Drug Monograph

Drug/Drug Class: **Tresiba™ (insulin degludec) injection / Long-acting Insulin**

Prepared for: MO HealthNet
Prepared by: Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Tresiba™ long-acting insulin comes in 3 mL prefilled insulin pens. It is available in 2 strengths, 100 units/mL and 200 units/mL. Manufacturer: Novo Nordisk, Plainsboro, NJ, 08536
Summary of Findings:	In noninferiority trials, the efficacy of Tresiba™ was evaluated in patients with type 1 or type 2 diabetes mellitus. In patients with type 1 diabetes, when given at the same time each day (N=629) or alternating times of the day (N=493), it was noninferior to insulin glargine, and when given at the same time each day it was noninferior to insulin detemir (N=455). Mean HbA1c reductions ranged from 0.36-0.71% with Tresiba™ and approximately 40% of patients achieved an HbA1c of < 7% across studies. In 5 randomized, open-label studies involving 3601 patients with type 2 diabetes, Tresiba™ administered at the same time each day or at any time of the day was noninferior to insulin glargine for reductions in HbA1c when used as add-on therapy to oral antidiabetic agents and/or insulin. Mean HbA1c reductions ranged from 1.03-1.42% with Tresiba™, and 38.9-52.2% of patients achieved an HbA1c of < 7%. When used as add-on therapy to oral antidiabetic agents in a randomized trial, it significantly reduced mean HbA1c levels (-1.52% vs -1.09%) compared with sitagliptin (N=447). In patients with type 2 diabetes receiving background therapy of Tresiba™ and metformin, additional HbA1c reductions of 0.74% were achieved with add-on liraglutide and 0.39% with add-on insulin aspart (N=177).
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [3]

Approximately 21 million people in the United States have been diagnosed with diabetes according to the Centers for Disease Control and Prevention. Over time, diabetes increases the risk of serious health complications, including heart disease, blindness, nerve and kidney damage. Improvement in blood sugar control can reduce the risk of some of these long-term complications.

Dosage Form(s) [1]

Tresiba™ long-acting insulin comes in 3 mL prefilled insulin pens. It is available in 2 strengths, 100 units/mL of insulin degludec and 200 units/mL of insulin degludec.

Manufacturer [1]

Novo Nordisk, Plainsboro, NJ, 08536

Indication(s) [1]

Tresiba™ is indicated to improve glycemic control in both type 1 and type 2 diabetes mellitus.

Clinical Efficacy [1-3] (mechanism of action/pharmacology, comparative efficacy)

Tresiba™ is a long-acting basal insulin. It lowers blood glucose by stimulating peripheral glucose uptake and by inhibiting hepatic glucose production, lipolysis, and proteolysis.

Pharmacokinetics:

	Tresiba™
Metabolism	Forms all inactive metabolites
Half-life	25 hours
Protein binding	>99% protein bound

Tresiba™ was noninferior to insulin glargine in a randomized trial of patients with type 1 diabetes.

Type 1 Diabetes Mellitus

STUDY DESIGN	Randomized, open-label, active-controlled, 52-week clinical trial (N=629).
INCLUSION CRITERIA	Adult patients with type 1 diabetes.
EXCLUSION CRITERIA	Not specified.

TREATMENT REGIMEN	Patients were randomized to receive Tresiba™ once daily with the evening meal or insulin glargine 100 units/mL once daily for 52 weeks. Insulin aspart was administered before each meal.
RESULTS	Tresiba™ was found to be noninferior to insulin glargine, with both treatments reducing HbA1c by approximately 0.35% from a baseline mean HbA1c of 7.7% in each group. An HbA1c of < 7% was achieved by 39.8% of the Tresiba™ group and 42.7% of the insulin glargine group.
SAFETY	Not specified.

Tresiba™ was noninferior to insulin glargine in a randomized trial in insulin-naïve patients with type 2 diabetes.

Type 2 Diabetes Mellitus Studies

STUDY DESIGN	Randomized, open-label, active-controlled, 52-week clinical trial (N=1030).
INCLUSION CRITERIA	Insulin-naïve adult patients with type 2 diabetes inadequately controlled on oral antidiabetic agents.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive Tresiba™ once daily with the evening meal or insulin glargine 100 units/mL once daily for 52 weeks. Metformin, with or without a DPP-4 inhibitor, was continued in both treatment groups.
RESULTS	Tresiba™ was found to be noninferior to insulin glargine, with reductions in HbA1c of 1.06% in the Tresiba™ group and 1.15% in the insulin glargine group from a baseline mean HbA1c of 8.2% in each group. An HbA1c <7% was achieved by 51.7% of the Tresiba™ group and 54.1% of the insulin glargine group.
SAFETY	Not specified.

Contraindications [(1)]

- During episodes of hypoglycemia
- Hypersensitivity to Tresiba™ or any product component.

