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

REZVOGLAR (insulin glargine-aglr) injection, for subcutaneous use
Initial U.S. Approval: 2021

REZVOGLAR (insulin glargine-aglr) is biosimilar* to LANTUS (insulin glargine)

--------------------------- **INDICATIONS AND USAGE** ---------------------------
REZVOGLAR™ is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. (1)

Limitations of Use:
Not recommended for treating diabetic ketoacidosis. (1)

-----------------------**DOSAGE AND ADMINISTRATION**-----------------------
- Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use. (2.1, 2.3, 2.4)
- Administer subcutaneously into the abdominal area, thigh, or deltoid once daily at any time of day, but at the same time every day. (2.1)
- Do not dilute or mix with any other insulin or solution. (2.1)
- Rotate injection sites to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. (2.2)
- Closely monitor glucose when changing to REZVOGLAR and during initial weeks thereafter. (2.4)

----------------------**DOSAGE FORMS AND STRENGTHS**---------------------
Injection: 100 units/mL (U-100) available as:
- 3 mL single-patient-use REZVOGLAR™ KwikPen® prefilled pen (3)

----------------------------- **CONTRAINDICATIONS** ----------------------------
- During episodes of hypoglycemia. (4)
- Hypersensitivity to insulin glargine products or any excipient in REZVOGLAR. (4)

-----------------------**WARNINGS AND PRECAUTIONS**-----------------------
- *Never share* a REZVOGLAR KwikPen prefilled pen between patients, even if the needle is changed. (5.1)
- *Hyperglycemia or hypoglycemia with changes in insulin regimen:* Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased frequency of blood glucose monitoring. (5.2)
- *Hypoglycemia:* May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, coadministered glucose lowering medications, meal pattern, physical activity; and in patients with renal or hepatic impairment and hypoglycemia unawareness. (5.3, 6.1)
- *Medication Errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4, 6.3)
- *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue REZVOGLAR. Monitor and treat if indicated. (5.5, 6.1)
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk of 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 of TZD if heart failure occurs. (5.7)

------------------------------**ADVERSE REACTIONS**------------------------------
Adverse reactions commonly associated with insulin glargine products include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema, and weight gain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) 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)
- *Antiadrenergic 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.

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of REZVOGLAR has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

17   PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1   INDICATIONS AND USAGE

REZVOGLAR™ is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

Limitations of Use

REZVOGLAR is not recommended for the treatment of diabetic ketoacidosis.

2   DOSAGE AND ADMINISTRATION

2.1   Important Administration Instructions

- Administer REZVOGLAR subcutaneously once daily at any time of day but at the same time every day.
- Prior to initiation of REZVOGLAR, train patients on proper use and injection technique.
- Patient should follow the Instructions for Use to correctly administer REZVOGLAR.
- Administer REZVOGLAR subcutaneously into the abdominal area, thigh, or deltoid, and rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis *[see Warnings and Precautions (5.2), Adverse Reactions (6)]*.
- During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring *[see Warnings and Precautions (5.2)]*.
- Visually inspect REZVOGLAR KwikPen prefilled pens for particulate matter and discoloration prior to administration. Only use if the solution is clear and colorless with no visible particles.
- The REZVOGLAR KwikPen prefilled pen dials in 1-unit increments.
- Use REZVOGLAR KwikPen prefilled pen with caution in patients with visual impairment who may rely on audible clicks to dial their dose.
- Refrigerate unused (unopened) REZVOGLAR KwikPen prefilled pens.
- Do not administer intravenously or via an insulin pump.
- Do not dilute or mix REZVOGLAR with any other insulin or solution.
- The REZVOGLAR KwikPen prefilled pen is for single patient use only *[see Warnings and Precautions (5.1)]*.

2.2   General Dosing Instructions

- Individualize and adjust the dosage of REZVOGLAR based on the individual's metabolic needs, blood glucose monitoring results and glycemic control goal.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), during acute illness, or changes in renal or hepatic function. Dosage adjustments should only be made under medical supervision with appropriate glucose monitoring *[see Warnings and Precautions (5.2)]*.

2.3   Initiation of REZVOGLAR Therapy

Type 1 Diabetes

- In patients with type 1 diabetes, REZVOGLAR must be used concomitantly with short-acting insulin. The recommended starting dose of REZVOGLAR in patients with type 1 diabetes should be approximately one-third of the total daily insulin requirements. Short-acting, premeal insulin should be used to satisfy the remainder of the daily insulin requirements.

Type 2 Diabetes

- The recommended starting dose of REZVOGLAR in patients with type 2 diabetes who are not currently treated with insulin is 0.2 units/kg or up to 10 units once daily. One may need to adjust the amount and timing of short- or rapid-acting insulins and dosages of any oral antidiabetic drugs.

2.4   Changing to REZVOGLAR from Other Insulin Therapies

- If changing patients from once-daily insulin glargine, 300 units/mL, to once-daily REZVOGLAR, the recommended initial REZVOGLAR dose is 80% of the insulin glargine, 300 units/mL dose that is being discontinued. This dose reduction will lower the likelihood of hypoglycemia *[see Warnings and Precautions (5.3)]*.
- If changing from a treatment regimen with an intermediate or long-acting insulin to a regimen with REZVOGLAR, a change in the dose of the basal insulin may be required and the amount and timing of the shorter-acting insulins and doses of any oral antidiabetic drugs may need to be adjusted.
- If changing patients from once-daily NPH insulin to once-daily REZVOGLAR, the recommended initial REZVOGLAR dose is the same as the dose of NPH that is being discontinued.

- If changing patients from twice-daily NPH insulin to once-daily REZVOGLAR, the recommended initial REZVOGLAR dosage is 80% of the total NPH dose that is being discontinued. This dosage reduction will lower the likelihood of hypoglycemia *[see Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 units per mL (U-100) clear and colorless solution available as:
- 3 mL single-patient-use REZVOGLAR KwikPen prefilled pen

4 CONTRAINDICATIONS

REZVOGLAR is contraindicated:
- during episodes of hypoglycemia *[see Warnings and Precautions (5.3)]*.
- in patients with hypersensitivity to insulin glargine products or any of the excipients in REZVOGLAR *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a REZVOGLAR KwikPen Prefilled Pen Between Patients

REZVOGLAR KwikPen prefilled pens must 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 an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia *[see Warnings and Precautions (5.3)]* or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to unaffected area) has been reported to result in hypoglycemia *[see Adverse Reactions (6)]*.

Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. For patients with type 2 diabetes, dosage adjustments of concomitant oral and antidiabetic products may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulins, including insulin glargine products. 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).

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.

Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin 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 insulin glargine products 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 *[see Clinical Pharmacology (12.2)]*. 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 coadministered 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)]*.

Risk Mitigation Strategies for Hypoglycemia

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.

The long-acting effect of insulin glargine products may delay recovery from hypoglycemia.

5.4 Medication Errors

Accidental mix-ups among insulin products, particularly between long-acting insulins and rapid-acting insulins, have been reported. To avoid medication errors between REZVOGLAR and other insulins, instruct patients to always check the insulin label before each injection *[see Adverse Reactions (6.3)]*.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulins, including insulin glargine products. If hypersensitivity reactions occur, discontinue REZVOGLAR; treat per standard of care and monitor

until symptoms and signs resolve *[see Adverse Reactions (6.1)]*. REZVOGLAR is contraindicated in patients who have had hypersensitivity reactions to insulin glargine products or one of the excipients in REZVOGLAR *[see Contraindications (4)]*.

5.6   Hypokalemia

All insulins, including insulin glargine products, 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 serum potassium concentrations).

5.7   Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

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 heart failure. Patients treated with insulin, including REZVOGLAR, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If 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 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 data in Table 1 reflect the exposure of 2327 patients with type 1 diabetes to insulin glargine or NPH. The type 1 diabetes population had the following characteristics: Mean age was 38.5 years. Fifty four percent were male, 96.9% were Caucasian, 1.8% were Black or African American and 2.7% were Hispanic. The mean BMI was 25.1 kg/m^2.

