PDL DRUG REVIEW

Proprietary Name: Tresiba® FlexTouch
Common Name: insulin degludec injection
PDL Category: Insulins

Comparable Products	Preferred Drug List Status
Lantus SoloSTAR	Preferred with Conditions
Levemir FlexTouch	Preferred with Conditions

Summary

Pharmacology/Usage: Insulin degludec injection is a long-acting basal human insulin analog. It differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached. Insulin and its analogs lower blood glucose (BG) by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production.

Indication: To improve glycemic control in adults with diabetes mellitus (DM). Tresiba® is not recommended for the treatment of diabetic ketoacidosis.

This is a pregnancy category C medication. The safety and efficacy for use in the pediatric population have not been established.

Dosage Forms: Clear solution for injection: 100U/ml or 200U/ml in a 3ml FlexTouch disposable prefilled pen

Recommended Dosage: Inject Tresiba® subcutaneously (SC) into the thigh, upper arm, or abdomen once daily at any time of the day. Individualize and titrate the dose based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal. The recommended starting dose in insulin naïve patients with type 2 DM is 10U once daily. For patients with type 1 DM, the general rule is 0.2 to 0.4U/kg to calculate the initial total daily insulin dose for insulin naïve patients. If patients are already on insulin therapy, start Tresiba® at the same unit dose as the total daily long or intermediate-acting insulin unit dose.

It is recommended to rotate the sites of injection to reduce the risk of lipodystrophy. Do not dilute or mix Tresiba® with any other insulin products or solutions. Do not perform dose conversion when using the Tresiba® U-100 or U-200 FlexTouch pens. The dose window for both pens shows the number of insulin units to be delivered and no conversion is needed. Do not transfer Tresiba® from the Tresiba® pen to a syringe. Last, Tresiba® should not be administered IV, IM, or in an insulin infusion pump.

While clinically relevant pharmacokinetic differences were not seen when use of Tresiba® was compared between patients with and without hepatic or renal impairment, glucose monitoring should be increased and adjust the Tresiba® dose on an individual basis in this population with hepatic or renal impairment.

Drug Interactions: Drugs that may increase the risk of hypoglycemia include: antidiabetic drugs, ACE-Inhibitors, ARBS, disopyramide, fibrates, fluoxetine, MAO Inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs, sulfonamide antibiotics, GLP-1 receptor agonists, DDP-4 inhibitors, and SGLT2 inhibitors. Dose reductions and increased frequency of glucose monitoring may be needed with concomitant use of any of these drugs and Tresiba®. Drugs that may decrease the blood glucose lowering effect of Tresiba® include: atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens, protease inhibitors, somatropin, sympathomimetic agents, and thyroid hormones. Dose increases and increased frequency of glucose monitoring may be required with concomitant use. Drugs that may increase or decrease the blood glucose lowering effect of Tresiba® include: alcohol, beta-blockers, clonidine, and lithium salts. Dose adjustments and increased frequency of blood glucose monitoring may be required if used concomitantly. Drugs that may blunt signs/symptoms of hypoglycemia include: beta-blockers, clonidine, guanethidine, and reserpine. Increased frequency of glucose monitoring may be required with concomitant use.

Common Adverse Drug Reactions: *There was no placebo data to compare with Tresiba®. Listed % incidence for adverse drug reactions= reported % incidence for drug (Tresiba®) in patients with type 1 DM.* The most frequently reported adverse events included nasopharyngitis (23.9%), upper respiratory tract infection (11.9%), headache (11.8%), sinusitis (5.1%), and gastroenteritis (5.1%).

Hypoglycemia is the most frequently reported adverse reaction of insulin, including Tresiba®. Rates of severe hypoglycemia in a 52 week study of patients on insulin aspart and Tresiba® was 12.3%. Other reported reactions included lipodystrophy (0.3%), injection site reactions (3.8%), weight gain (average of 1.8kg in type 1 DM and an average of 3.0kg in type 2 DM patients), and peripheral edema (0.9% of patients with type 1 DM and 3% of patients with type 2 DM).

Hypokalemia may occur with all insulin products, including Tresiba®. It is recommended to monitor potassium levels in patients at risk for hypokalemia if indicated (e.g. patients taking potassium-lowering medications).

Contraindications: During episodes of hypoglycemia; in patients with hypersensitivity to Tresiba® or one of its excipients

Manufacturer: Novo Nordisk

Analysis: Numerous studies were performed to assess the safety and efficacy of Tresiba® when used in adults with either type 1 (in combination with mealtime insulin) or type 2 DM (in combination with mealtime insulin or in combination with common oral antidiabetic agents. All studies were randomized, open-label studies.

