 to U-500 insulin; an increase in mild hypoglycemic events as well as an increase in weight gain and total daily insulin dose have been reported.²⁰ An algorithm for switching patients from insulin U-100 to Humulin R U-500 has been proposed in literature; however, definitive dosing adjustment guidelines for this do not currently exist.²⁰

Insulin lispro U-200 (Humalog) was approved in 2015 and is 2 times more concentrated than insulin U-100. It is the only concentrated bolus insulin available. It is considered to be bioequivalent to lispro U-100 and provides similar rates of glycemic control and hypoglycemia.¹⁷ Dose conversion is not needed when switching between the formulations.¹² Insulin lispro U-200 contains more units of insulin per pen (Table 2¹¹⁻¹⁶) and is a good option for patients who require high mealtime doses of insulin or use a large number of bolus insulin pens each month.

Two concentrated basal insulin formulations also approved in 2015 include insulin glargine U-300 (Toujeo) and insulin degludec U-200 (Tresiba). Insulin glargine U-300 is 3 times more concentrated than U-100 insulin, while insulin degludec U-200 is 2 times more concentrated than insulin U-100. When making the switch from once-daily Lantus to Toujeo, the same starting insulin dose can be used.^{14,16} However, patients controlled on Lantus may need a higher daily dose of Toujeo to maintain the same level of glycemic control.¹⁴ Therefore, frequent blood sugar monitoring should be encouraged to make appropriate insulin adjustments. When switching from long-acting or intermediate-acting insulins, the same total daily dose of insulin degludec can be used.¹¹ Compared with Lantus, Toujeo and Tresiba provide similar glycemic control to Lantus and they have a duration of more than 24 hours.^{17,21-24} Both products also have a lower risk of nocturnal hypoglycemia than does Lantus with Toujeo providing less overall hypoglycemia and less weight gain than Lantus.²²⁻²⁴ Toujeo is available in a 1.5-mL pen, which contains 450 units of insulin.¹⁴ Both Tresiba U-100 and U-200 are available in 3-mL pen formulations.¹¹ Although Tresiba U-100 contains 300 units of insulin and can deliver up to 80 units of insulin per dose, Tresiba U-200 contains 600 units and can deliver up to 160 units of insulin per dose (Table 2¹¹⁻¹⁵).¹¹ Therefore, Tresiba U-200 is a good option for patients who are injecting large doses of insulin.

Ryzodeg 70/30, a combination of insulin degludec and insulin aspart in a 3-mL pre-filled pen, was approved around the same time as insulin degludec U-100 and U-200 in 2015. If patients administer Ryzodeg 70/30 on a once-daily schedule, then the dose should be taken with the main meal. If patients administer Ryzodeg 70/30 on a twice-daily schedule, then the doses should be taken with the 2 largest meals.²⁵ Because insulin adjustment is more difficult with insulin mixes, Ryzodeg 70/30 may have a limited role in clinical practice.

In 2015, the FDA approved Basaglar, a new brand of long-acting insulin glargine. Basaglar cannot be automatically substituted for Lantus, and a new prescription should be obtained prior to making the switch. Compared with Lantus in patients with T2D, Basaglar was comparable in glycemic control and rate of adverse reactions.^{17,26} When making the switch from Lantus to Basaglar, the insulin dose can remain the same.²⁶ Although Basaglar may not offer much clinical advantage over Lantus for patients with T2D, it may be a cheaper treatment option.

GLP-1 RECEPTOR AGONISTS

Lixisenatide (Adlyxin), a new GLP-1 RA, was approved in 2016. However, its use as a monotherapy may be limited, as there are already many medications in its class on the market. Lixisenatide may prove to be more useful when used in combination with another GLP-1 RA (see Soliqua, discussed below) in patients who are not controlled on basal insulin alone. As a monotherapy, lixisenatide is available in two 3-mL pre-filled pens: a 50 mcg/mL green pen (with 14 pre-set doses, 10 mcg per dose) and a 100 mcg/mL burgundy pen (with 14 pre-set doses, 20 mcg per dose).²⁷ The starter pack contains an initiation pen and a maintenance pen, as lixisenatide should be initiated with 10 mcg administered as a subcutaneous injection once daily for 14 days, after which the dose should be increased to 20 mcg once daily.²⁷

INSULIN/GLP-1 RECEPTOR AGONIST COMBINATION PRODUCTS

Combination products are beneficial for patients because they reduce the number of doses required for diabetes management. Combination products of basal insulin and GLP-1 receptor

agonists were approved by the FDA in 2016.

