HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RYZODEG 70/30 safely and effectively. See full prescribing information for RYZODEG 70/30.

RYZODEG® 70/30 (insulin degludec and insulin aspart injection), for subcutaneous use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
RYZODEG 70/30 is an insulin analog indicated to improve glycemic control in adults with diabetes mellitus (1).

Limitations of Use:
Not recommended for treating diabetic ketoacidosis.

----------DOSAGE AND ADMINISTRATION----------
- DO NOT dilute or mix RYZODEG 70/30 with any other insulin products or solutions (2.1).
- Rotate injection sites to reduce the risk of lipodystrophy (2.1).
- Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goal. (2.2, 2.3, 2.4, 2.5).
- Administer subcutaneously once or twice daily with any main meal (s) (2.2).
- Administer a rapid- or short-acting insulin at other meals if needed (2.2).
- Patients with type 1 diabetes will generally require a rapid-or short-acting insulin at meals when RYZODEG 70/30 is not administered (2.2).
- Adjust the dose according to fasting blood glucose measurements (2.2).
- The recommended time between dose increases is 3 to 4 days (2.2)
- Converting from other insulin therapies may require adjustment of timing and dose of RYZODEG 70/30 (2.4, 2.5).

----------DOSAGE FORMS AND STRENGTHS----------
RYZODEG 70/30 100 units/mL (U-100) available in:
- 3 mL FlexTouch® (3).

----------CONTRAINDICATIONS----------
- During episodes of hypoglycemia (4).
- Hypersensitivity to RYZODEG 70/30 or one of its excipients (4).

----------WARNINGS AND PRECAUTIONS----------
- *Never share* a RYZODEG 70/30 FlexTouch pen between patients, even if the needle is changed (5.1).
- *Hyper- or hypoglyemia with changes in insulin regimen:* Carry out under close medical supervision and increase frequency of blood glucose monitoring (5.2).
- *Hypoglycemia:* May be life-threatening. Increase monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness (5.3,5.4, 6.1).
- *Hypoglycemia due to medication errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. DO NOT transfer RYZODEG 70/30 into a syringe for administration as overdosage and severe hypoglycemia can result (5.4).
- *Hypersensitivity reactions*: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue RYZODEG 70/30, monitor and treat if indicated (5.5).
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated (5.6).
- *Fluid retention and heart failure with concomitant use of Thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs (5.7).

----------ADVERSE REACTIONS----------
Adverse reactions commonly associated with RYZODEG 70/30 are:
- hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at (1-800-727-6500) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- *Drugs that affect glucose metabolism:* Adjustment of insulin dosage may be needed; closely monitor blood glucose (7).
- *Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Signs and symptoms of hypoglycemia may be reduced or absent (7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: XX/201X

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RYZODEG 70/30 is indicated to improve glycemic control in adults with diabetes mellitus.

Limitations of Use

RYZODEG 70/30 is not recommended for the treatment of diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check insulin label before administration *[see Warnings and Precautions (5.4)]*.
- Inspect visually for particulate matter and discoloration. Only use RYZODEG 70/30 if the solution appears clear and colorless.
- Train patients on proper use and injection technique before initiating RYZODEG 70/30. Training reduces the risk of administration errors such as needle sticks and incomplete dosing.
- Inject RYZODEG 70/30 subcutaneously into the thigh, upper arm, or abdomen.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions (6.1)]*.
- DO NOT administer RYZODEG 70/30 intravenously, intramuscularly, or in an insulin infusion pump.
- DO NOT dilute or mix RYZODEG 70/30 with any other insulin products or solutions.

2.2 General Dosing Instructions

- Inject RYZODEG 70/30 subcutaneously once or twice daily with any main meal.
- Administer a rapid- or a short-acting insulin at other meals if needed.
- Patients with type 1 diabetes will generally require a rapid- or short-acting insulin at meals when RYZODEG 70/30 is not administered for optimal glucose control.
- Individualize and titrate the dose of RYZODEG 70/30 based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal *[see Warnings and Precautions (5.2)]*.
- Adjust the RYZODEG 70/30 dose according to blood glucose measurements before breakfast (fasting).
- The recommended time between dose increases is 3 to 4 days.
- Dose adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia *[see Warnings and Precautions (5.3)]*.
- If a dose of RYZODEG 70/30 is missed, the next dose should be taken with the next main meal of that day and thereafter resume the usual dosing schedule. Patients should not take an extra dose to make up for a missed dose.

2.3 Starting Dose in Insulin-Naïve Patients

Type 1 Diabetes Mellitus

The recommended starting dose of RYZODEG 70/30 in insulin-naïve patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be administered as a short- or rapid-acting insulin divided between each daily meal. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin-naïve patients with type 1 diabetes.

Type 2 Diabetes Mellitus

The recommended starting dose of RYZODEG 70/30 in insulin-naïve patients with type 2 diabetes mellitus is 10 units once daily.

2.4 Starting Dose in Patients with Type 1 or Type 2 Diabetes on a Once or Twice Daily Premix or Self-mix Insulin Alone or as Part of a Regimen of Multiple Daily Injections

- Start RYZODEG 70/30 at the same unit dose and injection schedule as the premix or self-mix insulin. In patients also using short- or rapid-acting insulin at mealtimes continue the short- or rapid-acting insulin at the same dose for meals NOT covered by RYZODEG 70/30.

2.5 Starting Dose in Patients with Type 1 or Type 2 Diabetes on a Once or Twice Daily Basal Insulin Alone or as Part of a Regimen of Multiple Daily Injections

- In patients with type 2 diabetes switching from a regimen that includes only a once- or twice-daily basal insulin, start RYZODEG 70/30 at the same unit dose and injection schedule. For patients switching from once-daily basal insulin to once-daily RYZODEG 70/30, monitor blood glucose after starting therapy due to the rapid-acting insulin component *[see Warnings and Precautions (5.2)]*.

- In patients switching from a multiple daily injections regimen that includes a basal and short- or rapid-acting insulin at mealtimes, start RYZODEG 70/30 once daily with the main meal at the same unit dose as the basal insulin. Continue the short- or rapid-acting insulin at the same dose for meals NOT covered by RYZODEG 70/30.

