Insulin Glargine U-300 (Toujeo)

National Drug Monograph

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Indication(s) Under Review	Long-acting human insulin analog to improve glycemic control in patients with type 2 diabetes.
Dosage Form(s) Under Review	300 units/mL insulin glargine in 1.5mL SoloStar disposable prefilled pen
REMS	☐ REMS ☒ No REMS *See Other Considerations for additional REMS information*

Executive Summary	
Efficacy	The 6 month EDITION trials found glargine-300 (Gla-300) to be non-inferior to glargine-100 (Gla-100).
Safety	Concern for dosing errors Confusion with Gla-100 (although label colors are different for the 2 products) Maximum glucose lowering effect of Gla-300 may take 5 days to fully manifest and the first dose may be insufficient to cover metabolic needs in the first 24 hours of use. Several categories of hypoglycemia were assessed. In general there was a tendency towards less hypoglycemia with Gla-300 (in some cases statistical significance was shown) than Gla-100.
Other Considerations	• Gla-300 has not been studied in patients with insulin resistance (e.g., total daily insulin dose >200U/d) • Not intended as a replacement for those requiring U500 insulin • Is administered via disposable prefilled Solostar pen • **Up to 80 units per injection can be administered. If a single dose exceeds 80 units, additional injection(s) will be needed (same as Gla-100)** • Appears to last a few hours longer than Gla-100 based on pharmacokinetic/pharmacodynamics studies • Patients will require a higher dose of Gla-300 to achieve glycemic control similar to Gla-100. In the T2DM EDITION trials, patients receiving Gla-300 required 11-15% more basal insulin than those receiving Gla-100. In the T1DM trial, the Gla-300 group required 17.5% more basal insulin than the Gla-100 group.

Background

Purpose for Review	The purpose of this monograph is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating insulin glargine U-300 (Gla-300) for possible addition to the VA National Formulary

Other Therapeutic Options

Formulary Alternatives	Other Considerations
Insulin glargine 100 units/mL* Insulin detemir* NPH insulin *VISNs can choose either as a preferred agent	Significantly lower cost than Gla-300
Non-formulary Alternatives	**Other Considerations**
U-500	Does not have a dedicated syringe or pen device; TB syringe (recommended by ISMP) or U-100 syringe is used Extensive patient training needed on how to properly draw up dose Potential for syringe-related dosing errors Requires 2 or more injections per day Can be used in an insulin pump U-500 behaves like basal and prandial insulin, so it is the sole source of exogenous insulin for the patient

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to July 16, 2015) using the search term insulin glargine 300. The search was limited to studies performed in humans and published in the English language.

Review of Efficacy

The FDA approval of Gla-300 was based on the phase 3a EDITION program which includes 3 randomized, open-label trials in patients with T2DM and 1 trial in those with T1DM. Trials were 6 months in duration + 6 month extensions (2 trials have 12-month data published). Of the T2DM trials, 2 were add-on to oral agents and the other was add-on to mealtime insulin ± metformin (**Table 1).** There are also 2 smaller trials (JP-1 and JP-2) conducted in Japanese patients (**Table 2**).

The primary outcome was change in A1C from baseline. The trials were designed to show non-inferiority versus Gla-100. If non-inferiority criteria were met, testing for superiority was conducted.

General **inclusion criteria:**

- EDITION 1: T2DM, age ≥18 years, A1C 7.0-10%, use of Gla-100 or NPH ≥42 units/day + mealtime insulin analog ± metformin for ≥1 year
- EDITION 2: T2DM, age ≥18 years, A1C 7.0-10% , use of Gla-100 or NPH ≥42 units/day + OADs for ≥1 year
- EDITION 3: T2DM, age ≥18 years, A1C 7.0-11%, used oral glucose medications for ≥ 6months; insulin naïve
- EDITION 4: T1DM > 1 year, age ≥18 years, use of any mealtime insulin analog ≥ 3 months, A1C 7-10%

Baseline characteristics of patients in EDITION 1-3 were mean A1C 8.3%, age 59 years, 53% male, weight 100kg, BMI 35 kg/m^2, duration of diabetes 13 years, 81% used metformin, 22% sulfonylureas, and DPP-4 inhibitors 10%.

Baseline characteristics of patients in EDITION 4 were A1C 8.1%, age 47.3 years, 57% male, weight 81.8kg, BMI 27.6 kg/m^2, duration of diabetes 21 years, 73.4% used glargine, 14% detemir, 2.7% NPH, 13% on twice daily basal insulin.