IGlarLixi (Soliqua 100/33) contains 100 units of insulin glargine and 33 mcg of lixisenatide per milliliter.⁵ Soliqua 100/33 pen delivers doses from 15 to 60 units with each injection.⁵ Alternative therapy should be considered for patients who require a Soliqua 100/33 daily dose below 15 units or over 60 units.⁵

IDegLira (Xultophy 100/3.6) contains 100 units of insulin degludec and 3.6 mg of liraglutide per milliliter.⁷ Xultophy 100/3.6 pen delivers doses from 10 to 50 units with each injection.⁷ Alternative therapy should be considered for patients who require a Xultophy 100/3.6 daily dose below 16 or over 50 units.⁷ The dosing and timing of administration for Soliqua and Xultophy are listed in Table 3.^{5,7}

TABLE 3. BASAL INSULIN/GLP-1 COMBINATION MEDICATIONS FOR T2D ⁷		
	LixiLan (Soliqua 100/33)	iDegLira (Xultophy 100/3.6)
Medications contained	Per 1 milliliter: 100 units insulin glargine 33 mcg lixisenatide	Per 1 milliliter: 100 units insulin degludec 3.6-mg liraglutide
How supplied	3-mL pre-filled pen 5 pens per package	3-mL pre-filled pen 5 pens per package
Dose	Patients on <30 units basal insulin or lixisenatide: 15 units daily Patients on 30-60 units of basal insulin: 30 units daily Administer within 1 hour prior to the first meal of the day	16 units daily Administer with or without food
Maximum dose	60 units	50 units

TD2 indicates type 2 diabetes.

Basal insulin plus GLP-1 RAs are associated with less hypoglycemia and with weight loss as opposed to weight gain; however, they may be costly as they are not available in generic formulation.²⁸ These medications were also found to be more likely to achieve glycemic control when used in combination versus alone.^{29,30} Some studies have even shown that these combination products have fewer gastrointestinal adverse effects than using GLP-1 RAs alone.^{17,30} Xultophy 100/3.6 carries a black box warning of risk of thyroid C-cell tumors in rats and mice.⁷ Soliqua and Adlyxin do not have this warning.

INHALED INSULIN

In 2014, the FDA approved Afrezza, a rapid-acting inhaled insulin administered prior to meals. Compared with insulin aspart, Afrezza has a lower risk of postprandial hypoglycemia and weight gain.¹⁷ Common adverse effects include cough and throat pain or irritation.³¹ It has a black box warning that the risk for acute bronchospasm has been observed in patients with asthma or chronic obstructive pulmonary disease (COPD). Therefore, Afrezza should not be used in patients with chronic lung disease, such as asthma or COPD.³¹ Before initiating Afrezza, providers should perform a detailed exam (including pulmonary function test) to rule out any potential lung disease.³¹ Afrezza should not be recommended to patients who smoke or have recently quit smoking (<6 months).³¹ Furthermore, because long-term pulmonary safety data are lacking, many clinicians may be apprehensive to recommend this insulin to patients.¹⁷ Afrezza

offers a unique route of administration and may be a good option for patients who do not like to inject insulin. It is supplied in color-coded single-use cartridges of 4, 8, or 12 units; they should be refrigerated if not in use.³¹ In 2007, Exubera, a rapid-acting inhaled insulin, experienced low sales and was removed from the market after just 1 year. Whether Afrezza will have the same fate remains to be seen.

CONCLUSION

As diabetes prevalence increases, more novel and combination products for diabetes management will become available. Providers should counsel patients on lifestyle changes and deliver patient-centered medication therapy for diabetes management. When choosing the most optimal diabetes therapy, the dosage form, risk of hypoglycemia, cost, and potential adverse events should be taken into consideration for each patient.

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