Warnings and Precautions [(1)]

- Fluid retention may occur with concomitant use of thiazolidinediones and may cause or

exacerbate congestive heart failure; monitoring recommended and dose reduction or discontinuation may be required.
- Changes in insulin type, manufacturer, or method may affect glycemic control; monitoring recommended.
- Hypoglycemia has been reported and may lead to seizures or death; increased risk with changes in meal pattern, physical activity, or concomitant medication, and in patients with renal or hepatic impairment; monitoring recommended.
- Hypokalemia may occur and could lead to respiratory paralysis, ventricular arrhythmia, and death; monitoring recommended.
- Severe, life-threatening generalized allergic reactions, including anaphylaxis, may occur; discontinue use.
- Accidental mix-ups between basal insulin products and other insulins have been reported; always check label before injection.
- Hypoglycemia may impair concentration ability and reaction time.
- Hepatic impairment; frequent monitoring and dosage adjustment may be necessary.
- Pen devices are for single patient use only and never to be shared, even if the needle is changed, due to increased risk for transmission of bloodborne pathogens.

Adverse Effects [1]

Hypoglycemia is the most common adverse effect, with severe hypoglycemia occurring in 10.4-12.7% of patients with type 1 diabetes and 0-4.5% of patients with type 2 diabetes. A severe hypoglycemic episode or plasma glucose of <56 mg/dL (with or without symptoms) was reported in 93-99.4% of patients with type 1 diabetes and 28.5-80.9% of patients with type 2 diabetes.

Common, ≥ 5%	Percentage of Patients
Nasopharyngitis	12.9-23.9%
Upper respiratory tract infection	8.4-11.9%
Headache	8.8-11.8%
Diarrhea	6.3%
Sinusitis	5.1%
Gastroenteritis	5.1%

Drug Interactions [1]

- Albuterol
- Antidiabetic agents
- Antihypertensive agents
- Antipsychotics, atypical
- Corticosteroids
- Danazol
- Disopyramide
- Diuretics
- Estrogens
- Fibrates
- Fluoxetine
- Isoniazid
- Lithium
- Monoamine oxidase inhibitors
- Niacin
- Otal contraceptives
- Pentamidine
- Pentoxifylline
- Phenothiazines
- Pramlintide
- Progestogens
- Propoxyphene
- Protease inhibitors
- Salicylates
- Somatostatin analogues: otreotide

- Sulfonamide antibiotics
- Thyroid hormones

Dosage and Administration [(1)]

Type 1 diabetes mellitus, insulin-naïve: Initial dosage is one-third to one-half of the total daily insulin dosage; administer remainder of daily insulin dosage as short-acting insulin divided between meals. Type 2 diabetes mellitus, insulin-naïve: Initial dosage is 10 units subQ once daily. Individualize dose, administer in thigh, upper arm, or abdomen, and adjust dosage every 3 to 4 days as clinically indicated.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	COST*/ PEN
Insulin degludec	Tresiba	Novo Nordisk	100 units/ml, 3 ml prefilled pen	$76.87
			200 units/ml, 3 ml prefilled pen	$153.75
Insulin detemir	Levemir Flexpen	Novo Nordisk	100 units/ml, 3 ml prefilled pen	$50.18
Insulin glargine	Lantus Solostar	Sanofi-Aventis	100 units/ml, 3 ml prefilled pen	$46.63
Insulin glargine, recombinant	Toujeo	Sanofi-Aventis	300 units/mL, 1.5 mL prefilled pen	$75.32

* Wholesale Acquisition Cost

Conclusion

Tresiba™ is a subcutaneous, once-daily, basal insulin indicated to improve glycemic control in adults with diabetes mellitus. In randomized trials in patients with type 1 diabetes, Tresiba™ was noninferior to insulin glargine (N=629) and insulin detemir (N=455). Tresiba™ reduced mean HbA1c by 0.36-0.71% and approximately 40% of patients achieved an HbA1c <7% across studies. In 5 randomized studies in patients with type 2 diabetes (N=3601), Tresiba™ was noninferior to insulin glargine when used as add-on therapy to oral antidiabetic agents and/or insulin. It was superior to sitagliptin in a randomized trial of 447 patients. Tresiba™ reduced mean HbA1c by 1.03-1.52% and 38.9-53.2% of patients achieved an HbA1c <7%. Tresiba™ has a long duration of activity (42 hours), allowing for administration at various times throughout the day without significantly losing efficacy. Hypoglycemia is the most common adverse effect. Severe hypoglycemia occurred in 10.4-12.7% of patients with type 1 diabetes and up to 4.5% of patients with type 2 diabetes. Other common adverse effects include nasopharyngitis, upper respiratory tract infection, and headache.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1. Product Information: Tresiba®, insulin degludec injection. Novo Nordisk, Plainsboro, NJ,

09/2015.
2. Mathieu C, Rodbard HW, Cariou B et al: A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). Diabetes Obes Metab 2014; 16(7):636-644.
3. FDA approves two new drug treatments for diabetes mellitus. Retrieved 01/20/16 from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm464321.htm

Prepared by: Erica Schenewerk, 2016 Pharm D candidate
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