Type 1 DM Studies: There were 3 studies performed to assess the efficacy of Tresiba® in this population. The table below includes specific details of the studies.

Study #	N	Duration of study	Treatment Arms
Study 1	629	52 weeks	Tresiba® QPM + insulin aspart AC vs insulin glargine U100 QD + insulin aspart AC
Study 2	455	26 weeks	Tresiba® + insulin aspart AC vs insulin detemir QPM (or BID after 8W) + insulin aspart AC
Study 3	493	26 weeks	Tresiba® QPM + insulin aspart AC vs Tresiba® at any time QD + insulin aspart AC vs insulin glargine U100 QD + insulin aspart AC

A reduction in HbA1c from baseline to the end of the study was the primary outcome, and results for Study 1 and 2 can be found in the table below.

	Study 1		Study 2	
Outcome	Tresiba®	insulin glargine	Tresiba®	insulin detemir
HbA1c baseline (%)	7.7	7.7	8.0	8.0
HbA1c end of trial (%)	7.3	7.3	7.3	7.3
Adjusted mean change from baseline	-0.36	-0.34	-0.71	-0.61
Estimated treatment difference	-0.01		-0.09	
Proportion achieving HbA1c <7%	39.8%	42.7%	41.1%	37.3%
FPG baseline (mg/dl)	165	174	178	171
FPG end of trial (mg/dl)	141	149	131	161
FPG adjusted mean change from baseline	-27.6	-21.6	-43.3	-13.5

At the end of study 1 and study 2, the difference in HbA1c reduction between Tresiba® and insulin glargine U100 (Study 1) and insulin detemir (Study 2) met the pre-specified non-inferiority margin.

Study 3 included one treatment arm where patients were randomized to Tresiba® taken any time of the day to assess a worst-case scenario injection schedule. In this arm, Tresiba® was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. At the end of the study, the difference in HbA1c reduction from baseline between Tresiba® given at alternating times and insulin glargine U100 was 0.17% and met the pre-specified non-inferiority margin. Please refer to the table below for further results.

Outcome	Tresiba® QPM	Tresiba® alternating	insulin glargine
HbA1c baseline (%)	7.7	7.7	7.7
HbA1c end of trial (%)	7.3	7.3	7.1
Adjusted mean change from baseline	-0.41	-0.40	-0.57
Estimated treatment difference	-	0.17	
Proportion achieving HbA1c <7%	37%	37.2%	40.9%
FPG baseline (mg/dl)	179	173	175
FPG end of trial (mg/dl)	133	149	151
FPG adjusted mean change from baseline	-41.8	-24.7	-23.9

Type 2 DM Studies: There were 6 randomized open-label, multicenter studies to assess the safety and efficacy of Tresiba® as compared to insulin glargine with or without oral antidiabetic medications or as compared to sitagliptin.

Study 4 (52 weeks duration) and Study 5 (26 weeks duration) randomized patients to Tresiba® (study 1) or Tresiba® U200 (study 2) QPM as compared to insulin glargine. Metformin alone or in combination with a DPP-4 inhibitor was used as background therapy in both treatment arms in both studies. All patients were insulin naïve patients. The table below illustrates the results of both studies.

	Study 4 (N=1030)		Study 5 (N=457)	
Outcome	Tresiba® QPM	insulin glargine	Tresiba® U200	insulin glargine
HbA1c baseline (%)	8.2	8.2	8.3	8.2

	Study 4 (N=1030)		Study 5 (N=457)	
Outcome	Tresiba® QPM	insulin glargine	Tresiba® U200	insulin glargine
HbA1c end of trial (%)	7.1	7.0	7.0	6.9
Adjusted mean change from baseline	-1.06	-1.15	-1.18	-1.22
Estimated treatment difference	0.09		0.04	
Proportion achieving HbA1c <7%	51.7%	54.1%	52.2%	55.9%
FPG baseline (mg/dl)	174	174	172	174
FPG end of trial (mg/dl)	106	115	106	113
FPG adjusted mean change from baseline	-68	-60.2	-71.1	-63.5

Study 6 was a 26 week study that included insulin naïve patients (N=453) inadequately controlled on ≥1 oral antidiabetic agents (OADs) at baseline and were then randomized to Tresiba® QPM or insulin glargine U100. Pre-trial OADs were continued as background treatment, except for DPP-4 inhibitors or TZDs. At the end of the 26 week study, the difference in HbA1c reduction from baseline between Tresiba® and insulin glargine was 0.11% and met the pre-specified non-inferiority margin. The adjusted mean change from baseline in HbA1c was -1.42 for the Tresiba® arm as compared with -1.52 with the insulin glargine arm. 40.8% of the Tresiba® arm achieved HbA1c <7% as compared to 48.6% of the insulin glargine group.