The data in Table 2 reflect the exposure of 1563 patients with type 2 diabetes to insulin glargine or NPH. The type 2 diabetes population had the following characteristics: Mean age was 59.3 years. Fifty eight percent were male, 86.7% were Caucasian, 7.8% were Black or African American and 9% were Hispanic. The mean BMI was 29.2 kg/m^2.

The frequencies of adverse events during insulin glargine clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Adverse Events in Pooled Clinical Trials up to 28 Weeks Duration in Adults with Type 1 Diabetes (adverse events with frequency ≥5%)

	Insulin Glargine, % (n=1257)	NPH, % (n=1070)
Upper respiratory tract infection	22.4	23.1
Infection*	9.4	10.3
Accidental injury	5.7	6.4
Headache	5.5	4.7

* Body system not specified

Table 2: Adverse Events in Pooled Clinical Trials up to 1 Year Duration in Adults with Type 2 Diabetes (adverse events with frequency ≥5%)

	Insulin Glargine, % (n=849)	NPH, % (n=714)
Upper respiratory tract infection	11.4	13.3
Infection*	10.4	11.6
Retinal vascular disorder	5.8	7.4

* Body system not specified

Table 3: Adverse Events in a 5 Year Trial of Adults with Type 2 Diabetes (adverse events with frequency ≥10%)

	Insulin Glargine, % (n=514)	NPH, % (n=503)
Upper respiratory tract infection	29.0	33.6
Edema peripheral	20.0	22.7
Hypertension	19.6	18.9
Influenza	18.7	19.5
Sinusitis	18.5	17.9
Cataract	18.1	15.9
Bronchitis	15.2	14.1
Arthralgia	14.2	16.1
Pain in extremity	13.0	13.1
Back pain	12.8	12.3
Cough	12.1	7.4
Urinary tract infection	10.7	10.1
Diarrhea	10.7	10.3
Depression	10.5	9.7
Headache	10.3	9.3

Table 4: Adverse Events in a 28-Week Clinical Trial of Children and Adolescents with Type 1 Diabetes (adverse events with frequency ≥5%)

	Insulin Glargine,% (n=174)	NPH, % (n=175)
Infection*	13.8	17.7
Upper respiratory tract infection	13.8	16.0
Pharyngitis	7.5	8.6
Rhinitis	5.2	5.1

* Body system not specified

Severe Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulins, including insulin glargine products *[see Warnings and Precautions (5.3)]*. Tables 5, and 6, and 7 summarize the incidence of severe hypoglycemia in the insulin glargine individual clinical trials. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL (≤56 mg/dL in the 5-year trial and ≤36 mg/dL in the ORIGIN trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

Percentages of insulin glargine-treated adult patients experiencing severe symptomatic hypoglycemia in the insulin glargine clinical trials, *[see Clinical Studies (14)]* were comparable to percentages of NPH-treated patients for all treatment regimens (see Table 5 and 6). In the pediatric phase 3 clinical trial, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult trials with type 1 diabetes.

Table 5: Severe Symptomatic Hypoglycemia in Patients with Type 1 Diabetes

	Study A Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study B Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study C Type 1 Diabetes Adults 16 weeks In combination with insulin lispro		Study D Type 1 Diabetes Pediatrics 26 weeks In combination with regular insulin	
	Insulin Glargine N=292	NPH N=293	Insulin Glargine N=264	NPH N=270	Insulin Glargine N=310	NPH N=309	Insulin Glargine N=174	NPH N=175
Percent of patients	10.6	15.0	8.7	10.4	6.5	5.2	23.0	28.6

Table 6: Severe Symptomatic Hypoglycemia in Patients with Type 2 Diabetes

	Study E Type 2 Diabetes Adults 52 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 28 weeks In combination with regular insulin		Study G Type 2 Diabetes Adults 5 years In combination with regular insulin	
	Insulin Glargine N=289	NPH N=281	Insulin Glargine N=259	NPH N=259	Insulin Glargine N=513	NPH N=504
Percent of patients	1.7	1.1	0.4	2.3	7.8	11.9

Table 7 displays the proportion of patients experiencing severe symptomatic hypoglycemia in the insulin glargine and Standard Care groups in the ORIGIN Trial *[see Clinical Studies (14)]*.

Table 7: Severe Symptomatic Hypoglycemia in the ORIGIN Trial

	ORIGIN Trial Median duration of follow-up: 6.2 years	
	Insulin Glargine (N=6231)	Standard Care (N=6273)
Percent of patients	5.6	1.8

Peripheral Edema
Some patients taking insulin glargine products have experienced sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.
Lipodystrophy
Administration of insulin subcutaneously, including insulin glargine products, has resulted in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients *[see Dosage and Administration (2.2)]*.
Insulin Initiation and Intensification of Glucose Control
Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.
Weight gain
Weight gain has occurred with some insulin therapies including insulin glargine products and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.
Allergic Reactions
Local allergy
As with any insulin therapy, patients taking insulin glargine products may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in insulin glargine-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site did not result in discontinuation of therapy.
Systemic allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including insulin glargine products and may be life threatening.

6.2   Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other insulin glargine products may be misleading. All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of insulin glargine, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

6.3   Postmarketing Experience

The following adverse reactions have been identified during postapproval use of insulin glargine products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly rapid-acting insulins, have been accidentally administered instead of insulin glargine products *[see Patient Counseling Information (17)]*. To avoid medication errors between REZVOGLAR and other insulins, patients should be instructed to always verify the insulin label before each injection.

Localized cutaneous amyloidosis at the injection site has occurred. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

7   DRUG INTERACTIONS

Table 8 includes clinically significant drug interactions with REZVOGLAR.

Table 8: Clinically Significant Drug Interactions with REZVOGLAR

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, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when REZVOGLAR is coadministered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of REZVOGLAR	
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 REZVOGLAR is coadministered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of REZVOGLAR	
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 REZVOGLAR is coadministered 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 REZVOGLAR is coadministered with these drugs.

8   USE IN SPECIFIC POPULATIONS

8.1   Pregnancy

Risk Summary

Published studies with use of insulin glargine products during pregnancy have not reported a clear association with insulin glargine products and adverse developmental outcomes *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

Rats and rabbits were exposed to insulin glargine in animal reproduction studies during organogenesis, respectively 50 times and 10 times the human subcutaneous dose of 0.2 units/kg/day. Overall, the effects of insulin glargine did not generally differ from those observed with regular human insulin *(see Data)*.

The estimated background risk of major birth defects is 6% to 10% in women with pregestational diabetes with an HbA1c >7 and has been reported to be as high as 20% to 25% in women with an HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

<u>Clinical Considerations</u>
Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

<u>Data</u>
Human Data

Published data do not report a clear association with insulin glargine products and major birth defects, miscarriage, or adverse maternal or fetal outcomes when insulin glargine is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations including small sample size and some lacking comparator groups.

Animal Data

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 50 times the recommended human subcutaneous starting dose of 0.2 units/kg/day (0.007 mg/kg/day) based on a mg/kg basis. In rabbits, doses of 0.072 mg/kg/day, which is approximately 10 times the recommended human subcutaneous starting dose of 0.2 units/kg/day based on a mg/kg basis, were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

8.2   Lactation
<u>Risk Summary</u>

There are either no or only limited data on the presence of insulin glargine products in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous insulin is present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for REZVOGLAR and any potential adverse effects on the breastfed child from REZVOGLAR or from the underlying maternal condition.

8.4   Pediatric Use

The safety and effectiveness of insulin glargine products have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes *[see Clinical Studies (14.2)]*. The safety and effectiveness of insulin glargine products in pediatric patients younger than 6 years of age with type 1 diabetes and pediatric patients with type 2 diabetes have not been established.

The dosage recommendation when changing to REZVOGLAR in pediatric patients (age 6 to 15 years) with type 1 diabetes is the same as that described for adults *[see Dosage and Administration (2.2, 2.4) and Clinical Studies (14)]*. As in adults, the dosage of REZVOGLAR must be individualized in pediatric patients (age 6 to 15 years) with type 1 diabetes based on metabolic needs and frequent monitoring of blood glucose.