3 DOSAGE FORMS AND STRENGTHS

RYZODEG 70/30 is available as a clear and colorless solution for injection in:

- 100 units/mL (U-100): 3 mL FlexTouch disposable prefilled pen

4 CONTRAINDICATIONS

RYZODEG 70/30 is contraindicated:

- During episodes of hypoglycemia *[see Warnings and Precautions (5.3)]*.
- In patients with hypersensitivity to RYZODEG 70/30 or one of its excipients *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a RYZODEG 70/30 FlexTouch Pen Between Patients

RYZODEG 70/30 FlexTouch disposable prefilled pen should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, adjustments in concomitant oral anti-diabetic treatment may be needed. When converting from other insulin therapies to RYZODEG 70/30 follow dosing recommendations *[see Dosage and Administration (2.4, 2.5)]*.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of insulin, including RYZODEG 70/30 *[see Adverse Reactions (6.1)]*. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). RYZODEG 70/30, or any insulin, should not be used during episodes of hypoglycemia *[see Contraindications (4)]*.

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) *[see Drug Interactions (7)]*, or in patients who experience recurrent hypoglycemia.

<u>Risk Factors for Hypoglycemia</u>

The risk of hypoglycemia generally increases with intensity of glycemic control. The risk of hypoglycemia after an injection is related to the duration of action of the insulin *[see Clinical Pharmacology (12.2)]* and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of RYZODEG 70/30 may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature.

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication *[see Drug Interactions (7)]*. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations (8.6, 8.7)]*.

<u>Risk Mitigation Strategies for Hypoglycemia</u>

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced

symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between insulin products have been reported. To avoid medication errors between RYZODEG 70/30 and other insulins, instruct patients to always check the insulin label before each injection.

Do not transfer RYZODEG 70/30 from the RYZODEG 70/30 pen to a syringe. The markings on the insulin syringe will not measure the dose correctly and can result in overdosage and severe hypoglycemia *[see Dosage and Administration (2.1) and Warnings and Precautions (5.3)]*.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including RYZODEG 70/30. If hypersensitivity reactions occur, discontinue RYZODEG 70/30; treat per standard of care and monitor until symptoms and signs resolve. RYZODEG 70/30 is contraindicated in patients who have had hypersensitivity reactions to insulin degludec, insulin aspart, or one of the excipients *[see Contraindications (4)]*.

5.6 Hypokalemia

All insulin products, including RYZODEG 70/30, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to potassium concentrations).

5.7 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR Gamma Agonist

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists can cause dose related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with insulin, including RYZODEG 70/30 and a PPAR-gamma agonist should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6 ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Hypersensitivity and allergic reactions *[see Warnings and Precautions (5.5)]*
- Hypokalemia *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of RYZODEG 70/30 in subjects with type 1 diabetes or type 2 diabetes was evaluated in five treat-to-target trials of 6-12 month duration *[see Clinical Studies (14)]*.

The data in Table 1 reflect the exposure of 362 patients with type 1 diabetes to RYZODEG 70/30, with a mean exposure duration to RYZODEG 70/30 of 43 weeks. The mean age was 41 years and 1% were older than 75 years. Fifty-two percent were male, 91% were White, 3% were Black or African American and 3% were Hispanic. The mean body mass index (BMI) was 26 kg/m^2. The mean duration of diabetes was 17 years and the mean HbA_{1c} at baseline was 8.3%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 19%, 25%, 6% and 4% respectively. The mean eGFR at baseline was 88 mL/min/1.73 m^2 and 6% of patients had an eGFR less than 60 mL/min/1.73 m^2.

The data in Table 2 reflect the exposure of 998 patients with type 2 diabetes to RYZODEG 70/30 with a mean exposure duration to RYZODEG 70/30 of 24 weeks. The mean age was 58 years and 3% were older than 75 years. Fifty-four percent were male, 44% were White, 4% were Black or African American and 6% were Hispanic. The mean BMI was 29 kg/m^2. The mean duration of diabetes was 12 years and the mean HbA_{1c} at baseline was 8.5%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported for 15%, 21%, 10% and 1% respectively. At baseline, the mean eGFR was 84 mL/min/1.73 m^2 and 11% of patients had an eGFR less than 60 mL/min/1.73 m^2.

Common adverse reactions (excluding hypoglycemia) occurring in RYZODEG 70/30-treated subjects during clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Table 1 and Table 2, respectively. Common adverse reactions were defined as reactions occurring in ≥5% of the population studied. Hypoglycemia is not shown in these tables but discussed in a dedicated subsection below.

Table 1: Adverse Reactions Occurring in ≥5% of RYZODEG 70/30-Treated Patients with Type 1 Diabetes Mellitus

Adverse Reaction	**RYZODEG 70/30 (N=362)**
Nasopharyngitis	24.6%
Headache	9.7%
Upper respiratory tract infection	9.1%
Influenza	6.9%

Table 2: Adverse Reactions Occurring in ≥5% of RYZODEG 70/30-Treated Patients with Type 2 Diabetes Mellitus

Adverse Reaction	**RYZODEG 70/30 (N=998)**
Nasopharyngitis	11.1%
Upper respiratory tract infection	5.7%
Headache	5.6%

Hypoglycemia
Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including RYZODEG 70/30 *[see Warnings and Precautions (5.3)]*. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for RYZODEG 70/30 with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that occur in clinical practice.

Rates of hypoglycemia by trial are shown in Table 3 for type 1 diabetes and Table 4 for type 2 diabetes for patients treated with RYZODEG 70/30 *[see Clinical Studies (14)]*. Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. A Novo Nordisk hypoglycemia episode was defined as a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Table 3: Percent (%) of Patients with Type 1 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia[§] on RYZODEG 70/30 in Adult Clinical Trials

	Study A **RYZODEG 70/30 OD* +** **INSULIN ASPART BID**,** **52 weeks** **(N= 362)**
Severe hypoglycemia	
Percent of patients	13.3%
Novo Nordisk hypoglycemia[§]	
Percent of patients	95.0%

*OD: once daily
**BID: twice daily
[§]Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Table 4: Percent (%) of Patients with Type 2 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia[§] on RYZODEG 70/30 in Adult Clinical Trials

	Study B **RYZODEG 70/30 OD*** **insulin naïve, previously on 2 or more OADs*****	**Study C** **RYZODEG 70/30 OD*** **previously on basal insulin OD and 1 or more OADs*****	**Study D** **RYZODEG 70/30 BID**** **previously on OD*/BID premix/self-mix, ±OADs*****	**Study E** **RYZODEG 70/30 BID**** **previously on OD*/BID basal/premix/self-mix, ±OADs*****

	(N=265)	(N=230)	(N=224)	(N=279)
Severe hypoglycemia				
Percent of patients	0.4%	0%	3.1%	1.4%
Novo Nordisk hypoglycemia				
Percent of patients	49.8%	52.6%	66.1%	73.5%

*OD: once daily
**BID: twice daily
***OAD: oral anti-diabetic agent
[§]Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including RYZODEG 70/30 and may be life threatening *[see Warnings and Precautions (5.5)]*. Hypersensitivity (manifested with swelling of tongue and lips, diarrhea, nausea, tiredness and itching) and urticaria were reported in 0.5% of patients treated with RYZODEG 70/30.