Dosing of study drug

In EDITIONS 1 and 2, patients previously receiving once daily glargine or NPH started the same dose used prior to randomization. Those receiving prior twice daily NPH had their study drug dose reduced by approximately 20%. The same held for EDITION 4 except that patients previously receiving detemir could be enrolled; dosing of study drug was handled same as those on prior NPH.

In EDITIONS 1-3, study drug was administered in the evening (from before the evening meal until bedtime) at the same time each day for each individual patient. In EDITION 4, the injection was administered either in the morning between pre-breakfast and pre-lunch or evening (same as in EDITION 1-3).

Study drug was adjusted once weekly to a pre-breakfast SMBG goal of 80-100mg/dl based on the median of the previous 3 days. Adjustments for both groups were restricted to changes divisible by 3 units, the smallest adjustment possible for Gla-300 due to the characteristics of the pen injector. Split dosing of study drug was given for those requiring >80 U of Gla-100 or >180U of Gla-300 (EDITION 1) and >80 U of Gla-100 or >90U of Gla-300 (EDITION 3).

Mealtime insulin was administered in EDITION 1 and 4. Mealtime insulin doses were adjusted at the discretion of the investigator after optimizing the basal dose (EDITION 1). In EDITION 4, the prestudy dose was used and titrated to a 2-h postprandial SMBG goal of <160mg/dL while avoiding hypoglycemia.

Oral antiglycemic medication use was as follows: In EDITION 1, metformin was continued at prestudy dose. In EDITION 2, OADs were continued at prestudy dose; prior SUs were discontinued. In EDITION 3, OADs were continued prestudy dose; prior SUs, meglitinides, and agents not approved for combination with insulin were discontinued.

Rescue treatment was allowed in EDITION 2 and 3 at the investigators discretion.

Glycemic Efficacy

EDITION 1-4 Trials (Table 1): In the 6-month EDITION trials, Gla-300 was found to be noninferior to Gla-100 in reducing A1C. However, the 12-month data for EDITION 1 showed significantly greater reduction in A1C with Gla-300 than Gla-100 (0.86% vs. 0.69. Patients will require a higher dose of Gla-300 to achieve glycemic control similar to Gla-100. In the T2DM EDITION trials, patients receiving Gla-300 required 11-15% more basal insulin than those receiving Gla-100. In the T1DM trial, the Gla-300 group required 17.5% more basal insulin than the Gla-100 group. The dose of rapid acting insulin was similar between the 2 groups. Change in fasting glucose was similar between Gla-300 and Gla-100.

Japanese Trials (Table 2): In JP-1, patients with T1DM were randomized to Gla-300 or Gla-100 in addition to rapid acting insulin. In JP-2, patients with T2DM were randomized to Gla-300 or Gla-100 in addition to their usual oral agents. There was no significant difference in change in A1C between the 2 treatment groups.

Treatment Satisfaction

There was no difference in treatment satisfaction between Gla-300 and Gla-100.

Table 1: Selected Outcomes in the EDITION Trials (Glycemic Improvement, Insulin Dose, Weight)