Study 7 included patients (N=687) inadequately controlled on basal insulin alone, OADs alone, or both basal insulin and OADs who were randomized to Tresiba® QPM, Tresiba® QD at any time of each day, or insulin glargine U100. Tresiba® in the any time of the day arm was dosed in the morning on Monday, Wednesday, and Friday and in the evening on Tuesday, Thursday, Saturday, and Sunday. Up to 3 OADs (including metformin, sulfonylureas, glinides, or TZDs) were given as background treatment. At the end of week 26, the difference in HbA1c reduction from baseline between Tresiba® at alternating times and insulin glargine was 0.04% and this met the pre-specified non-inferiority margin. The table below illustrates more results of this study.

Outcome	Tresiba® QPM	Tresiba® alternating	insulin glargine
HbA1c baseline (%)	8.4	8.5	8.4
HbA1c end of trial (%)	7.3	7.2	7.1
Adjusted mean change from baseline	-1.03	-1.17	-1.21
Estimated treatment difference	-	0.04	
Proportion achieving HbA1c <7%	40.8%	38.9%	43.9%
FPG baseline (mg/dl)	158	162	163
FPG end of trial (mg/dl)	105	105	112
FPG adjusted mean change from baseline	-54.2	-55.0	-47.5

Study 8 was a 52 week study that included patients (N=992) inadequately controlled on premix insulin, bolus insulin alone, basal insulin alone, OADs alone or any combination thereof who were then randomized to Tresiba® QPM or insulin glargine U100. Insulin aspart was used in each treatment arm before each meal, in addition to up to 2 of the following OADs (metformin or pioglitazone) as background treatment. At week 52, Tresiba® as compared to insulin glargine met the pre-specified non-inferiority margin. The following table illustrates the results.

Outcome	Tresiba® QPM	insulin glargine
HbA1c baseline (%)	8.3	8.4

Outcome	Tresiba® QPM	insulin glargine
HbA1c end of trial (%)	7.1	7.1
Adjusted mean change from baseline	-1.10	-1.18
Estimated treatment difference	0.08	
Proportion achieving HbA1c <7%	49.5%	50.0%
FPG baseline (mg/dl)	166	166
FPG end of trial (mg/dl)	122	127
FPG adjusted mean change from baseline	-40.6	-35.3

Study 9 included patients (N=447) inadequately controlled on ≥1 OAD at baseline and were randomized to Tresiba® QD at any time of the day or sitagliptin QD. In addition, up to 2 of the following OADs (metformin, sulfonylurea, or pioglitazone) were also given as background treatment. At the end of the 26 week study, Tresiba® resulted in a significantly greater reduction in mean HbA1c as compared to sitagliptin (p<0.001). The table below illustrates the results.

Outcome	Tresiba® QD	sitagliptin
HbA1c baseline (%)	8.8	9.0
HbA1c end of trial (%)	7.2	7.7
Adjusted mean change from baseline	-1.52	-1.09
Estimated treatment difference	-0.43	
Proportion achieving HbA1c <7%	40.9%	27.9%
FPG baseline (mg/dl)	170	179
FPG end of trial (mg/dl)	112	154
FPG adjusted mean change from baseline	-61.4	-22.3

Place in Therapy: Tresiba® is a long-acting insulin analog (insulin degludec) indicated for use in adults with type 1 or type 2 DM that is available as a FlexTouch prefilled pen with 2 strengths (100U or 200U). Numerous studies in various patient populations found Tresiba® to be non-inferior to insulin glargine long-acting insulin for HbA1c reduction. Lantus® is a long-acting insulin glargine that is available in a concentration of 100U that is indicated for both adults and children with type 1 DM and in adults with type 2 DM.

There is no evidence at this time to support that Tresiba® FlexTouch is safer or more effective than the currently available, more cost effective medications. It is therefore recommended that Tresiba® FlexTouch remain non-preferred and require prior authorization and be available to the few who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Tresiba [package insert]. Plainsboro, NJ: Novo Nordisk, Inc; 2015.
[2] Lantus [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2015.