Lipodystrophy

Long-term use of insulin, including RYZODEG 70/30, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy *[see Dosage and Administration (2.1)]*. In the clinical program, lipodystrophy was reported in 0.1% of patients treated with RYZODEG 70/30.

Injection Site Reactions

Patients taking RYZODEG 70/30 may experience injection site reactions, including injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection site mass. In the clinical program, injection site reactions occurred in 2.0% of patients treated with RYZODEG 70/30.

Weight Gain

Weight gain can occur with insulin therapy, including RYZODEG 70/30, and has been attributed to the anabolic effects of insulin. In the clinical program, patients with type 1 diabetes treated with RYZODEG 70/30 gained an average of 2.8 kg and patients with type 2 diabetes treated with RYZODEG 70/30 gained an average of 1.6 kg.

Peripheral Edema

Insulin, including RYZODEG 70/30, may cause sodium retention and edema. In the clinical program, peripheral edema occurred in 2.2% of patients with type 1 diabetes mellitus and 1.8% of patients with type 2 diabetes mellitus treated with RYZODEG 70/30.

6.2 Immunogenicity

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to RYZODEG 70/30 with the incidence of antibodies in other studies or to other products, may be misleading.

In studies of type 1 diabetes patients, 95.9% of patients who received RYZODEG 70/30 once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 89% that were positive at baseline, while 13% of these patients were positive for anti-IAsp antibodies at least once during the studies, including 6.4% who were positive at baseline. In studies of type 2 diabetes patients, 67.5% of patients who received RYZODEG 70/30 once daily were positive for AIA at least once during the studies, including 45.4% that were positive at baseline, while 17.1% of these patients were positive for anti-IAsp antibodies at least once during the studies, including 12.3% who were positive at baseline. The antibody incidence rates for type 2 diabetes may be underreported due to potential assay interference by endogenous insulin in samples in these patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper- or hypoglycemia.

The incidence of anti-insulin degludec antibodies has not been established.

7 DRUG INTERACTIONS

Table 5 includes clinically significant drug interactions with RYZODEG 70/30.

Table 5: Clinically Significant Drug Interactions with RYZODEG 70/30

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors.
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of RYZODEG 70/30	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in

	oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of RYZODEG 70/30	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine.
Intervention:	Increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate well-controlled clinical studies of the use of insulin degludec/insulin aspart in pregnant women. Patients should be advised to discuss with their health care provider if they intend to or if they become pregnant. Because animal reproduction studies are not always predictive of human response, insulin degludec/insulin aspart should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

An open-label, randomized study compared the safety and efficacy of NOVOLOG (insulin aspart, the rapid-acting component of RYZODEG 70/30) versus human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies (insulin aspart: 157, human insulin: 165). Two-thirds of the enrolled patients were already pregnant when they entered the study. Since only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Mean HbA_{1c} of ~ 6% was observed in both groups during pregnancy, and there was no significant difference in the incidence of maternal hypoglycemia.

Subcutaneous reproduction and teratology studies have been performed with insulin degludec/insulin aspart, and human insulin (NPH) as a comparator in rats. In these studies, insulin degludec/insulin aspart was given to rats during organogenesis. The effect of insulin degludec/insulin aspart was consistent with those observed with human insulin as both caused

visceral/skeletal abnormalities in rats at dose of 30 U/kg/day (approximately 8 times the human subcutaneous dose of 1.08 U/kg/day based on U/body surface area).

Subcutaneous reproduction and teratology studies have been performed with insulin degludec (basal component of insulin degludec/insulin aspart) and human insulin (NPH) as a comparator in rats and rabbits. In these studies, insulin was given to female rats before mating throughout pregnancy until weaning, and to rabbits during organogenesis. The effect of insulin degludec was consistent with those observed with human insulin, as both caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at an insulin degludec dose of 21 U/kg/day (approximately 5 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day) and in rabbits at a dose of 3.3 U/kg/day (approximately 10 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day). The effects are probably secondary to maternal hypoglycemia.

Subcutaneous reproduction and teratology studies have been performed with NOVOLOG (insulin aspart, the rapid-acting component of RYZODEG 70/30) and regular human insulin in rats and rabbits. In these studies, insulin aspart was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of insulin aspart did not differ from those observed with subcutaneous regular human insulin. Insulin aspart, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and in rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits, based on U/body surface area.

8.3 Nursing Mothers

It is unknown whether insulin degludec/aspart is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when insulin degludec/insulin aspart is administered to a nursing mother. Women with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

In rats, the basal component of insulin degludec/insulin aspart, insulin degludec, was secreted in milk and the concentration in milk was lower than in plasma.

8.4 Pediatric Use

The safety and efficacy of RYZODEG 70/30 in children and adolescents under the age of 18 years have not been established.

8.5 Geriatric Use

In clinical studies *[see Clinical Studies (14)]* a total of 9 (2.5%) of the 362 RYZODEG 70/30-treated patients with type 1 diabetes were 65 years or older and 4 (1.1%) were 75 years and older. A total of 256 (25.7%) of the 998 RYZODEG 70/30-treated patients with type 2 diabetes

were 65 years or older and 32 (3.2%) were 75 years and older. Differences in safety or effectiveness were not suggested in subgroup analyses comparing subjects older than 65 years to younger subjects.

Nevertheless, greater caution should be exercised when RYZODEG 70/30 is administered to geriatric patients since greater sensitivity of some older individuals to the effects of RYZODEG 70/30 cannot be ruled out. The initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be more difficult to recognize in the elderly.