	EDITION 1 (Type 2) 6-month data		EDITION 1 (Type 2) 12-month data		EDITION 2 (Type 2) 6-month data		EDITION 2 (Type 2) 12-month data		EDITION 3 (Type 2) 6-month data		EDITION 4 (Type 1) 6-month data	
	Gla-300 + RAI ±MET	Gla-100+ RAI ±MET	Gla-300 + RAI ±MET	Gla-100+ RAI ±MET	Gla-300 + OHA	Gla-100+ OHA	Gla-300 + OHA	Gla-100+ OHA	Gla-300 + OHA	Gla-100+ OHA	Gla-300 + RAI	Gla-100+ RAI
n	404	403	404	402	403	405	403	405	432	430	274	275
DM therapy at screening	Basal +mealtime insulin ±MET		Basal +mealtime insulin ±MET		Basal insulin +OHAs		Basal insulin +OHAs		Insulin naïve +OHAs		Basal +mealtime insulin	
Baseline A1C (%)	8.15	8.16	8.15	8.16	8.3	8.3	8.3	8.3	8.5	8.6	8.1	8.1
Δ A1C (%)	-0.83	-0.83	-0.86*	-0.69	-0.57	-0.56	Mean tx diff -0.06% [95% CI -0.22, 0.10]		-1.42	-1.46	-0.42	-0.44
A1C<7% (%)	39.6	40.9	-	-	30.6	30.4	NS	NS	43.1	42.1	16.8	15
Baseline FPG (mg/dL)	157	160	157	160	148	142	148	142	179	184	186	199
Δ FPG (mg/dL)	-23	-25	-29.6	-26.0	-18	-22	Mean tx diff 0.18mg/dL [-0.22, 0.57]		-61.4	-68.4	-17	-20
Rescue (%)	NA	NA	NA	NA	5.7	4.9	8.2	10.1	3.0	2.0	NA	NA
Basal dose U/kg/d (U/d)												
Baseline	0.67 (70)	0.67 (70.3)			0.66(64.1)	0.68 (65.7)			NA	NA	0.38	0.37
Final	0.97 (103)	0.88 (94)	1.03 (NS)	0.90 (NS)	0.92 (91)	0.84 (82)	0.97	0.87	0.62 (59.4)	0.53 (52)	0.47	0.40
Mealtime dose (U/kg/d)												
Baseline	0.54	0.54			NA	NA	NA	NA	NA	NA	0.34	0.33
Final	0.55	0.55	0.55	0.56							0.33	NS
Baseline weight (kg)	106.2	106.4	106.2	106.4	98.7	98.0	98.7	98.0	95.1	95.6	81.9	81.8
Δ Weight (kg)	0.9	0.9	1.2	1.4	0.08*	0.66	0.4*	1.2	0.49	0.71	0.51*	1.06

Abbreviations: FPG=fasting plasma glucose; Gla=glargine; MET=metformin; NA=not applicable; NS=not shown; OHA=oral hypoglycemic agent; RAI=rapid-acting insulin analog; sx=symptomatic; TDI=total daily insulin

*Significant vs. Gla-100

Table 2: A1C, Weight, and Insulin Dose in the JP Trials

	JP-1 (Type 1)		JP-2 (Type 2)	
	Gla-300+RAI	Gla-100+ RAI	Gla-300 + OHA	Gla-100+ OHA
n	121	122	120	121
Baseline A1C (%)	8.1	8.1	8.0	8.1
Δ A1C (%)	-0.30	-0.43	-0.45	-0.55
A1C<7% (%)	15.6	20	25	24.2
Final total insulin dose (U/kg/day)	0.79	0.74	0.35	0.30
Weight (kg)	-0.1	0.4	-0.62	0.37

Table 3: Hypoglycemia (EDITION 1-4)