In the pediatric clinical trial, pediatric patients (age 6 to 15 years) with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia compared to the adults in trials with type 1 diabetes *[see Adverse Reactions (6.1)]*.

8.5   Geriatric Use

Of the total number of subjects in controlled clinical studies of patients with type 1 and type 2 diabetes who were treated with insulin glargine, 15% were ≥65 years of age and 2% were ≥75 years of age. The only difference in safety or effectiveness in the subpopulation of patients ≥65 years of age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in the insulin glargine and NPH treatment groups.

Nevertheless, caution should be exercised when REZVOGLAR is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

8.6   Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of insulin glargine products has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for REZVOGLAR in patients with hepatic impairment *[see Warnings and Precautions (5.3)]*.

8.7   Renal Impairment

The effect of renal impairment on the pharmacokinetics of insulin glargine products has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Frequent glucose monitoring and dose adjustment may be necessary for REZVOGLAR in patients with renal impairment *[see Warnings and Precautions (5.3)]*.

8.8   Obesity

In controlled clinical trials, subgroup analyses based on BMI did not show differences in safety and efficacy between insulin glargine and NPH.

10   OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.6)]*. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. 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 recurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

11   DESCRIPTION

Insulin glargine-aglr is a recombinant human insulin analog that is a long-acting, parenteral blood-glucose-lowering agent *[see Clinical Pharmacology (12)]*. Insulin glargine-aglr has low aqueous solubility at neutral pH. At pH 4 insulin glargine-aglr is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine-aglr are slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak. This profile allows once-daily dosing as a basal insulin. Insulin glargine-aglr is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. Insulin glargine-aglr differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. Chemically, insulin glargine-aglr is 21^A-Gly-30^B-a-L-Arg-30^Bb-L-Arg-human insulin and has the empirical formula $C_{267}H_{404}N_{72}O_{78}S_6$ and a molecular weight of 6063 Da. Insulin glargine-aglr has the following structural formula:
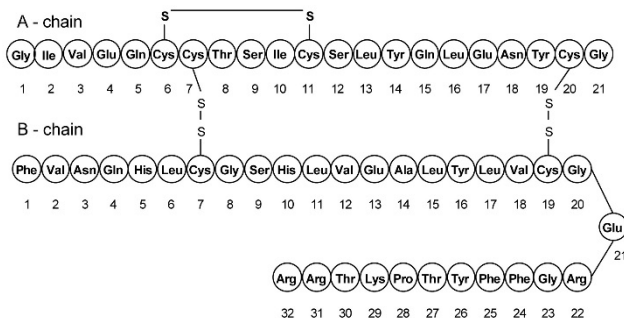
REZVOGLAR (insulin glargine-aglr) injection is a sterile solution of insulin glargine-aglr for subcutaneous use. REZVOGLAR consists of insulin glargine-aglr dissolved in a clear, colorless aqueous fluid. Each milliliter of REZVOGLAR (insulin glargine-aglr) injection contains 100 units (3.6378 mg) insulin glargine-aglr.

The 3 mL prefilled pen presentation contains the following inactive ingredients per mL: glycerin (17 mg/mL), metacresol (2.7 mg/mL), zinc oxide (content adjusted to provide 30 mcg zinc ion), and Q.S. to 1 mL with Water for Injection, USP.

The pH is adjusted by addition of aqueous solutions of hydrochloric acid 10% and/or sodium hydroxide 10%. REZVOGLAR has a pH of approximately 4.

**12   CLINICAL PHARMACOLOGY**

12.1   Mechanism of Action

The primary activity of insulin, including insulin glargine products, 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 inhibits lipolysis and proteolysis, and enhances protein synthesis.

12.2   Pharmacodynamics

In clinical studies, the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous insulin glargine is approximately the same as that for human insulin. Figure 1 shows results from a study in patients with type 1 diabetes conducted for a maximum of 24 hours after the injection. The median time between injection and the end of pharmacological effect was 14.5 hours (range: 9.5 to 19.3 hours) for NPH insulin, and 24 hours (range: 10.8 to >24.0 hours) (24 hours was the end of the observation period) for insulin glargine.

Figure 1: Activity Profile in Patients with Type 1 Diabetes
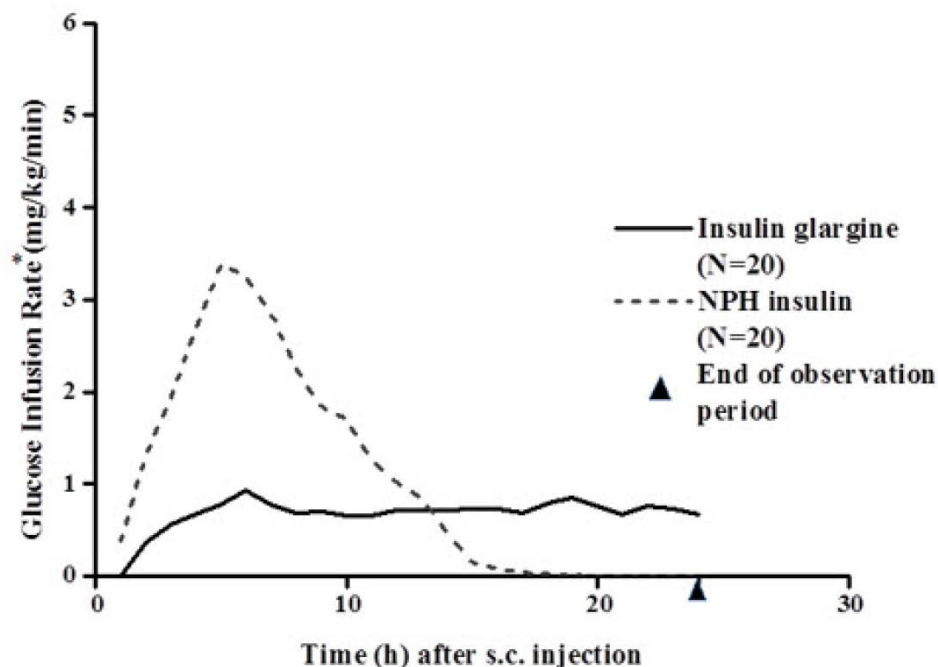
* Determined as amount of glucose infused to maintain constant plasma glucose levels

The duration of action after abdominal, deltoid, or thigh subcutaneous administration was similar. The time course of action of insulins, including insulin glargine products, may vary between individuals and within the same individual.

12.3   Pharmacokinetics

Absorption and Bioavailability

After subcutaneous injection of insulin glargine in healthy subjects and in patients with diabetes, the insulin serum concentrations indicated a slower, more prolonged absorption and a relatively constant concentration/time profile over 24 hours with no pronounced peak in comparison to NPH insulin.

Metabolism and Elimination

A metabolism study in humans indicates that insulin glargine is partly metabolized at the carboxyl terminus of the B chain in the subcutaneous depot to form two active metabolites with in vitro activity similar to that of human insulin, M1 (21^A-Gly-insulin) and M2 (21^A-Gly-des-30^B-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

Specific Populations

Age, race, and gender

Effect of age, race, and gender on the pharmacokinetics of insulin glargine products has not been evaluated. However, in controlled clinical trials in adults (n=3890) and a controlled clinical trial in pediatric patients (n=349), subgroup analyses based on age, race, and gender did not show differences in safety and efficacy between insulin glargine and NPH insulin *[see Clinical Studies (14)]*.

Obesity

Effect of Body Mass Index (BMI) on the pharmacokinetics of insulin glargine products has not been evaluated.

