NEW DRUG APPROVAL

Brand Name	Rezvoglar™
Generic Name	insulin glargine-aglr
Drug Manufacturer	Eli Lilly and Company

Indications for Use

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.

Limitations of Use: Not recommended for treating diabetic ketoacidosis.

New Drug Approval

FDA approval date: December 17, 2021

Review designation: N/A

Type of review: Biologic License Application (BLA): 761215

Dispensing restriction: N/A

Therapeutic Class

Insulin, Long-Acting

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood glucose. Hyperglycemia, also called raised blood glucose or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurred before the age of 70 years. Another 460 000 kidney disease deaths were caused by diabetes and raised blood glucose causes around 20% of cardiovascular deaths.

Between 2000 and 2019, there was a 3% increase in age-standardized mortality rates from diabetes. In lower-middle-income countries, the mortality rate due to diabetes increased 13%.

By contrast, the probability of dying from any one of the four main noncommunicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases or diabetes) between the ages of 30 and 70 decreased by 22% globally between 2000 and 2019.

Type 1 diabetes

Type 1 diabetes (previously known as insulin-dependent, juvenile or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin. In 2017 there were 9 million people with type 1 diabetes; the majority of them live in high-income countries. Neither its cause nor the means to prevent it are known.

Symptoms include excessive excretion of urine (polyuria), thirst (polydipsia), constant hunger, weight loss, vision changes, and fatigue. These symptoms may occur suddenly.

Type 2 diabetes

Type 2 diabetes (formerly called non-insulin-dependent, or adult-onset) results from the body's ineffective use of insulin. More than 95% of people with diabetes have type 2 diabetes. This type of diabetes is largely the result of excess body weight and physical inactivity.

Symptoms may be similar to those of type 1 diabetes but are often less marked. As a result, the disease may be diagnosed several years after onset, after complications have already arisen.

Until recently, this type of diabetes was seen only in adults but it is now also occurring increasingly frequently in children.

Gestational diabetes

Gestational diabetes is hyperglycemia with blood glucose values above normal but below those diagnostics of diabetes. Gestational diabetes occurs during pregnancy. Women with gestational diabetes are at an increased risk of complications during pregnancy and at delivery. These women and possibly their children are also at increased risk of type 2 diabetes in the future.

Gestational diabetes is diagnosed through prenatal screening, rather than through reported symptoms.

Impaired glucose tolerance and impaired fasting glycaemia

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate conditions in the transition between normality and diabetes. People with IGT or IFG are at high risk of progressing to type 2 diabetes, although this is not inevitable.

Efficacy

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. In general, the reduction in glycated hemoglobin (HbA1c) with insulin glargine was similar to that with NPH insulin.

Clinical Studies in Adult and Pediatric Patients with Type 1 Diabetes

Adult Patients with Type 1 Diabetes

In two clinical studies (Studies A and B), adult 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 years. The majority of patients were White (99%) and 56% were male. The mean BMI was approximately 24.9 kg/m^2. The mean duration of diabetes was 16 years.

In Study B, the average age was 39 years. The majority of patients were White (95%) and 51% were male. The mean BMI was approximately 25.8 kg/m^2. The mean duration of diabetes was 17 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 years. The majority of patients were White (97%) and 51% were male. The mean BMI was approximately 25.6 kg/m^2. The mean duration of diabetes was 19 years.

In these 3 adult studies, insulin glargine and NPH insulin had similar effects on HbA1c with a similar overall rate of severe symptomatic hypoglycemia.

Table 1: Type 1 Diabetes Mellitus – Adults						
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 study 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

Pediatric Patients with Type 1 Diabetes

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 (97%) and 52% were male. The mean BMI was approximately 18.9 kg/m^2. The mean duration of diabetes was 5 years. Similar effects on HbA1c were observed in both treatment groups.

Table 2: Type 1 Diabetes Mellitus – Pediatric Patients		
Treatment duration **Treatment in combination with**	**Study D** **28 weeks** **Regular insulin**	
	Insulin Glargine + Regular insulin	**NPH + Regular insulin**

Table 2: Type 1 Diabetes Mellitus – Pediatric Patients		
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

Clinical Studies in Adults with Type 2 Diabetes

In a randomized, controlled clinical study (Study E) in 570 adults with type 2 diabetes, insulin glargine was evaluated for 52 weeks in combination with oral antidiabetic medications (a sulfonylurea, metformin, acarbose, or combinations of these drugs). The average age was 60 years old. The majority of patients were White (93%) and 54% were male. The mean BMI was approximately 29.1 kg/m^2. The mean duration of diabetes was 10 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. The rate of severe symptomatic hypoglycemia was similar in insulin glargine and NPH insulin treated patients.