	EDITION 1 (Type 2) 6-month data		EDITION 1 (Type 2) 12-month data		EDITION 2 (Type 2) 6-month data		EDITION 2 (Type 2) 12-month data		EDITION 3 (Type 2) 6-month data		EDITION 4 (Type 1) 6-month data	
	Gla-300 + RAI ±MET	Gla-100+ RAI ±MET	Gla-300 + RAI ±MET	Gla-100+ RAI ±MET	Gla-300 + OHA	Gla-100+ OHA	Gla-300 + OHA	Gla-100+ OHA	Gla-300 + OHA	Gla-100+ OHA	Gla-300 + RAI	Gla-100+ RAI
n	404	403	404	402	403	405	403	405	432	430	274	275
Hypoglycemia % (E/pt-yr)												
Any	83.4 (26.37)	88.6 (28.08)	NS	NS	71.5* (14.37)	79.3 (18.96)	79.9 (11.87)	83.0 (13.70)	NS	NS	NS	NS
Documented sx ≤70	70 (13.48)	77.9 (14.76)	74.8* (12.07)	82.8 (11.7)	49.6* (6.76)	57.4 (8.11)	58.8 (5.71)	63.3 (5.74)	30.6 (2.33*)	35.8 (3.76)	85 (NS)	83.6 (NS)
Documented sx ≤54	37.4 (2.43)	41.5 (2.65)	46 (2.19)	50.7 (2.08)	20.6 (1.11)	26.8 (1.46)	27.5 (0.92)	29.8 (0.94)	7.6* (0.24)	13.9 (0.45)	69 (NS)	69.8 (NS)
Severe	5.0 (0.27)	5.7 (0.24)	6.7 (0.19)	7.5 (0.14)	1.0 (0.03)	1.5 (0.06)	1.7 (0.03)	1.5 (0.03)	0.9 (0.02)	0.9 (0.02)	6.6 (NS)	9.5 (NS)
Asymptomatic ≤70	63.1 (11.39)	68.2 (11.24)	70.5 (9.75)	73.4 (8.79)	NS	NS	NS	NS	NS	NS	NS	NS
Confirmed ≤70 or severe	81.9 (25.48)	87.8 (26.76)	85.9* (22.34)	91.5 (20.99)	70* (14.01)	77.3 (18.14)	78.4 (11.60)	82.0 (13.18)	46.2 (6.41*)	52.5 (8.50)	93.1(78.4)	93.5 (72.5)
Nocturnal Hypoglycemia % (E/pt-yr)												
Any	45.3 (3.32)	59.7 (4.57)	NS	NS	30.5* (1.98)	41.6 (3.95)	39.7 (1.80*)	46.1 (2.94)	NS	NS	NS	NS
Documented sx ≤70	35.9 (1.92)	48.3 (3.22)	44.6* (1.83*)	57.2 (2.49)	22.6* (1.25)	31.0 (2.30)	29.5 (1.17)	34.2 (1.60)	12.4 (0.76)	15.5 (0.84)	59.1 (NS)	57.8 (NS)
Documented sx ≤54	12.1 (0.46)	16.9 (0.64)	19.8 (0.47)	22.9 (0.51)	8.2 (0.27)	11.6 (0.57)	12.7 (0.27)	13.3 (0.37)	3.2 (0.10)	6.4 (0.18)	40.9 (NS)	38.9 (NS)
Severe	2.0 (0.06)	2.5 (0.08)	2.5 (0.04)	3.2 (0.05)	0 (0)	0.5 (0.01)	0.2 (0.00)	0.5 (0.01)	0 (0)	0 (0)	2.2 (NS)	2.5 (NS)
Asymptomatic ≤70	20.8 (1.10)	25.4 (0.88)	29.2 (0.97)	31.1 (0.63)	NS	NS	NS	NS	NS	NS	NS	NS
Confirmed ≤70 or severe	44.6 (3.13)	57.5 (4.20)	54.5* (2.88)	64.7 (3.19)	28.3* (1.89)	39.9 (3.68)	37.5* (1.74*)	44.6 (2.77)	17.9* (1.31)	23.5 (1.34)	68.6 (8.0)	70.2 (8.9)

Abbreviations: Gla=glargine; MET=metformin; NS=not shown; OHA=oral hypoglycemic agent; RAI=rapid-acting insulin analog; sx=symptomatic
*Significant vs. Gla-100

Definitions of hypoglycemia:
Any hypoglycemia: events whether confirmed by SMBG or not and whether symptomatic or asymptomatic
Documented symptomatic= symptomatic event with SMBG ≤70 or ≤54mg/dL
Severe=events requiring assistance by another person to administer carbohydrate, glucagon, or other therapy
Asymptomatic= asymptomatic event with SMBG ≤70mg/dL
Confirmed or severe= documented symptomatic or asymptomatic events + severe events

Potential Off-Label Use

None

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	None
Contraindications	• During episodes of hypoglycemia • Hypersensitivity to insulin glargine or its excipients
Warnings/ Precautions	Never share glargine 300 Solostar pen between patients even if the needle is changed Hypoglycemia or hypoglycemia with changes in insulin regimen: The onset of action of Gla-300 develops over 6 hours. The full glucose lowering effect may not be seen for at least 5 days. Patients who were changed to Gla-300 from other basal insulins had a higher average fasting plasma glucose levels in the first weeks of therapy compared to those who were switched toGla-100. Higher doses of Gla-300 were needed to achieve similar levels of glucose control compared to Gla-100 Medication Errors: Potential for mix-up between different types of insulin. Instruct patients to always check the insulin label before each injection As with other insulin products, there is a risk for hypersensitivity and allergic reactions, hypokalemia, and fluid retention/heart failure with concomitant use of thiazolidinediones.
Safety Considerations	*Hypoglycemia* Overall and nocturnal hypoglycemia as percentage of patients experiencing ≥ 1 event and annualized rates was assessed according to several predefined categories (**Table 3**). In general there was a tendency towards less hypoglycemia with Gla-300, with some cases being statistically significant, than Gla-100. It has been speculated that the smoother pharmacokinetic and pharmacodynamics profile of Gla-300 may explain the lower risk of hypoglycemia. A main secondary endpoint for EDITIONS 1-3 was the percentage of patients with one or more confirmed (≤70mg/dL) nocturnal or severe nocturnal hypoglycemic events from **week 9 to month 6** (**Table 4**). In EDITION 1 and 2, Gla-300 resulted in significantly fewer episodes compared to Gla-100; the difference in EDITION 3 was not significant.