13   NONCLINICAL TOXICOLOGY

13.1   Carcinogenesis, Mutagenesis, Impairment of Fertility

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which was for the rat approximately 65 times the recommended human subcutaneous starting dose of 0.2 units/kg/day (0.007 mg/kg/day) on a mg/kg basis. Histiocytomas were found at injection sites in male rats and mice in

acid vehicle containing groups and are considered a response to chronic tissue irritation and inflammation in rodents. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

In a combined fertility and prenatal and postnatal study of insulin glargine in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which was approximately 50 times the recommended human subcutaneous starting dose of 0.2 units/kg/day (0.007 mg/kg/day) maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH insulin.

14   CLINICAL STUDIES

14.1   Overview of Clinical Studies

The safety and effectiveness of insulin glargine given once-daily at bedtime was compared to that of once-daily and twice-daily NPH insulin in open-label, randomized, active-controlled, parallel studies of 2,327 adult patients and 349 pediatric patients with type 1 diabetes mellitus and 1,563 adult patients with type 2 diabetes mellitus (*see* Tables 9 - 11). In general, the reduction in glycated hemoglobin (HbA1c) with insulin glargine was similar to that with NPH insulin.

14.2   Clinical Studies in Adult and Pediatric Patients with Type 1 Diabetes

In two clinical studies (Studies A and B), patients with type 1 diabetes (Study A; n=585, Study B; n=534) were randomized to 28 weeks of basal-bolus treatment with insulin glargine or NPH insulin. Regular human insulin was administered before each meal. Insulin glargine was administered at bedtime. NPH insulin was administered either as once daily at bedtime or in the morning and at bedtime when used twice daily.

In Study A, the average age was 39.2 years. The majority of patients were White (99%) and 55.7% were male. The mean BMI was approximately 24.9 kg/m^2. The mean duration of diabetes was 15.5 years.

In Study B, the average age was 38.5 years. The majority of patients were White (95.3%) and 50.6% were male. The mean BMI was approximately 25.8 kg/m^2. The mean duration of diabetes was 17.4 years.

In another clinical study (Study C), patients with type 1 diabetes (n=619) were randomized to 16 weeks of basal-bolus treatment with insulin glargine or NPH insulin. Insulin lispro was used before each meal. Insulin glargine was administered once daily at bedtime and NPH insulin was administered once or twice daily. The average age was 39.2 years. The majority of patients were White (96.9%) and 50.6% were male. The mean BMI was approximately 25.6 kg/m^2. The mean duration of diabetes was 18.5 years.

In these 3 studies, insulin glargine and NPH insulin had similar effects on HbA1c (*see* Table 9) with a similar overall rate of severe symptomatic hypoglycemia *[see Adverse Reactions (6.1)]*.

Table 9: Type 1 Diabetes Mellitus – Adult

Treatment duration Treatment in combination with	Study A 28 weeks Regular insulin		Study B 28 weeks Regular insulin		Study C 16 weeks Insulin lispro	
	Insulin Glargine	NPH	Insulin Glargine	NPH	Insulin Glargine	NPH
Number of subjects treated	292	293	264	270	310	309
HbA1c						
Baseline HbA1c	8.0	8.0	7.7	7.7	7.6	7.7
Adjusted mean change at trial end	+0.2	+0.1	-0.2	-0.2	-0.1	-0.1
Treatment Difference (95% CI)	+0.1 (0.0; + 0.2)		+0.1(-0.1; + 0.2)		0.0 (+0.1; + 0.1)	
Basal insulin dose						
Baseline mean	21	23	29	29	28	28
Mean change from baseline	-2	0	-4	+2	-5	+1
Total insulin dose						
Baseline mean	48	52	50	51	50	50
Mean change from baseline	-1	0	0	+4	-3	0
Fasting blood glucose (mg/dL)						
Baseline mean	167	166	166	175	175	173
Adj. mean change from baseline	-21	-16	-20	-17	-29	-12
Body weight (kg)						
Baseline mean	73.2	74.8	75.5	75.0	74.8	75.6
Mean change from baseline	0.1	-0.0	0.7	1.0	0.1	0.5

Type 1 Diabetes – Pediatric (*see* Table 10)

In a randomized, controlled clinical study (Study D), pediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. Insulin glargine was administered once daily at bedtime and NPH insulin was administered once or twice daily. The average age was 11.7 years. The majority of patients were White (96.8%) and 51.9% were male. The mean BMI was approximately 18.9 kg/m^2. The mean duration of diabetes was 4.8 years. Similar effects on HbA1c (*see* Table 10) were observed in both treatment groups *[see Adverse Reactions (6.1)]*.

Table 10: Type 1 Diabetes Mellitus – Pediatric

Treatment duration Treatment in combination with	Study D 28 weeks Regular insulin	
	Insulin Glargine + Regular Insulin	NPH + Regular Insulin
Number of subjects treated	174	175
HbA1c		
Baseline mean	8.5	8.8
Change from baseline (adjusted mean)	+0.3	+0.3
Difference from NPH (adjusted mean) (95% CI)	0.0 (-0.2; +0.3)	
Basal insulin dose		
Baseline mean	19	19
Mean change from baseline	-1	+2
Total insulin dose		
Baseline mean	43	43
Mean change from baseline	+2	+3
Fasting blood glucose (mg/dL)		
Baseline mean	194	191
Mean change from baseline	-23	-12
Body weight (kg)		
Baseline mean	45.5	44.6
Mean change from baseline	2.2	2.5

14.3   Clinical Studies in Adults with Type 2 Diabetes

In a randomized, controlled clinical study (Study E) (n=570), insulin glargine was evaluated for 52 weeks in combination with oral antidiabetic medications (a sulfonylurea, metformin, acarbose, or combination of these drugs). The average age was 59.5 years. The majority of patients were White (92.8%) and 53.7% were male. The mean BMI was approximately 29.1 kg/m^2. The mean duration of diabetes was 10.3 years. Insulin glargine administered once daily at bedtime was as effective as NPH insulin administered once daily at bedtime in reducing HbA1c and fasting glucose (*see* Table 11). The rate of severe symptomatic hypoglycemia was similar in insulin glargine and NPH insulin treated patients *[see Adverse Reactions (6.1)]*.

In a randomized, controlled clinical study (Study F), in patients with type 2 diabetes not using oral antidiabetic medications (n=518), a basal-bolus regimen of insulin glargine once daily at bedtime or NPH insulin administered once or twice daily was evaluated for 28 weeks. Regular human insulin was used before meals, as needed. The average age was 59.3 years. The majority of patients were White (80.7%) and 60% were male. The mean BMI was approximately 30.5 kg/m^2. The mean duration of diabetes was 13.7 years. Insulin glargine had similar effectiveness as either once- or twice daily NPH insulin in reducing HbA1c and fasting glucose (*see* Table 11) with a similar incidence of hypoglycemia *[see Adverse Reactions (6.1)]*.

In a randomized, controlled clinical study (Study G), patients with type 2 diabetes were randomized to 5 years of treatment with once-daily insulin glargine or twice-daily NPH insulin. For patients not previously treated with insulin, the starting dose of insulin glargine or NPH insulin was 10 units daily. Patients who were already treated with NPH insulin either continued on the same total daily NPH insulin dose or started insulin glargine at a dose that was 80% of the total previous NPH insulin dose. The primary endpoint for this study was a comparison of the progression of diabetic retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. HbA1c change from baseline was a secondary endpoint. Similar glycemic control in the 2 treatment groups was desired in order to not confound the interpretation of the retinal data. Patients or study personnel used an algorithm to adjust the insulin glargine and NPH insulin doses to a target fasting plasma glucose ≤100 mg/dL. After the insulin glargine or NPH insulin dose was adjusted, other anti-diabetic agents, including premeal insulin were to be adjusted or added. The average age was 55.1 years. The majority of patients were White (85.3%) and 53.9% were male. The mean BMI was approximately 34.3 kg/m^2.

The mean duration of diabetes was 10.8 years. The insulin glargine group had a smaller mean reduction from baseline in HbA1c compared to the NPH insulin group, which may be explained by the lower daily basal insulin doses in the insulin glargine group (*see* Table 11). The incidences of severe symptomatic hypoglycemia were similar between groups *[see Adverse Reactions (6.1)]*.