In a randomized, controlled clinical study (Study F), in adult 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 years. The majority of patients were White (81%) and 60% were male. The mean BMI was approximately 30.5 kg/m^2. The mean duration of diabetes was 14 years. Insulin glargine had similar effectiveness as either once- or twice daily NPH insulin in reducing HbA1c and fasting glucose with a similar incidence of hypoglycemia.

In a randomized, controlled clinical study (Study G), adult 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 dosage 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 dosage that was 80% of the total previous NPH insulin dosage. 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 dosages to a target fasting plasma glucose ≤100 mg/dL. After the insulin glargine or NPH insulin dosage was adjusted, other antidiabetic agents, including premeal insulin were to be adjusted or added. The average age was 55 years. The majority of patients were White (85%) and 54% were male. The mean BMI was approximately 34.3 kg/m^2. The mean duration of diabetes was 11 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. The incidences of severe symptomatic hypoglycemia were similar between groups.

Table 3: Type 2 Diabetes Mellitus - Adults

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

Table 3: Type 2 Diabetes Mellitus - Adults						
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**
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)

Additional Clinical Studies in Adults with Diabetes Type 1 and Type 2

Different Timing of Insulin Glargine Administration in Diabetes Type 1 and Diabetes Type 2

The safety and efficacy of once daily insulin glargine administered either at pre-breakfast, pre-dinner, or at bedtime were evaluated in a randomized, controlled clinical study in adult patients with type 1 diabetes (Study H; n=378). Patients were also treated with insulin lispro at mealtime. The average age was 41 years. All patients were White (100%) and 54% were male. The mean BMI was approximately 25.3 kg/m^2. The mean duration of diabetes was 17 years.

Insulin glargine administered at pre-breakfast or at pre-dinner (both once daily) resulted in similar reductions in HbA1c compared to that with bedtime administration. In these patients, data are available from 8-point home glucose monitoring. The maximum mean blood glucose was observed just prior to insulin glargine injection regardless of time of administration. In this study, 5% of patients in the insulin glargine-breakfast group discontinued treatment because of lack of efficacy. No patients in the other two groups (pre-dinner, bedtime) discontinued for this reason.

The safety and efficacy of once daily 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 antidiabetic therapy. All patients in this study also received glimepiride 3 mg daily. The average age was 61 years. The majority of patients were White (97%) and 54% were male. The mean BMI was approximately 28.7 kg/m^2. The mean duration of diabetes was 10 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.

Table 4: Study of Different Times of Once Daily Insulin Glargine 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 Before Breakfast	**Insulin Glargine Before Dinner**	**Insulin Glargine Bedtime**	**Insulin Glargine Before 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

Table 4: Study of Different Times of Once Daily Insulin Glargine 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 Before Breakfast	Insulin Glargine Before Dinner	Insulin Glargine Bedtime	Insulin Glargine Before Breakfast	Insulin Glargine Bedtime	NPH Bedtime
Mean change from baseline	-0.2	-0.1	0.0	-1.3	-1.0	-0.8
Basal insulin dose (Units)						
Baseline mean	22	23	21	19	20	19
Mean change from baseline	5	2	2	11	18	18
Total insulin dose (Units)	--	--	--	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.

Progression of Retinopathy Evaluation in Adults with Diabetes Type 1 and Diabetes Type 2
Insulin glargine was compared to NPH insulin in a 5-year randomized clinical study 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 prespecified 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 5 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. In this study, the numbers of retinal adverse events reported for insulin glargine and NPH insulin treatment groups were similar for adult patients with type 1 and type 2 diabetes.

Table 5: 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 of Major Cardiovascular Outcomes in Patients with Established CV Disease or CV Risk Factors

The Outcome Reduction with Initial Glargine Intervention study (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 (CV) outcomes in 12,537 adults ≥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 CV disease or CV risk factors at baseline.

The objective of the study was to demonstrate that insulin glargine use could significantly lower the risk of major CV outcomes compared to standard care. There were two coprimary composite CV endpoints:

- The first coprimary endpoint was the time to first occurrence of a major adverse CV event defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke.
- The second coprimary 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.

Patients 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 patients were 75 years of age or older. The majority of patients 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 patients 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 the patients had had a prior CV event and 39% had documented coronary artery disease or other CV risk factors.

Vital status was available for 99.9% and 99.8% of patients randomized to insulin glargine and standard care respectively at end of study. 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 study was 6.5% and 6.8% in the insulin glargine and standard care group respectively. The median dose of insulin glargine at end of study 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 CV outcomes was similar between groups (*see* Table 6). All-cause mortality was also similar between groups.

Table 6: Cardiovascular Outcomes in ORIGIN in Patients with Established CV Disease or CV Risk Factors – 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 study, the overall incidence of cancer (all types combined) or death from cancer (Table 7) was similar between treatment groups.

Table 7: 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)

Adverse reactions commonly associated with insulin glargine products include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema, and weight gain.