Table 4: Confirmed (≤70mg/dL) Nocturnal or Severe Nocturnal Hypoglycemic Events (week 9 to month 6)

	EDITION 1	EDITION 2	EDITION 3
Gla-300 %(E/pt-yr)	36.1 (2.97)	21.6 (1.94)	16 (NS)
Gla-100 %(E/pt-yr)	45.8 (4.05)	27.9 (3.19)	17 (NS)
RR [95%CI] Based on % pts	0.79 [0.67, 0.93]*	0.77 [0.61, 0.99]*	0.89 [0.66, 1.20]

*significant vs. Gla-100

%= percentage of patients experiencing ≥ 1 event; NS=not shown; RR=relative risk

Cardiovascular Safety

No trials have been conducted with Gla-300. A cardiovascular outcomes trial (ORIGIN) has been conducted with Gla-100 compared to standard of care evaluating time to first occurrence of a major adverse cardiovascular event (MACE). MACE was defined as the composite of CV death, nonfatal MI, and nonfatal stroke. The incidence of MACE was similar between Gla-100 and standard of care HR=1.02 [95%CI 0.94, 1.11]. It is unknown whether the results from this trial can be applied to

Gla-300.

Malignancy
There were concerns that Gla-100 might predispose to cancer. The ORIGINS trial showed that the hazards ratio of cancer and death from cancer were 0.99[95%CI 0.88, 1.11] and 0.94 [95%CI 0.77, 1.15] respectively. It is unknown whether the results from this trial can be applied to Gla-300.

Injection site reactions
In EDITION 1-3, injection site reactions were reported in 2.4% and 3.1% of patients receiving Gla-300 and Gla-100 respectively. However, 12-month data from EDITION 1 reported injection site reactions in 3% of Gla-300 and 1.5% of Gla-100 patients whereas the 12 month data from EDITION 2, the incidence was 1.2% and 3.0% respectively. In EDITION 4, injection site reactions were reported in 2.2% and 1.5% patients respectively.

Immunogenicity
Anti-insulin antibodies were similar between Gla-300 and Gla-100 across the EDITION 1-4 trials.

Weight
Mean weight change in a pooled analysis of the 3 T2DM trials was 0.51kg and 0.79kg for Gla-300 and Gla-100 respectively. Treatment difference -0.28 [95%CI -0.55, -0.01], p=0.039. The 12-month data for EDITION 1-2 continued to show less weight gain with Gla-300 (statistically significant in EDITION 2). In EDITION 4, there was significantly less weight gain with Gla-300 than Gla-100 (0.51kg and 1.06kg respectively). **Table 1**

The JP trials showed a slight decrease in mean weight with Gla-300 and a slight increase in weight with Gla-100 (**Table 2**).

Adverse Reactions

Common adverse reactions

Common AEs, defined as reactions occurring in ≥5% of the population were nasopharyngitis and upper respiratory tract infection.

Table 5: Adverse Events Occurring in ≥5% of the Population

	T2DM (n=1,242)	T1DM (n=304)
Nasopharyngitis	7.1	12.8
Upper Respiratory Tract Infection	5.7	9.5

Death/Serious adverse reactions (SAE)

None of the deaths were considered to be related to study drug. There was no discussion on whether any of the SAEs were thought to be related to study drug.

Table 6: Deaths and Serious Adverse Events

		EDITION 1 6 month	EDITION 1 12 month	EDITION 2	EDITION 2 12 month	EDITION 3	EDITION 4
Deaths * (n)	Gla-300	1	2	2	4	1	1
	Gla-100	2	4	0	2	0	0
SAE (%)	Gla-300	6.4	13	3.7	7.4	6.0	6.2
	Gla-100	5.2	15	3.7	7.4	6.0	8.0

*In EDITION 1, 3 additional deaths occurred after treatment discontinuation

Discontinuations due to adverse reactions

Table 7: Discontinuations from Study due to Adverse Events

		EDITION 1 6 month	EDITION 1 12 month	EDITION 2	EDITION 2 12 month	EDITION 3	EDITION 4
D/C due to AE (%)	Gla-300	1.5	2.2	1.5	2.7	1.0	1.1
	Gla-100	1.7	3.5	1.0	1.7	1.0	1.1