Table 11: Type 2 Diabetes Mellitus - Adult

Treatment duration Treatment in combination with	Study E 52 weeks Oral agents		Study F 28 weeks Regular insulin		Study G 5 years Regular insulin	
	Insulin Glargine	NPH	Insulin Glargine	NPH	Insulin Glargine	NPH
Number of subjects treated	289	281	259	259	513	504
HbA1c						
Baseline mean	9.0	8.9	8.6	8.5	8.4	8.3
Adjusted mean change from baseline	-0.5	-0.4	-0.4	-0.6	-0.6	-0.8
Insulin glargine – NPH	-0.1		+0.2		+0.2	
95% CI for Treatment difference	(-0.3; +0.1)		(0.0; +0.4)		(+0.1; +0.4)	
Basal insulin dose*						
Baseline mean	14	15	44.1	45.5	39	44
Mean change from baseline	+12	+9	-1	+7	+23	+30
Total insulin dose*						
Baseline mean	14	15	64	67	48	53
Mean change from baseline	+12	+9	+10	+13	+41	+40
Fasting blood glucose (mg/dL)						
Baseline mean	179	180	164	166	190	180
Adj. mean change from baseline	-49	-46	-24	-22	-45	-44
Body weight (kg)						
Baseline mean	83.5	82.1	89.6	90.7	100	99
Adj. mean change from baseline	2.0	1.9	0.4	1.4	3.7	4.8

* In Study G, the baseline dose of basal or total insulin was the first available on-treatment dose prescribed during the study (on visit month 1.5)

Insulin Glargine Timing of Daily Dosing (*see* Table 12)

The safety and efficacy of insulin glargine administered pre-breakfast, pre-dinner, or at bedtime were evaluated in a randomized, controlled clinical study in patients with type 1 diabetes (Study H; n=378). Patients were also treated with insulin lispro at mealtime. The average age was 40.9 years. All patients were White (100%) and 53.7% were male. The mean BMI was approximately 25.3 kg/m^2. The mean duration of diabetes was 17.3 years. Insulin glargine administered at different times of the day resulted in similar reductions in HbA1c compared to that with bedtime administration (*see* Table 12). In these patients, data are available from 8-point home glucose monitoring. The maximum mean blood glucose was observed just prior to injection of insulin glargine regardless of time of administration.

In this study, 5% of patients in the insulin glargine-breakfast arm discontinued treatment because of lack of efficacy. No patients in the other two arms discontinued for this reason. The safety and efficacy of insulin glargine administered pre-breakfast or at bedtime were also evaluated in a randomized, active-controlled clinical study (Study I, n=697) in patients with type 2 diabetes not adequately controlled on oral anti-diabetic therapy. All patients in this study also received glimepiride 3 mg daily. The average age was 60.8 years. The majority of patients were White (96.6%) and 53.7% were male. The mean BMI was approximately 28.7 kg/m^2. The mean duration of diabetes was 10.1 years. Insulin glargine given before breakfast was at least as effective in lowering HbA1c as insulin glargine given at bedtime or NPH insulin given at bedtime (*see* Table 12).

Table 12: Insulin Glargine Timing of Daily Dosing in Type 1 (Study H) and Type 2 (Study I) Diabetes Mellitus

Treatment duration Treatment in combination with	Study H 24 weeks Insulin lispro			Study I 24 weeks Glimepiride		
	Insulin Glargine Breakfast	Insulin Glargine Dinner	Insulin Glargine Bedtime	Insulin Glargine Breakfast	Insulin Glargine Bedtime	NPH Bedtime
Number of subjects treated[*]	112	124	128	234	226	227
HbA1c						
Baseline mean	7.6	7.5	7.6	9.1	9.1	9.1
Mean change from baseline	-0.2	-0.1	0.0	-1.3	-1.0	-0.8
Basal insulin dose (U)						
Baseline mean	22	23	21	19	20	19
Mean change from baseline	5	2	2	11	18	18
Total insulin dose (U)				NA†	NA	NA
Baseline mean	52	52	49			
Mean change from baseline	2	3	2			
Body weight (kg)						
Baseline mean	77.1	77.8	74.5	80.7	82	81
Mean change from baseline	0.7	0.1	0.4	3.9	3.7	2.9

[*] Intent to treat.

† Not applicable.

Five-year Trial Evaluating the Progression of Retinopathy

Retinopathy was evaluated in the insulin glargine clinical studies by analysis of reported retinal adverse events and fundus photography. The numbers of retinal adverse events reported for insulin glargine and NPH insulin treatment groups were similar for patients with type 1 and type 2 diabetes.

Insulin glargine was compared to NPH insulin in a 5-year randomized clinical trial that evaluated the progression of retinopathy as assessed with fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Scale (ETDRS). Patients had type 2 diabetes (mean age 55 years) with no (86%) or mild (14%) retinopathy at baseline. Mean baseline HbA1c was 8.4%. The primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. Patients with pre-specified postbaseline eye procedures (pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also considered as 3-step progressors regardless of actual change in ETDRS score from baseline. Retinopathy graders were blinded to treatment group assignment. The results for the primary endpoint are shown in Table 13 for both the per-protocol and intent-to-treat populations, and indicate similarity of insulin glargine to NPH in the progression of diabetic retinopathy as assessed by this outcome.

Table 13: Number (%) of Patients with 3 or More Step Progression on ETDRS Scale at Endpoint

	Insulin Glargine (%)	NPH (%)	Difference[*,†] (SE)	95% CI for difference
Per-protocol	53/374 (14.2%)	57/363 (15.7%)	-2.0% (2.6%)	-7.0% to +3.1%
Intent-to-Treat	63/502 (12.5%)	71/487 (14.6%)	-2.1% (2.1%)	-6.3% to +2.1%

[*] Difference = Insulin Glargine – NPH.

† Using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata (cutoff 9.0%) as the classified independent variables, and with binomial distribution and identity link function.

The ORIGIN Study

The Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomized, 2-by-2, factorial design study. One intervention in ORIGIN compared the effect of insulin glargine to standard care on major adverse cardiovascular outcomes in 12,537 participants ≥50 years of age with abnormal glucose levels (i.e., impaired fasting glucose [IFG] and/or impaired glucose tolerance [IGT]) or early type 2 diabetes mellitus and established cardiovascular (i.e., CV) disease or CV risk factors at baseline.

The objective of the trial was to demonstrate that use of insulin glargine could significantly lower the risk of major cardiovascular outcomes compared to standard care. Two co-primary composite cardiovascular endpoints were used in ORIGIN. The first co-primary endpoint was the time to first occurrence of a major adverse cardiovascular event defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke. The second co-primary endpoint was the

time to the first occurrence of CV death or nonfatal myocardial infarction or nonfatal stroke or revascularization procedure or hospitalization for heart failure.

Participants were randomized to either insulin glargine (N=6264) titrated to a goal fasting plasma glucose of ≤95 mg/dL or to standard care (N=6273). Anthropometric and disease characteristics were balanced at baseline. The mean age was 64 years and 8% of participants were 75 years of age or older. The majority of participants were male (65%). Fifty nine percent were Caucasian, 25% were Latin, 10% were Asian and 3% were Black. The median baseline BMI was 29 kg/m^2. Approximately 12% of participants had abnormal glucose levels (IGT and/or IFG) at baseline and 88% had type 2 diabetes. For patients with type 2 diabetes, 59% were treated with a single oral antidiabetic drug, 23% had known diabetes but were on no antidiabetic drug and 6% were newly diagnosed during the screening procedure. The mean HbA1c (SD) at baseline was 6.5% (1.0). Fifty-nine percent of participants had had a prior cardiovascular event and 39% had documented coronary artery disease or other cardiovascular risk factors.