8.6 Renal Impairment

In clinical studies *[see Clinical Studies (14)]* a total of 18 (5%) of the 362 RYZODEG 70/30-treated patients with type 1 diabetes had an eGFR less than 60 mL/min/1.73 m^2 or less and 1 (0.3%) had an eGFR less than 30 mL/min/1.73 m^2 or less. A total of 111 (11%) of the 998 RYZODEG 70/30-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73 m^2 and no subjects had an eGFR less than 30 mL/min/1.73 m^2.

No differences in the pharmacokinetics of the individual components of RYZODEG 70/30, insulin degludec or insulin aspart, were identified in separate studies comparing healthy subjects and subjects with renal impairment *[see Clinical Pharmacology (12.3)]*. However, as with all insulin products, glucose monitoring should be intensified and the RYZODEG 70/30 dosage adjusted on an individual basis in patients with renal impairment.

8.7 Hepatic Impairment

No differences in the pharmacokinetics of the individual components of RYZODEG 70/30, insulin degludec or insulin aspart, were identified in separate studies comparing healthy subjects and subjects with hepatic impairment (mild, moderate, and severe hepatic impairment) *[see Clinical Pharmacology (12.3)]*. However, as with all insulin products, glucose monitoring should be intensified and the RYZODEG 70/30 dosage adjusted on an individual basis in patients with hepatic impairment.

10 OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.6)]*. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

11 DESCRIPTION

RYZODEG 70/30 (insulin degludec and insulin aspart injection) is a human insulin analog solution containing 70% insulin degludec and 30% insulin aspart for subcutaneous injection. It consists of insulin degludec, a long-acting insulin, and insulin aspart, a rapid-acting insulin both

of which function as parenteral blood-glucose-lowering agents *[see Clinical Pharmacology (12)]*.

Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin) and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin degludec has a molecular formula of $C_{274}H_{411}N_{65}O_{81}S_6$ and a molecular weight of 6103.97.

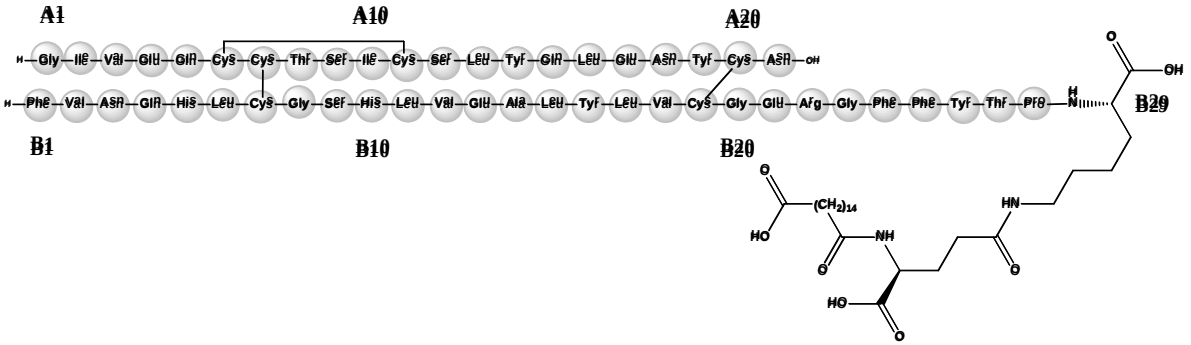

Figure 1: Structural formula of insulin degludec

Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin aspart has a molecular formula of $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

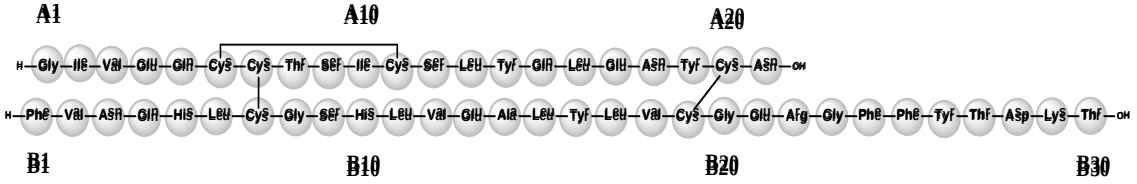

Figure 2: Structural formula of insulin aspart

RYZODEG 70/30 is a sterile, aqueous, clear, and colorless solution and contains a total of 100 Units of insulin degludec and insulin aspart mixture per mL, glycerol 19 mg/mL, metacresol 1.72 mg/mL, phenol 1.50 mg/mL, sodium chloride 0.58 mg/mL, zinc 27.4 mcg/mL and water for injection. RYZODEG 70/30 has a pH of approximately 7.4. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of insulin, including RYZODEG 70/30, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis. The insulin

degludec component in RYZODEG 70/30 forms multi-hexamers when injected into the subcutaneous tissue resulting in a subcutanous insulin degludec depot. The protracted time action profile of RYZODEG 70/30 is predominantly due to delayed absorption of insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin. Insulin aspart monomers are released rapidly into the circulation.

12.2 Pharmacodynamics

The pharmacodynamic profile of RYZODEG 70/30 reflects the action profiles of rapid-acting insulin aspart and long-acting insulin degludec.

The pharmacodynamic profile for RYZODEG 70/30 given as single dose subcutaneous injections of 0.8 U/kg dose in a euglycemic clamp study in patients with type 1 diabetes, is shown in Figure 3. The mean maximum glucose lowering effect (GIR_{max}) of a 0.8 U/kg dose of RYZODEG 70/30 was 6.9 mg/kg/min, which was observed at a median of 2.3 hours post-dose.
In patients with type 1 diabetes mellitus and type 2 diabetes mellitus, RYZODEG 70/30 has an onset of action that rapidly follows injection. Basal insulin degludec in RYZODEG 70/30 provides a glucose lowering effect over 24 hours upon once-daily administration. The duration of action of a single-dose of RYZODEG 70/30 may extend beyond 24 hours (Figure 3) due to the presence of the basal component, insulin degludec.