Safety

ADVERSE EVENTS

The data in Table 8 reflect the exposure of 2327 patients with type 1 diabetes to insulin glargine or NPH in Studies A, B, C, and D. The type 1 diabetes population had the following characteristics: Mean age was 39 years. Fifty-four

percent were male, 97% were Caucasian, 2% were Black or African American and 3% were Hispanic. The mean BMI was 25.1 kg/m^2.

The data in Table 9 reflect the exposure of 1563 patients with type 2 diabetes to insulin glargine or NPH in Studies E, F, and G. The type 2 diabetes population had the following characteristics: Mean age was 59 years. Fifty-eight percent were male, 87% were Caucasian, 8% were Black or African American and 9% were Hispanic. The mean BMI was 29.2 kg/m^2.

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

Table 8: Adverse Reactions Occurring ≥5% in Pooled Clinical Studies up to 28 Weeks Duration in Adults with Type 1 Diabetes

	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 9: Adverse Reactions Occurring ≥5% in Pooled Clinical Studies up to 1 Year Duration in Adults with Type 2 Diabetes

	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 10: Adverse Reactions Occurring ≥10% in a 5-Year Study of Adults with Type 2 Diabetes

	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

Table 10: Adverse Reactions Occurring ≥10% in a 5-Year Study of Adults with Type 2 Diabetes		
	Insulin Glargine, % (n=514)	NPH, % (n=503)
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 11: Adverse Reactions Occurring ≥5% in a 28-Week Clinical Study in Pediatric Patients with Type 1 Diabetes		
	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 was the most commonly observed adverse reaction in patients treated with insulin glargine. Below tables summarize the incidence of severe hypoglycemia in insulin glargine clinical studies. 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 study and ≤36 mg/dL in the ORIGIN study) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

Percentages of insulin glargine-treated adult patients who experienced severe symptomatic hypoglycemia in the insulin glargine clinical studies were comparable to percentages of NPH-treated patients for all treatment regimens. In the pediatric clinical study, pediatric patients with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult studies with type 1 diabetes.

Table 12: 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 13: 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 14: Severe Symptomatic Hypoglycemia in the ORIGIN Study		
	ORIGIN Study 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.

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 insulin including insulin glargine products and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Hypersensitivity Reactions

Local Reactions

Patients taking insulin glargine experienced injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. In clinical studies in adult patients, there was a higher incidence of injection site pain in insulin glarginetreated 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 Reactions

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

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 clinical studies of insulin glargine, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

WARNINGS & PRECAUTIONS

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.

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 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. 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.

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) or in patients who experience recurrent hypoglycemia. The long-acting effect of insulin glargine products may delay recovery from 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 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.Patients with renal or hepatic impairment may be at higher risk of hypoglycemia.

Risk Mitigation Strategies for 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.

Hypoglycemia Due to 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.

Hypersensitivity 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.

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).

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.

CONTRAINDICATIONS

- During episodes of hypoglycemia.
- Hypersensitivity to insulin glargine products or any of the excipients in Rezvoglar™.

Clinical Pharmacology

MECHANISMS 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.

Dose & Administration

ADULTS

- Administer Rezvoglar™ subcutaneously once daily at any time of day but at the same time every day.
- Individualize and adjust the dosage of Rezvoglar™ based on the patient'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.
- In patients with type 1 diabetes, Rezvoglar™ must be used concomitantly with short-acting insulin.

Recommended Starting Dosage in Patients with Type 1 Diabetes

The recommended starting dosage of Rezvoglar™ in patients with type 1 diabetes is approximately one-third of the total daily insulin requirements. Use short-acting, premeal insulin to satisfy the remainder of the daily insulin requirements.

Recommended Starting Dosage in Patients with Type 2 Diabetes

The recommended starting dosage 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.

Switching to Rezvoglar™ from Other Insulin Therapies

Dosage adjustments are recommended to lower the risk of hypoglycemia when switching patients to Rezvoglar™ from other insulin therapies. When switching from:

- Once-daily insulin glargine, 300 units/mL, to once-daily Rezvoglar™ (100 units/mL), the recommended starting Rezvoglar™ dosage is 80% of the insulin glargine, 300 units/mL dosage that is being discontinued.
- Once-daily NPH insulin to once-daily Rezvoglar™, the recommended starting Rezvoglar™ dosage is the same as the dosage of NPH that is being discontinued.
- Twice-daily NPH insulin to once-daily Rezvoglar™, the recommended starting Rezvoglar™ dosage is 80% of the total NPH dosage that is being discontinued.

PEDIATRICS

The dosage recommendation in pediatric patients (age 6 to 15 years) with type 1 diabetes is the same as that described for adults.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 100 units/mL (U-100) available as: 3 mL single-patient-use Rezvoglar™ KwikPen prefilled pen.