Vital status was available for 99.9% and 99.8% of participants randomized to insulin glargine and standard care respectively at end of trial. The median duration of follow-up was 6.2 years (range: 8 days to 7.9 years). The mean HbA1c (SD) at the end of the trial was 6.5% (1.1) and 6.8% (1.2) in the insulin glargine and standard care group respectively. The median dose of insulin glargine at end of trial was 0.45 U/kg. Eighty-one percent of patients randomized to insulin glargine were using insulin glargine at end of the study. The mean change in body weight from baseline to the last treatment visit was 2.2 kg greater in the insulin glargine group than in the standard care group.

Overall, the incidence of major adverse cardiovascular outcomes was similar between groups (*see* Table 14). All-cause mortality was also similar between groups.

Table 14: Cardiovascular Outcomes in ORIGIN – Time to First Event Analyses

	Insulin Glargine N=6264	Standard Care N=6273	Insulin Glargine vs. Standard Care
	n (Events per 100 PY)	n (Events per 100 PY)	Hazard Ratio (95% CI)
Coprimary endpoints			
CV death, nonfatal myocardial infarction, or nonfatal stroke	1041 (2.9)	1013 (2.9)	1.02 (0.94, 1.11)
CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure or revascularization procedure	1792 (5.5)	1727 (5.3)	1.04 (0.97, 1.11)
Components of coprimary endpoints			
CV death	580	576	1.00 (0.89, 1.13)
Myocardial Infarction (fatal or nonfatal)	336	326	1.03 (0.88, 1.19)
Stroke (fatal or nonfatal)	331	319	1.03 (0.89, 1.21)
Revascularizations	908	860	1.06 (0.96, 1.16)
Hospitalization for heart failure	310	343	0.90 (0.77, 1.05)

In the ORIGIN trial, the overall incidence of cancer (all types combined) or death from cancer (Table 15) was similar between treatment groups.

Table 15: Cancer Outcomes in ORIGIN – Time to First Event Analyses

	Insulin Glargine N=6264	Standard Care N=6273	Insulin Glargine vs. Standard Care
	n (Events per 100 PY)	n (Events per 100 PY)	Hazard Ratio (95% CI)
Cancer endpoints			
Any cancer event (new or recurrent)	559 (1.56)	561 (1.56)	0.99 (0.88, 1.11)
New cancer events	524 (1.46)	535 (1.49)	0.96 (0.85, 1.09)
Death due to Cancer	189 (0.51)	201 (0.54)	0.94 (0.77, 1.15)

16   HOW SUPPLIED/STORAGE AND HANDLING

16.1   How Supplied

REZVOGLAR (insulin glargine-aglr) injection is supplied as a clear, colorless, sterile solution containing 100 units per mL (U-100) available in:

REZVOGLAR	Total Volume	NDC Number	Package Size
REZVOGLAR single-patient-use KwikPen	3 mL	0002-8980-05 (HP-8980)	5 pens

The prefilled pen REZVOGLAR KwikPen dials in 1 unit increments.
Needles are not included in the packs.
This device is recommended for use with Becton, Dickinson & Company's insulin pen needles which are sold separately.

16.2 Storage
Dispense in the original sealed carton with the enclosed Instructions for Use.
REZVOGLAR should not be stored in the freezer and should not be allowed to freeze. Discard REZVOGLAR if it has been frozen. Protect REZVOGLAR from direct heat and light.
Storage conditions are summarized in the following table:

	Not In-Use (unopened) Refrigerated (36°F to 46°F [2°C to 8°C])	Not In-Use (unopened) Room Temperature (up to 86°F [30°C])	In-Use (opened) (see temperature below)
3 mL single-patient-use prefilled pen REZVOGLAR KwikPen	Until expiration date	28 days	28 days Room temperature only (up to 86°F [30°C]) (Do not refrigerate)

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
Never Share a REZVOGLAR KwikPen Prefilled Pen Between Patients
Advise patients that they must never share a REZVOGLAR KwikPen prefilled pen with another person, even if the needle is changed. Sharing 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 *[see Warnings and Precautions (5.3)]*.
Advise patients that changes in insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision *[see Warnings and Precautions (5.2)]*.
Medication errors
Instruct patients to always check the insulin label before each injection *[see Warnings and Precautions (5.4)]*.
Administration
Advise patients that REZVOGLAR must NOT be diluted or mixed with any other insulin or solution and that REZVOGLAR must only be used if the solution is clear and colorless with no particles visible. *[see Dosage and Administration (2)]*.

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Patient Information

REZVOGLAR™ (REHZ-voh-glahr)
(insulin glargine-aglr) injection for subcutaneous use, 100 Units/mL (U-100)

Do not share your REZVOGLAR™ KwikPen® with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is REZVOGLAR?

- REZVOGLAR is a long-acting man-made insulin used to control high blood sugar in adults with diabetes mellitus.
- REZVOGLAR is not for use to treat diabetic ketoacidosis.
- It is not known if REZVOGLAR is safe and effective in children less than 6 years of age with type 1 diabetes.
- It is not known if REZVOGLAR is safe and effective in children with type 2 diabetes.

Who should not use REZVOGLAR?

Do not use REZVOGLAR if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to insulin glargine products or any of the ingredients in REZVOGLAR. See the end of this Patient Information leaflet for a complete list of ingredients in REZVOGLAR.

What should I tell my healthcare provider before using REZVOGLAR?

Before using REZVOGLAR, tell your healthcare provider about all your medical conditions including if you:

- have liver or kidney problems.
- take other medicines, especially ones called TZDs (thiazolidinediones).
- have heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with REZVOGLAR.
- are pregnant, planning to become pregnant, or are breastfeeding. It is not known if REZVOGLAR may harm your unborn baby or breastfeeding baby.

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins and herbal supplements.

Before you start using REZVOGLAR, talk to your healthcare provider about low blood sugar and how to manage it.

How should I use REZVOGLAR?

- Read the detailed **Instructions for Use** that come with your REZVOGLAR KwikPen single-patient-use prefilled pen.
- Use REZVOGLAR exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much REZVOGLAR to use and when to use it.
- Know the amount of REZVOGLAR you use. **Do not** change the amount of REZVOGLAR you use unless your healthcare provider tells you to.
- Check your insulin label each time you give your injection to make sure you are using the correct insulin.
- REZVOGLAR comes in a KwikPen single-patient-use prefilled pen that you must use to give your REZVOGLAR. The dose indicator on your pen shows your dose of REZVOGLAR. Do not make any dose changes unless your healthcare provider tells you to.
- **Do not** use a syringe to remove REZVOGLAR from your KwikPen disposable prefilled pen.
- **Do not** re-use needles. Always use a new needle for each injection. Re-use of needles increases your risk of having blocked needles, which may cause you to get the wrong dose of REZVOGLAR. Using a new needle for each injection lowers your risk of getting an infection. If your needle is blocked, follow the instructions in **Step 3** of the **Instructions for Use.**

- You may take REZVOGLAR at any time during the day but you must take it at the same time every day.

- REZVOGLAR is injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).

- Do not use REZVOGLAR in an insulin pump or inject REZVOGLAR into your vein (intravenously).

- **Change (rotate) your injection sites within area you chose with each dose** to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.

  - o **Do not** use the exact same spot for each injection.

  - o **Do not** inject where the skin has pits, is thickened, or has lumps.

  - o **Do not** inject where skin is tender, bruised, scaly or hard, or into scars or damaged skin.

- **Do not** mix REZVOGLAR with any other type of insulin or liquid medicine.

- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugar should be and when you should check your blood sugar levels.

Keep REZVOGLAR and all medicines out of the reach of children.

Your dose of REZVOGLAR may need to change because of:

- change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of the medicines you take.

What should I avoid while using REZVOGLAR?

While using REZVOGLAR do not:

- drive or operate heavy machinery, until you know how REZVOGLAR affects you.

- drink alcohol or use over-the-counter medicines that contain alcohol.

What are the possible side effects of REZVOGLAR and other insulins?

REZVOGLAR may cause serious side effects that can lead to death, including:

- **low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:

  - dizziness or light-headedness, sweating, confusion, headache, blurred vision, slurred speech, shakiness, fast heartbeat, anxiety, irritability or mood change, hunger.