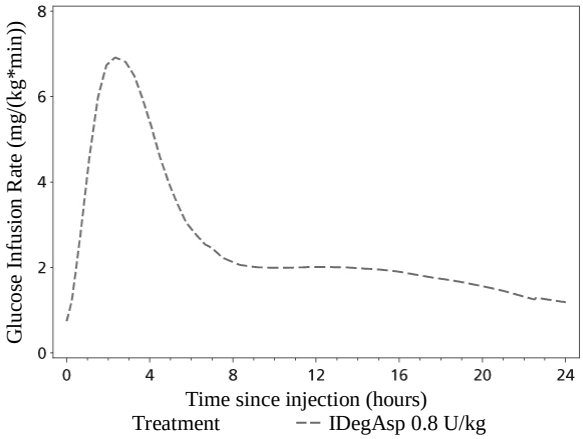

Figure 3: GIR profile of RYZODEG 70/30 after single 0.8 U/kg dose administration in patients with type 1 diabetes mellitus

The total and maximum glucose-lowering effect of RYZODEG 70/30 increases linearly with increasing doses from 0.4 U/kg to 0.8 U/kg in patients with type 1 diabetes mellitus and type 2 diabetes mellitus. Steady-state background glucose-lowering, attributable to the long-acting, insulin degludec component, will occur after 3 to 4 days of dose administration. However, the magnitude of the glucose-lowering effect at steady-state is reduced in type 2 diabetic subjects in comparison to type 1 diabetic subjects given the same unit/kg RYZODEG 70/30 dose.

12.3 Pharmacokinetics

Absorption

The concentration-time profile following a single subcutaneous dose of 0.4, 0.6, and 0.8 U/kg RYZODEG 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus showed increased exposure with increasing dose for both components of RYZODEG 70/30 (insulin degludec and insulin aspart).

Insulin aspart showed dose proportional increase in maximum concentration (C_{max}) and slightly more than dose proportional increase in overall exposure $AUC_{0\text{-}12h}$ following single subcutaneous administration of RYZODEG 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus.

Insulin degludec showed dose proportional increase in C_{max} and $AUC_{0\text{-}120h}$ following single subcutaneous administration of RYZODEG 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus.

The median onset of appearance for the insulin aspart component was 14 minutes after injection with a peak concentration after 72 minutes. Steady state serum concentrations of the insulin degludec component of RYZODEG 70/30 were reached after 3 to 4 days of dose administrations *[see Dosage and Administration (2.2)]*.

Distribution
The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. Insulin aspart has low binding to plasma proteins, <10%, similar to regular human insulin.

Elimination
The half-life after subcutaneous administration is determined primarily by the rate of absorption from the subcutaneous tissue. The half-life of the basal component (insulin degludec) at steady state is approximately 25 hours independent of dose. Degradation of insulin degludec is similar to that of human insulin. All metabolites formed are inactive.

Specific Populations
As with other insulin preparations, RYZODEG 70/30 should always be titrated according to individual requirements.

Geriatrics-
Pharmacokinetic and pharmacodynamic responses of RYZODEG 70/30 were investigated in 13 younger adult (18−35 years) and 15 geriatric (≥65 years) subjects with T1DM following two single s.c. dose administrations of 0.5 U/kg: one of RYZODEG 70/30 and one of NOVOLOG MIX 70/30. The total exposure of insulin aspart in RYZODEG 70/30 (based on $AUC_{IAsp,0\text{-}12h,SD}$) tended to be higher in geriatric subjects than in younger adult subjects. The total exposure of insulin degludec in RYZODEG 70/30 (based on $AUC_{IDeg,0\text{-}120h,SD}$) and the pharmacodynamic response to RYZODEG 70/30 (based on $AUC_{GIR,0\text{-}24h}$) was similar in younger adult and geriatric subjects with T1DM, albeit higher between subject variability among the geriatric subjects.

Gender-

The effect of gender on the pharmacokinetics of the separate components of RYZODEG 70/30, insulin degludec and insulin aspart, was examined in across trial analyses of the pharmacokinetic and pharmacodynamic studies. Overall, there were no clinically relevant differences in the pharmacokinetic properties of insulin degludec or insulin aspart between female and male subjects.

Obesity-
The effect of BMI on the pharmacokinetics of the separate components of RYZODEG 70/30, insulin degludec and insulin aspart, was explored in cross-trial analyses of the pharmacokinetic and pharmacodynamic studies. For subjects with type 1 diabetes, there was no relationship between exposure of insulin degludec and BMI. For subjects with type 1 and type 2 diabetes, a trend for decrease in glucose-lowering effect of insulin degludec with increasing BMI was observed. For insulin aspart, there was no relationship between BMI and exposure in subjects with T1DM or T2DM.

Race and Ethnicity-
The effect of race and ethnic origin on the pharmacokinetics of RYZODEG 70/30 has not been studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a pharmacokinetic and pharmacodynamic study in Black or African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus. There were no statistically significant differences between the racial and ethnic groups investigated.

Pregnancy-
The effect of pregnancy on the pharmacokinetics and pharmacodynamics of RYZODEG 70/30 has not been studied *[see Use in Specific Populations (8.1)]*.

Renal Impairment-
The effect of renal impairment on the pharmacokinetics of RYZODEG 70/30 has not been studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a pharmacokinetic study in 32 subjects (n=4-8/group) with normal or impaired renal function/end-stage renal disease following administration of a single subcutaneous dose (0.4 U/kg) of insulin degludec. Renal function was defined using creatinine clearance (Cl_{cr}) as follows: ≥90 mL/min (normal), 60-89 mL/min (mild), 30-59 mL/min (moderate) and <30 mL/min (severe). Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total ($AUC_{IDeg,0-120h,SD}$) and peak exposure of insulin degludec were on average about 10-25% and 13-27% higher, respectively, in subjects with mild to severe renal impairment, except subjects with ESRD, who showed similar exposure as compared to subjects with normal renal function. No systematic trend was noted for this increase in exposure across different renal impairment subgroups. Hemodialysis did not affect clearance of insulin degludec ($CL/F_{IDeg,SD}$) in subjects with ESRD.

A single subcutaneous dose of 0.08 U/kg NOVOLOG (insulin aspart, the rapid-acting component of RYZODEG 70/30) was administered in a study to subjects with either normal, mild, moderate or severe (but not requiring hemodialysis) renal impairment. In this study, there was no apparent effect of creatinine clearance values on AUC and C_{max} of insulin aspart.

Hepatic Impairment-
The effect of hepatic impairment on the pharmacokinetics of RYZODEG 70/30 has not been studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a pharmacokinetic study in 24 subjects (n=6/group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a single subcutaneous dose (0.4 U/kg) of insulin degludec. No differences in the pharmacokinetics of insulin degludec were identified between healthy subjects and subjects with hepatic impairment *[see Use in Specific Populations (8.7)]*.