Drug Interactions

Drug-drug interactions	Same as those reported for the insulin class
Drug-food interactions	None
Drug-lab interactions	None

Risk Evaluation

As of May 2015

Sentinel event advisories	! The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used. Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Insulin glargine 300 units/mL	Insulin glulisine	None	None	Insulin glargine 100 units/mL Insulin aspart (VA LASA list)
Toujeo Solostar	None	None	None	Tyvaso Forteo

Other Considerations

Storage

Unopened pens should be stored in a refrigerator (36-46°F). Open (in-use) pens should be kept at **room temperature** away from direct heat and light. The pen must be discarded 28 days after being opened.

Pharmacokinetics/Pharmacodynamics

In a randomized, double-blind, crossover study, the pharmacokinetics and pharmoacodynamics of Gla-300 and Gla-100 were compared in patients with T1DM (n=18) using euglycemic clamp method. Patients received 0.4 units/kg of either drug for 8 days and were crossed-over to the other drug for an additional 8 days. Assessments were made under steady state conditions. There was less swing in insulin concentration over 24 hours and longer duration of action (approximately 5 h) with Gla-300 than Gla-100.

Dosing and Administration

- Insulin naïve T1DM: approximately 1/3-1/2 of the total daily insulin dose given as Gla-300. As a general rule, 0.2 to 0.4units/kg can be used to calculate initial daily dose. The maximum glucose lowering effect of Gla-300 may take 5 days to fully manifest and the first dose may be insufficient to cover metabolic needs in the first 24 hours of use.
- Insulin naïve T2DM: recommended starting dose is 0.2 Units/kg once daily. The dose of other anti-diabetic drugs may need to be adjusted to minimize risk of hypoglycemia

- T1DM or T2DM already on insulin therapy: The starting dose of Gla-300 can be the same as the patient's once daily long-acting dose. Patients previously receiving Gla-100 will need a higher dose of Gla-300 to maintain the same level of glycemic control.

When changing patients from twice daily NPH to once daily Gla-300, recommend started Gla-300 at 80% of the total daily NPH dose

- The dosage of Gla-300 ranges from 1 to 80 units per one injection
- The dose of Gla-300 should be titrated no more frequently than every 3-4 days

Special Populations (Adults)

	Comments
Elderly	9.8% and 26.3% of the studied population with T1DM and T2DM respectively were ≥65 years old (2% and 3% respectively were ≥75 years old). There were no overall differences in efficacy and safety between the older and younger age groups.
Pregnancy	There are no clinical studies of the use of Gla-300 in pregnant women. Because animal reproduction studies are not always predictive of human response, Gla-300 should be used in pregnancy during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	Endogenous insulin is found in human milk. It is unknown whether glargine is excreted in human milk; therefore, use Gla-300 with caution. Women who are lactating may require adjustment of their insulin dose.
Renal Impairment	P-kinetics has not been studied in those with renal impairment. Other studies with human insulin have shown increased levels of insulin in patients with renal failure. Frequent glucose monitoring and dosage adjustment may be necessary.
Hepatic Impairment	P-kinetics has not been studied in those with hepatic impairment; may require dosage adjustment.
Pharmacogenetics/genomics	None

Projected Place in Therapy

There is no clear projected place in therapy with Gla-300 over Gla-100. It was hoped that Gla-300 could be used in patients with insulin resistance requiring high daily doses of insulin. However, the Gla-300 and Gla-100 Solostar pens both administer a maximum of 80 units in a single injection; therefore, multiple injections are needed for doses >80 units with either insulin.

Use of Gla-300 should be restricted to endocrinologists, diabetologists, or other locally designated expert.

Glargine-300 might be considered in patients with persistent hypoglycemia only after other interventions have been made to address the hypoglycemia (e.g., dosage adjustment of insulin/DM medications, timing of meals/snacks, exercise, etc.).

Pharmacokinetic/pharmacodynamic studies have shown that Gla-300 has a slightly longer duration of action than Gla-100; however, more research is needed to determine whether these findings provide a clinical benefit. For patients with <24 hour coverage with Gla-100 a trial of Gla-300 might be considered on a case-by-case basis after consideration for split dosing or other interventions are given.

References

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Prepared by Deb Khachikian, PharmD