- **severe allergic reaction (whole body reaction). Get medical help right away if you have any of these signs or symptoms of a severe allergic reaction:**

  - a rash over your whole body, trouble breathing, a fast heartbeat, or sweating.

- **low potassium in your blood (hypokalemia).**

- **heart failure.** Taking certain diabetes pills called TZDs (thiazolidinediones) with REZVOGLAR may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with REZVOGLAR. Your healthcare provider should monitor you closely while you are taking TZDs with REZVOGLAR. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:

  - shortness of breath, swelling of your ankles or feet, sudden weight gain.

Treatment with TZDs and REZVOGLAR may need to be changed or stopped by your healthcare provider if you have new or worse heart failure.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

The most common side effects of REZVOGLAR include:

- low blood sugar (hypoglycemia), weight gain; allergic reactions, including reactions at your injection site, skin thickening or pits at the injection site (lipodystrophy).

These are not all the possible side effects of REZVOGLAR. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of REZVOGLAR.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. **Do not** use REZVOGLAR for a condition for which it was not prescribed. **Do not** give REZVOGLAR to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about REZVOGLAR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about REZVOGLAR that is written for healthcare professionals. For more information about REZVOGLAR call 1-800-545-5979 or go to the website www.xxxxxxxxx.com.

What are the ingredients in REZVOGLAR?

- **Active ingredient:** insulin glargine-aglr

- **Inactive ingredients:** glycerin, m-cresol, zinc, and Water for Injection, USP

Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH.

Patient Information issued: December 2021

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This Patient Information has been approved by the U.S. Food and Drug Administration

Instructions for Use

REZVOGLAR™ KwikPen® Single-Patient-Use Prefilled Pen
(insulin glargine-aglr)
injection for subcutaneous use
100 units/mL, 3 mL single-patient-use prefilled pen

Your healthcare professional has decided that REZVOGLAR KwikPen is right for you. Talk with your healthcare professional about proper injection technique before using REZVOGLAR KwikPen.

Read these instructions carefully before using your REZVOGLAR KwikPen ("Pen"). If you are not able to follow all the instructions completely on your own, use REZVOGLAR KwikPen only if you have help from a person who is able to follow the instructions.

Do not share your REZVOGLAR KwikPen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

People who are blind or have vision problems should not use REZVOGLAR KwikPen single-patient-use prefilled pen without help from a person trained to use REZVOGLAR KwikPen single-patient-use prefilled pen.

Follow these instructions completely each time you use REZVOGLAR KwikPen to ensure that you get an accurate dose. If you do not follow these instructions you may get too much or too little insulin, which may affect your blood glucose.

REZVOGLAR KwikPen is a disposable pen for the injection of insulin. Each REZVOGLAR KwikPen contains in total 300 units of insulin. You can give doses from 1 to 80 units in steps of 1 unit. If you need a dose greater than 80 units, you should give it as two or more injections. The Pen plunger moves with each injection, but you may not notice that it moves. The plunger will only move to the end of the cartridge when all 300 units of insulin have been given.

Keep this leaflet for future reference.

If you have any questions about REZVOGLAR KwikPen or about diabetes, ask your healthcare professional, go to www.xxxxxx.com or call Eli Lilly and Company at 1-800-545-5979.

KwikPen Parts

Pen Cap   Cartridge Holder   Label   Dose Indicator

Cap Clip   Rubber Seal   Plunger   Pen Body   Dose Window   Dose Knob

**Pen Needle Parts
(Needles Not Included)**

**Dose Knob
with
green ring**

Paper Tab

Outer Needle
Shield

Inner
Needle
Shield
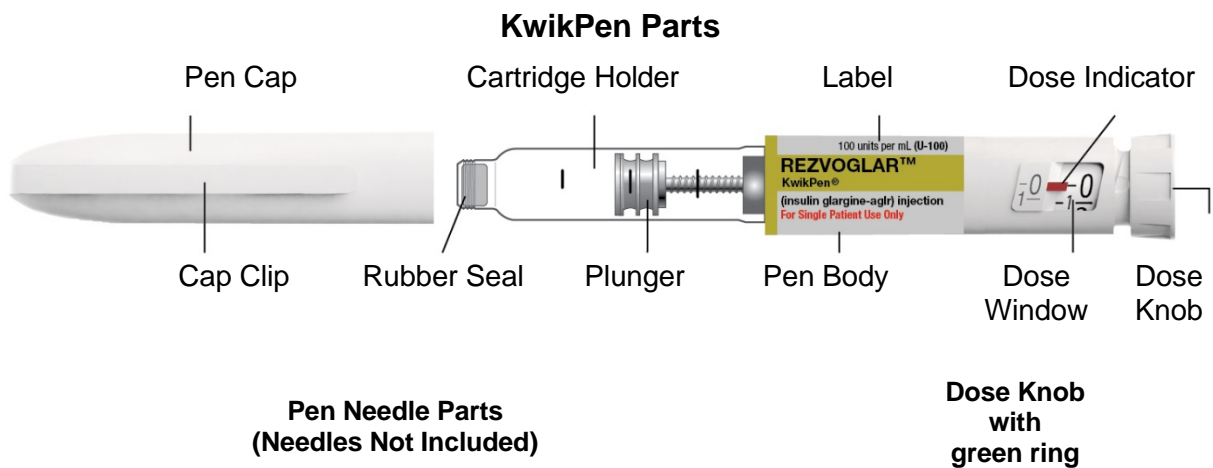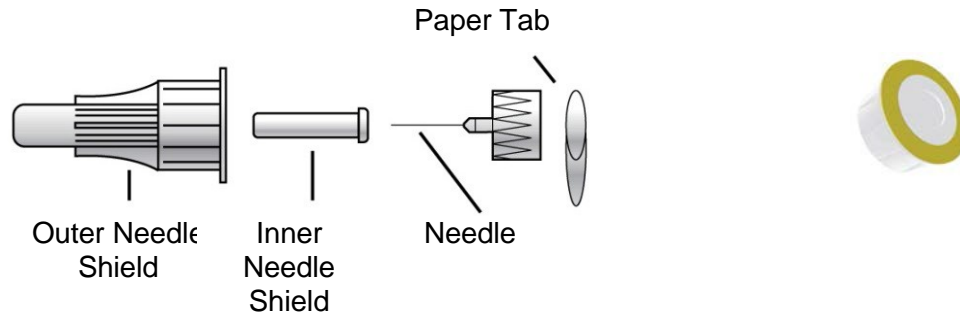
Needle

Important information for use of REZVOGLAR KwikPen:

- **Do not share your REZVOGLAR KwikPen with other people, even if the needle has been changed.** You may give other people a serious infection, or get a serious infection from them.
- Do not re-use needles. Always attach a new needle before each use.
- Use needles compatible with REZVOGLAR KwikPen. Becton, Dickinson and Company (BD) Pen Needles are recommended. These are sold separately. Contact your healthcare professional for further information.
- Always perform the safety test (prime the REZVOGLAR KwikPen) before each injection.
- Do not select a dose or press the Dose Knob without a needle attached.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use REZVOGLAR KwikPen if it is damaged or if you are not sure that it is working properly.
- Always have a spare REZVOGLAR KwikPen in case your Pen is lost or damaged.
- Change (rotate) your injection sites within the area you choose for each dose (see "**Places to inject**").

Places to inject

- Inject your insulin exactly as your healthcare provider has shown you.
- Inject your insulin under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
- **Do not** inject where the skin has pits, is thickened, or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- **Do not** try to change your dose while injecting.

Step 1. Check the insulin

    A. Check the Label on your Pen to make sure you have the correct insulin. The REZVOGLAR KwikPen is light grey with a light grey Dose Knob that has a green ring on the end. The label on the Pen is light grey with green color bars.

    B. Take off the Pen Cap.

    C. Check the appearance of your insulin. REZVOGLAR KwikPen contains a clear and colorless insulin. Do not use this Pen if the insulin is cloudy, colored or has particles or clumps in it.