A single subcutaneous dose of 0.06 U/kg insulin aspart, the rapid-acting component of RYZODEG 70/30, was administered in an open-label, single-dose study of 24 subjects (n=6/group) with different degrees of hepatic impairment (mild, moderate, and severe). In this study, there was no correlation between the degree of hepatic failure and any insulin aspart pharmacokinetic parameter.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of insulin degludec/insulin aspart (RYZODEG 70/30).

In a 52-week study including human insulin (NPH insulin) as comparator, Sprague-Dawley rats were dosed subcutaneously with insulin degludec, the basal component of insulin degludec/insulin aspart (RYZODEG 70/30), at 3.3, 6.7, and 10 U/kg/day resulting in 5 times the human exposure (AUC) when compared to a human subcutaneous dose of 1.08 U/kg/day RYZODEG 70/30. Human insulin was dosed at 6.7 U/kg/day. No treatment-related increases in incidences of hyperplasia, benign or malignant tumors were recorded in female mammary glands from rats dosed with insulin degludec and no treatment related changes in the female mammary gland cell proliferation were found using BrdU incorporation. Further, no treatment related changes in the occurrence of hyperplastic or neoplastic lesions were seen in other tissues in animals dosed with insulin degludec when compared to vehicle or human insulin.

In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with insulin aspart, the rapid-acting component of insulin degludec/insulin aspart (RYZODEG 70/30), at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, insulin aspart increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors found with insulin aspart was not significantly different from that found with regular human insulin. The relevance of these findings to humans is not known.

Genotoxicity testing of insulin degludec was not performed. Insulin aspart was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and ex vivo UDS test in rat liver hepatocytes.

In a combined fertility and embryo-fetal study in male and female rats, treatment with insulin degludec up to 21 U/kg/day (approximately 5 times the human subcutaneous dose of 0.75 U/kg/day, based on U/body surface area) prior to mating and in female rats during gestation had no effect on mating performance.

In fertility studies with insulin aspart (NOVOLOG) in male and female rats, at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

14 CLINICAL STUDIES

The efficacy of RYZODEG 70/30 administered once-daily with the main meal of the day in patients with type 1 diabetes and used with a mealtime insulin at remaining meals was evaluated in one randomized, open-label, treat-to-target, active-controlled trial. The efficacy of RYZODEG 70/30 administered once- or twice-daily with the main meal(s) in patients with type 2 diabetes when used with common oral anti-diabetic drugs was evaluated in four randomized, open-label, treat-to-target, active controlled trials.

Patients treated with RYZODEG 70/30 achieved levels of glycemic control similar to those treated with LANTUS (insulin glargine U-100) and LEVEMIR (insulin detemir) and NOVOLOG MIX 70/30 (biphasic insulin aspart 70/30).

14.1 Type 1 Diabetes – Adult

Study A: RYZODEG 70/30 Administered with the Main Meal in Combination with a Rapid-Acting Insulin Analog at Remaining Meals

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 548 patients with type 1 diabetes mellitus inadequately controlled on either a basal-bolus regimen or other insulin regimens at baseline. Patients were randomized to RYZODEG 70/30 once-daily administered at the main meal of the day or insulin detemir once-daily at the evening meal or at bedtime. Insulin aspart was administered for the remaining insulin requiring meals. In patients randomized to insulin detemir, a second dose of insulin detemir could be added at breakfast after 8 weeks if glycemic control was inadequate.

The mean age of the trial population was 41.3 years and mean duration of diabetes was 17.4 years. 49.6% were male. 90.3% were White, 2.9% Black or African American. 3.1% were Hispanic. 4.8 % of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was 26.4 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and insulin detemir was - 0.05% with a 95% confidence interval of [-0.18%, 0.08%] and met the pre-specified non-inferiority margin (0.4%). See Table 6.

Table 6: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Insulin Detemir in Patients with Type 1 Diabetes Mellitus Receiving Insulin Aspart at Mealtimes

	RYZODEG 70/30 +	Insulin detemir* + Insulin

	Insulin aspart	aspart
N	**366**	**182**
HbA_{1c} (%)		
Baseline	8.3	8.3
End of trial	7.6	7.6
Adjusted mean change from baseline ±	-0.75	-0.7
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin detemir	-0.05 [-0.18;0.08]	
Proportion Achieving HbA_{1c} < 7% at Trial End	24.6%	20.3%
FPG (mg/dL)		
Baseline	186	198
End of trial	156	155
Adjusted mean change from baseline	-29.7	-33.8
Total Daily insulin dose**		
Baseline mean	56 U	56 U
Mean dose after 26 weeks	69 U	79 U

*Dosed once-daily or twice daily
**Total daily insulin dose includes basal and bolus insulin doses
±The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study A, there were 12.6% of subjects in RYZODEG 70/30 and 13.7% Insulin detemir arms for whom data was missing at the time of the HbA_{1c} measurement.

14.2 Type 2 Diabetes – Adult

Study B: RYZODEG 70/30 Administered with the Main Meal as an Add-on to Metformin in Insulin Naïve Patients

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 529 insulin-naïve patients with type 2 diabetes mellitus inadequately controlled on oral anti-diabetic drugs at baseline. Patients were randomized to RYZODEG 70/30 once-daily at breakfast or insulin glargine U-100 once-daily according to approved labeling. Metformin (Met) was administered in both arms.

The mean age of the trial population was 56.9 years and mean duration of diabetes was 9.2 years. 49.3% were male. 72.4% were White, 6.4% Black or African American. 21.6% were Hispanic. 4.5% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was 30.7 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and insulin glargine U-100 was 0.03% with a 95% confidence interval of [-0.14%, 0.20%] and met the pre-specified non-inferiority margin (0.4%). See Table 7.

Table 7: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Insulin glargine U-100 in Insulin-Naïve Patients with Type 2 Diabetes Mellitus

	RYZODEG 70/30 + Met	**Insulin glargine U-100 + Met**
N	**266**	**263**
HbA_{1c} (%)		
Baseline	8.9	8.9
End of trial	7.2	7.2
Adjusted mean change from baseline [±]	-1.72	-1.75
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin glargine U-100	0.03 [-0.14;0.20]	
Proportion Achieving HbA_{1c} < 7% at Trial End	45.9%	45.6%
FPG (mg/dL)		
Baseline	183	187
End of trial	123	114
Adjusted mean change from baseline	-63.3	-72.5
Post Prandial Glucose (mg/dL)		
Prandial increment at breakfast, baseline	61	65
Prandial increment at breakfast, end of trial	34	62
Adjusted mean change from baseline	-27.2	-2.0
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin glargine U-100	-25.2 [-34.5; -15.9][1]	

Total Daily insulin dose		
Baseline mean	10 U	10 U
Mean dose after 26 weeks	66 U	59 U

[1]p<0.001, 1-sided p-value evaluated at 2.5% level for superiority
[±]The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study B, there were 17.7% of subjects in RYZODEG 70/30 and 12.9% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Study C: RYZODEG 70/30 Administered with the Main Meal for Patients Inadequately Controlled on Once-Daily Basal Insulin and Oral Agents

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 463 patients with type 2 diabetes mellitus inadequately controlled on basal insulin once-daily and oral antidiabetic drugs at baseline. Patients were randomized to RYZODEG 70/30 once-daily with either the evening meal or the largest meal of the day or insulin glargine U-100 once-daily according to approved labeling. The starting intervention insulin dose in units was determined by using the pre-trial basal insulin unit dose (1 to 1 unit conversion). The same oral anti-diabetic drugs were continued in both treatment arms which may have included any of the following used alone or in combination; Met, pioglitazone (Pio), DPP-4 inhibitors (DPP-4i) throughout the entire trial.

The mean age of the trial population was 58.1 years and mean duration of diabetes was 11.5 years. 56.6% were male. 56.4% were White, 8.0% Black or African American. 4.5% were Hispanic. 8.3% of patients had eGFR<60 mL/min/1.73m^2. The mean BMI was 30.1 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and insulin glargine U-100 was -0.03% with a 95% confidence interval of [-0.20%, 0.14%] and met the pre-specified non-inferiority margin (0.4%). See Table 8.

Table 8: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Insulin glargine U-100 in Patients with Type 2 Diabetes Mellitus

	RYZODEG 70/30 + Met ± Pio ± DPP-4i	**Insulin glargine U-100 + Met ± Pio ± DPP-4i**
N	**230**	**233**
HbA_{1c} (%)		
Baseline	8.3	8.4
End of trial	7.3	7.4
Adjusted mean change from baseline [±]	-1.00	-0.97
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin glargine U-100	-0.03 [-0.20;0.14]	
Proportion Achieving	40.0%	36.5%

HbA_{1c} < 7% at Trial End		
FPG (mg/dL)		
Baseline	144	141
End of trial	114	108
Adjusted mean change from baseline	-28.9	-34.9
Post Prandial Glucose (mg/dL)		
Prandial increment at dinner, baseline	48	55
Prandial increment at dinner, end of trial	22	46
Adjusted mean change from baseline	-32.3	-8.3
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Insulin glargine U-100	-23.9 [-34.7;-13.0][1]	
Total Daily insulin dose		
Baseline mean	28 U	31 U
Mean dose after 26 weeks	60 U	60 U

[1] $p<0.001$, 1-sided p-value evaluated at 2.5% level for superiority
[±] The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study C, there were 14.8 % of subjects in RYZODEG 70/30 and 12% Insulin glargine arms for whom data was missing at the time of the HbA_{1c} measurement.

Type 2 Diabetes – Adult, BID

Study D: RYZODEG 70/30 Administered with the Main Meal for Patients Inadequately Controlled on Once-Daily or Twice-Daily Pre-Mix or Self-mixed Insulin

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 446 patients with type 2 diabetes mellitus inadequately controlled on once- or twice-daily premixed or self-mixed insulin with or without background oral anti-diabetic agents. Patients were randomized to RYZODEG 70/30 or biphasic insulin aspart 70/30, both administered twice-daily before the breakfast and main evening meals. Subjects on premixed insulin twice-daily initiated trial insulin at the same dose as their premixed insulin (1 to 1 unit conversion). Subjects on a self-mixed regimen transfer to trial insulin at doses corresponding to their respective self-mixed pre-meal dose. Subjects previously receiving premixed or self-mixed insulin once-daily were to divide their dose into 2 equal doses. Patients continued on pre-trial oral background therapies which may have included any of the following used alone or in combination; Met, Pio, DPP-4i throughout the entire trial.

The mean age of the trial population was 58.7 years and mean duration of diabetes was 13.0 years. 55.6% were male. 52.5% were White, 0.2% Black or African American. 0.4% were Hispanic. 14.3% of patients had eGFR<60 mL/min/1.73 m^2. The mean BMI was 29.3 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and biphasic insulin aspart 70/30 was -0.03% with a 95% confidence interval of [-0.18%, 0.13%] and met the pre-specified non-inferiority margin (0.4%). See Table 9.

Table 9: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Biphasic Insulin aspart 70/30 in Patients with Type 2 Diabetes Mellitus

	RYZODEG 70/30 ± Met ± Pio ± DPP-4i	**Biphasic insulin aspart 70/30 ± Met ± Pio ± DPP-4i**
N	**224**	**222**
HbA_{1c} (%)		
Baseline	8.3	8.4
End of trial	7.1	7.1
Adjusted mean change from baseline [±]	-1.31	-1.29
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Biphasic insulin aspart 70/30	-0.03 [-0.18;0.13]	
Proportion Achieving HbA_{1c} < 7% at Trial End	50.4%	48.6%
FPG (mg/dL)		
Baseline	160	155
End of trial	104	123
Adjusted mean change from baseline	-50.4	-29.8
Total Daily insulin dose		
Baseline mean	54 U	51 U
Mean dose after 26 weeks	90 U	98 U

[±] The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study D, there were 12.1 % of subjects in RYZODEG 70/30 and 15.3% Biphasic insulin aspart 70/30 arms for whom data was missing at the time of the HbA_{1c} measurement.

Study E: RYZODEG 70/30 Administered with Any Main Meal for Patients Inadequately Controlled on Basal Insulin, Pre-Mix or Self-Mixed Insulin

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 422 patients with type 2 diabetes mellitus inadequately controlled on basal insulin, premixed or self-mixed insulin in a once- or twice-daily insulin with or without background Met. Patients were randomized to RYZODEG 70/30 or biphasic insulin aspart 70/30, both administered twice-daily at the breakfast and main evening meal. Subjects on once-daily insulin split the total dose of their previous insulin treatment into 2 equal doses of trial insulin for twice-daily administration. Subjects on twice-daily insulin transferred their doses on a unit-to-unit basis to the trial insulin. Patients on Met continued Met at their pre-trial dose.