Step 2. Attach the needle

Do not re-use needles. Always use a new sterile needle for each injection. This helps prevent contamination and potential needle blocks.

    A. Wipe the Rubber Seal with alcohol.

B. Remove the Paper Tab from a new needle.
C. Line up the needle with the Pen, and keep it straight as you attach it. Push the capped needle straight onto the REZVOGLAR KwikPen and twist the needle on until it is tight.

- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.
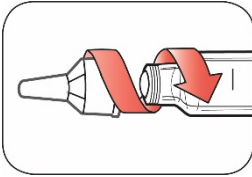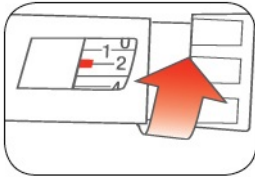

Step 3. Perform a Safety test (Prime your REZVOGLAR KwikPen)

<u>Always</u> perform the safety test (prime) before each injection.
Performing the safety test (priming) ensures that you get an accurate dose by:
- ensuring that Pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the Dose Knob.

B. Take off the Outer Needle Shield and keep it to remove the used needle after injection. Take off the Inner Needle Shield and discard it.

Keep   Throw Away
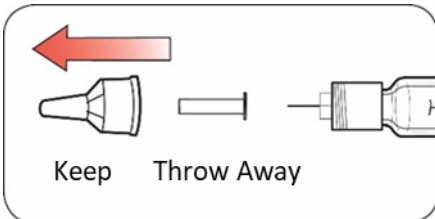
C. Hold the Pen with the needle pointing upwards.
D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.
E. Press the Dose Knob all the way in. Hold the Dose Knob in and **count to 5 slowly**. Check if insulin comes out of the needle tip.
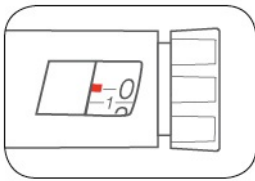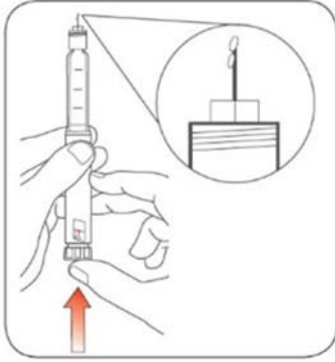
You may have to perform the safety test (prime) several times before insulin is seen.

- If no insulin comes out, check for air bubbles and repeat the safety test (prime) no more than 4 times.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your REZVOGLAR KwikPen may be damaged. Do not use this Pen.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

    A. Check that the dose window shows "0" following the safety test (priming).
    B. Select your required dose (in the example below, the selected dose is 8 units). If you turn past your dose, you can turn back down. The Dose Knob clicks as you turn it. Do not dial your dose by counting the clicks because you may dial the wrong dose.
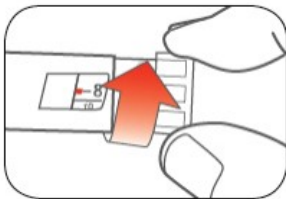
- Do not push the Dose Knob while turning, as insulin will come out.
- You cannot turn the Dose Knob past the number of units left in the Pen. Do not force the Dose Knob to turn. In this case, either you can inject what is remaining in the Pen and complete your dose with a new Pen or use a new Pen for your full dose.
  - o Even numbers are printed on the dial.
  - o Odd numbers, after the number 1, are shown as full lines.
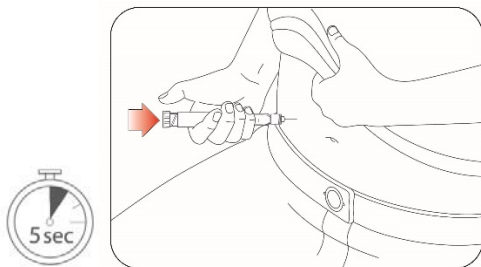- Always check the number in the Dose Window to make sure you have dialed the correct dose.
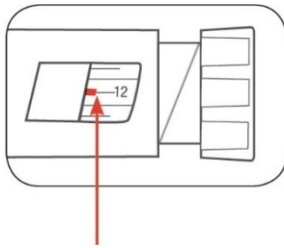
(Example: 12 units shown in the Dose Window)
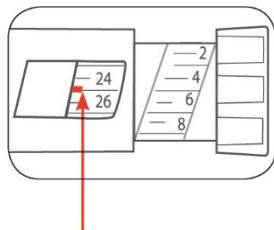
(Example: 25 units shown in the Dose Window)

Step 5. Inject the dose

A. Use the injection method as instructed by your healthcare professional.
B. Insert the needle into the skin.

C. Deliver the dose by pressing the Dose Knob in all the way. The number in the Dose Window will return to "0" as you inject.
Do not try to inject your insulin by turning the Dose Knob. You will **not** receive your insulin by turning the Dose Knob.
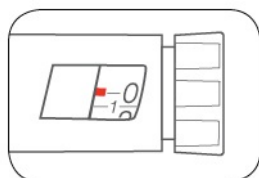
D. Keep the Dose Knob pressed all the way in.
<u>Slowly count to 5 before you withdraw the needle from the skin.</u> This ensures that the full dose will be delivered.
If you do not see "0" in the Dose Window, you did not receive your full dose. Do not redial. Insert the needle into your skin and finish your injection.
If you still do not think you received the full amount you dialed for your injection, do not start over or repeat the injection. Monitor your blood glucose and call your healthcare provider for further instructions.
If you normally need to give 2 injections for your full dose, be sure to give your second injection.

**Step 6. Remove and discard the needle**

Always remove the needle after each injection. Store REZVOGLAR KwikPen without a needle attached. This helps prevent:

- Contamination and/or infection.
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

   A. Put the Outer Needle Shield back on the needle, and use it to unscrew the needle from the Pen.

   To reduce the risk of accidental needle injury, never replace the Inner Needle Shield.
   - If your injection is given by another person, special caution must be taken by this person when removing and disposing the needle. Follow recommended safety measures for removal and disposal of needles (e.g., a one-handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.
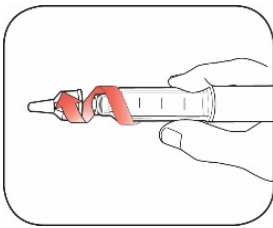
   B. Dispose of the needle safely. Used needles should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.
   If you are giving an injection to another person, you should remove the needle in an approved manner to avoid needle-stick injuries.
   C. Always put the Pen Cap back on the Pen by lining up the Cap Clip with the Dose Indicator and pushing straight on. Store the Pen until your next injection.

Storage Instructions

Please check the leaflet for the insulin for complete instructions on how to store REZVOGLAR KwikPen.

If your REZVOGLAR KwikPen is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Keep REZVOGLAR KwikPen out of the reach and sight of children.

Keep your REZVOGLAR KwikPen in cool storage (36°F–46°F [2°C–8°C]) until first use. **Do not** allow it to freeze. Do not put it next to the freezer compartment of your refrigerator or next to a freezer pack.

Once you take your REZVOGLAR KwikPen out of cool storage, for use or as a spare, you can use it for up to 28 days. During this time it can be safely kept at room temperature up to 86°F (30°C). Do not use it after this time. REZVOGLAR KwikPen in use must not be stored in a refrigerator.

Do not use REZVOGLAR KwikPen after the expiration date printed on the Label of the Pen or on the carton.

Protect REZVOGLAR KwikPen from heat and light.

Discard your used REZVOGLAR KwikPen as required by your local authorities.

Maintenance

Protect your REZVOGLAR KwikPen from dust and dirt.

You can clean the outside of your REZVOGLAR KwikPen by wiping it with a damp cloth.

Do not soak, wash, or lubricate the Pen as this may damage it.

Your REZVOGLAR KwikPen is designed to work accurately and safely. It should be handled with care. Avoid situations where REZVOGLAR KwikPen might be damaged. If you are concerned that your REZVOGLAR KwikPen may be damaged, use a new one.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Instructions for Use issued: December 2021