The mean age of the trial population was 59.8 years and mean duration of diabetes was 16.3 years. 54.5% were male. All patients were Asian. 17.2% of patients had eGFR <60 mL/min/1.73 m^2. The mean BMI was approximately 25.4 kg/m^2.

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and biphasic insulin aspart 70/30 was 0.05% with a 95% confidence interval of [-0.10%, 0.20%] and met the pre-specified non-inferiority margin (0.4%). See Table 10.

Table 10: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Biphasic Insulin aspart 70/30 in Asian Patients with Type 2 Diabetes Mellitus

	RYZODEG 70/30 ± Met	**Biphasic insulin aspart 70/30 ± Met**
N	**280**	**142**
HbA_{1c} (%)		
Baseline	8.4	8.4
End of trial	7.1	7.0
Adjusted mean change from baseline ±	-1.39	-1.44
Estimated treatment difference [95%CI] RYZODEG 70/30 v. Biphasic insulin aspart 70/30	0.05 [-0.10;0.20]	
Proportion Achieving HbA_{1c} < 7% at Trial End	48.2%	49.3%
FPG (mg/dL)		
Baseline	143	143
End of trial	97	116
Adjusted mean change from baseline	-45.3	-26.2
Total Daily insulin dose		
Baseline mean	37 U	37 U
Mean dose after 26 weeks	55 U	68 U

± The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
In Study E, there were 12.1 % of subjects in RYZODEG 70/30 and 10.6% Biphasic insulin aspart 70/30 arms for whom data was missing at the time of the HbA_{1c} measurement.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RYZODEG 70/30 is as a clear and colorless solution available as a 3mL FlexTouch disposable prefilled pen (see Table 11).

Table 11 Presentations of RYZODEG 70/30

RYZODEG 70/30	Total volume	Concentration	Total units available in presentation	NDC number	Max dose per injection	Dose increment	Package Size
U-100 FlexTouch	3 mL	100 units/mL	300 Units	0169-2770-15	80 Units	1 Unit	5 pens/pack

16.2 Recommended Storage

Unused RYZODEG 70/30 should be stored between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use RYZODEG 70/30 if it has been frozen.

Unopened FlexTouch disposable prefilled pen:
Not in-use (unopened) RYZODEG 70/30 disposable prefilled pen should be stored in a refrigerator 36°F to 46°F (2°C to 8°C). Discard after expiration date.

Open (In-Use) FlexTouch disposable prefilled pen:
The in-use RYZODEG 70/30 FlexTouch pen should be refrigerated (36°F - 46°F [2°C - 8°C]) or kept at room temperature (below 86°F [30°C]) away from direct heat and light. The opened (in-use) RYZODEG 70/30 FlexTouch pen may be used for up to 28 days (4 weeks) after being opened, if it is refrigerated or kept at room temperature.

The storage conditions are summarized in Table 12:

Table 12: Storage Conditions for RYZODEG 70/30 FlexTouch

	Not in-use (unopened)		In-use (opened)	
	Refrigerated (36°F - 46°F [2°C - 8°C])	**Room Temperature (below 86°F [30°C])**	**Room Temperature (below 86°F [30°C])**	**Refrigerated (36°F - 46°F [2°C - 8°C])**
3 mL RYZODEG 70/30 U100 FlexTouch	Until expiration date	28 days (4 weeks)	28 days (4 weeks)	28 days (4 weeks)

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information and Instructions for Use)

Never Share a RYZODEG 70/30 FlexTouch Pen Device Between Patients

Advise patients that they should never share a RYZODEG 70/30 FlexTouch pen device with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.1)]*.

Hyperglycemia or Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Inform patients of the symptoms of hypoglycemia. Inform patients that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Advise patients that changes in insulin regimen can predispose to hyper- or hypoglycemia. Advise patients that changes in insulin regimen should be made under close medical supervision *[see Warnings and Precautions (5.2)]*.

Medication errors

Inform patients to always check the insulin label before each injection *[see Warnings and Precautions (5.4)]*.

Instruct patients that when injecting RYZODEG 70/30, they must press and hold down the dose button until the dose counter shows 0 and then keep the needle in the skin and count slowly to 6. When the dose counter returns to 0, the prescribed dose is not completely delivered until 6 seconds later. If the needle is removed earlier, they may see a stream of insulin coming from the needle tip. If so, the full dose will not be delivered, (a possible under-dose may occur by as much as 20%), and they should increase the frequency of checking their blood glucose levels and possible additional insulin administration may be necessary.

- If 0 does not appear in the dose counter after continuously pressing the dose button, the patient may have used a blocked needle. In this case they would **not** have received **any** insulin—even though the dose counter has moved from the original dose that was set.
- If the patient did have a blocked or damaged needle, instruct them to change the needle as described in Step 15 of the Instructions for Use and repeat all steps in the IFU starting with a new needle and the section Preparing your RYZODEG 70/30 FlexTouch Pen. **Make sure the patient selects the full dose needed.**

If patients routinely do not hold the needle under the skin as recommended, the patient may need to slightly increase the dialed insulin dose to achieve the patient's glycemic targets.

Instruct patients to not re-use needles. A new needle must be attached before each injection. Reuse of needles increases the risk of blocked needles which may cause under-dosing or overdosing.

Instruct Patients to never use a syringe to remove RYZODEG 70/30 from the FlexTouch disposable insulin prefilled pen.

Administration
RYZODEG 70/30 must only be used if the solution is clear and colorless with no particles visible.
Patients must be advised that RYZODEG 70/30 must NOT be diluted or mixed with any other insulin or solution *[see Dosage and Administration (2.1)]*.

Management of Hypoglycemia and Handling of Special Situations
Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals *[see Warnings and Precautions (5.3)]*.

Refer patients to the RYZODEG 70/30 "Patient Information" for additional information about the potential side effects of insulin therapy, including lipodystrophy (and the need to rotate injection sites within the same body region), weight gain, allergic reactions, and hypoglycemia.

Women of Reproductive Potential
Advise patients to inform their health care professional if they are pregnant or are contemplating pregnancy.

Rx Only

Date of Issue: XX/201X
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RYZODEG® 70/30 is covered by US Patent Nos. 5,866,538, 7,615,532 and other patents pending.
FlexTouch® is covered by US Patent Nos. 6,899,699, 7,686,786, 8,672,898, 8,684,969, 8,920,383, 9,108,002, 9,132,239, D724,721, D734,450 and other patents pending.

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