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Revised: 09/15/24

Subject: Donislecel (Lantidra) allogeneic islet cell transplant

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Diabetes mellitus Type 1 (DM Type 1) is an endocrine disorder caused by insulin deficiency, which is usually the result of autoimmune pancreatic beta cell destruction. The loss of beta cells results in hyperglycemia and subsequent complications such as ketoacidosis, cardiovascular disease, nephropathy, and retinopathy. The onset of DM Type 1 can occur at any age, but commonly presents in childhood or adolescence. The most common symptoms include polyuria, polydipsia, polyphagia, and sudden weight loss, with about 30% of patients presenting with diabetic ketoacidosis (DKA).

All patients with DM Type 1 require insulin therapy. Most patients are treated with multiple daily injections; one to two injections of basal insulin daily and three or more injections daily of prandial insulin or the use of continuous subcutaneous insulin infusion via an insulin pump. Transplantation of beta cells has been proposed for DM Type 1 patients with frequent and severe metabolic complications, who have consistently failed to achieve control with insulin. Beta cell replacement may be accomplished through pancreas or islet transplantation in select patients; however, both procedures require lifelong immunosuppression. On June 28, 2023, donislecel-jujn (Lantidra), an allogeneic pancreatic islet cellular therapy manufactured from the pancreas of a single deceased donor, was approved by the FDA for the treatment of adults with DM Type 1 who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

Based on the prescribing information, the efficacy of donislecel-jujn (Lantidra) was evaluated in two prospective, open-label, single-arm studies (Study 1 and Study 2). Combined these studies enrolled 30 patients with DM Type 1 and hypoglycemic unawareness. The demographics were as follows: median age 46.5 (range: 21 – 67) years, 80% female, 100% white, and 97% non-Hispanic. All patients received at least one islet infusion with a maximum of three infusions (11 received one infusion, 12 received two

infusions, and 7 received three infusions). Enrolled patients received concomitant immunosuppressive therapy (i.e., anakinra, daclizumab, basiliximab, mycophenolate mofetil, etanercept, everolimus, sirolimus, tacrolimus, cyclosporine, anti-thymocyte immunoglobulin). Additionally, a glucagon-like peptide-1 (GLP-1) agonist (e.g., exenatide 5 mcg subcutaneously within 60 minutes before infusion), was administered and was supposed to be continued (5 mcg twice daily), for up to 6 months after transplant. The median donislecel-jujn (Lantidra) islet number per infusion was 399,178 equivalent islet number (EIN) (range 253,924 EIN to 858,856 EIN), and the median islet dose per infusion was 6,570 EIN/kg (range 4,186 EIN/kg to 13,633 EIN/kg). Overall, 21 patients did not require insulin therapy for a year or more, with 11 patients not needing insulin for one to five years and 10 patients not needing insulin for more than five years. Five patients did not achieve any days of insulin independence.

The most frequently reported adverse events associated with donislecel-jujn (Lantidra) included nausea, fatigue, anemia, diarrhea and abdominal pain. Some adverse reactions required immunosuppressants to be discontinued, which lead to the loss of transplanted beta cells.

POSITION STATEMENT:

The administration of donislecel (Lantidra) **meets the definition of medical necessity** when **ALL** of the following are met:

1. Member is 18 years of age or older
2. Diagnosis of type 1 diabetes mellitus
3. Unable to achieve target HbA1C goal despite both of the following (“a” and “b”): – documentation from the medical record and/or lab tests must be provided
    a. Intensive insulin management that includes coordination of diet and activity with physiologic insulin replacement (i.e., multiple daily injections of prandial and basal insulin or continuous subcutaneous insulin infusion)
    b. Intensive monitoring of blood glucose with either use of a continuous glucose monitor (CGM) or insulin pump
4. History of severe hypoglycemia as defined by both of the following (“a” and “b”): - documentation from the medical record and/or lab tests must be provided
    a. Reduced awareness of hypoglycemia, defined by the absence of adequate autonomic symptoms (e.g., palpitations, anxiety, sweating, confusion, sensation of warmth, weakness or fatigue, severe cognitive failure) at a plasma glucose levels of less than 54 mg/dL
    b. One or more episodes of severe hypoglycemia in the past 3 years which necessitated assistance from another person and was associated with either a blood glucose level less than 50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration
5. Member does not have **ANY** of the following (“a” to “h”):
    a. Previous renal transplant
    b. Positive T- and B-cell crossmatch between recipient serum and donor lymphocytes that indicates high risk for transplant rejection

c. Renal disease defined as recent (within the last 30 days) creatinine clearance less than 80 mL/min/1.73 m^2, serum creatinine greater than 1.5 mg/dL, or macroalbuminuria (urinary albumin excretion rate greater than 300 mg/24 hours)

d. Recent (within the last 30 days) liver function test panel with any value > 1.5 times normal upper limits

e. Increased risk of bleeding as defined by recent (within the last 30 days) hemoglobin (Hb) less than 12 gm/dL in women or less than 13 gm/dL in men, uncorrectable bleeding diathesis, use of coumadin or other antiplatelet or anticoagulant therapy, prothrombin time (PT) international normalized ratio (INR) > 1.5, or history of Factor V deficiency

f. History of prior portal vein thrombosis, excluding thrombosis of 2nd or 3rd order portal vein branches

g. Active infection such as hepatitis C, hepatitis B, HIV, or tuberculosis

h. Malignancies (with the exception of adequately treated basal or squamous cell carcinoma of the skin)

6. Donislecel (Lantidra) will be prescribed in combination with immunosuppressive therapy
7. Prescribed by a specialist who conducts islet cell transplantation such as an endocrinologist, hematologist, or hepatologist
8. The initial infusion of donislecel (Lantidra) will not exceed 5,000 equivalent islet number (EIN) per kg patient body weight.

Approval duration: 6 months

Continuation of donislecel (Lantidra) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the last 2 years before the authorization request must be submitted), OR the member has previously met all indication-specific initiation criteria.
2. Member has not achieved independence from exogenous insulin, is not at the target HbA1c goal, and continues to experience severe hypoglycemia episodes requiring intervention (e.g., oral carbohydrate, intravenous glucose, or glucagon administration) and hospitalization - documentation from the medical record and/or lab tests must be provided
3. The last donislecel (Lantidra) infusion was administered at least one year ago or longer.
4. Member has not received more than three total infusions of donislecel (Lantidra).
5. Member is adherent to the prescribed immunosuppressive therapy.
6. Member does not have **ANY** of the following (“a” to “h”):
    a. Previous renal transplant
    b. Positive T- and B-cell crossmatch between recipient serum and donor lymphocytes that indicates high risk for transplant rejection

c. Renal disease defined as recent (within the last 30 days) creatinine clearance less than 80 mL/min/1.73 m^2, serum creatinine greater than 1.5 mg/dL, or macroalbuminuria (urinary albumin excretion rate greater than 300 mg/24 hours)

d. Recent (within the last 30 days) liver function test panel with any value > 1.5 times normal upper limits

e. Increased risk of bleeding as defined by recent (within the last 30 days) hemoglobin (Hb) less than 12 gm/dL in women or less than 13 gm/dL in men, uncorrectable bleeding diathesis, use of coumadin or other antiplatelet or anticoagulant therapy, prothrombin time (PT) international normalized ratio (INR) > 1.5, or history of Factor V deficiency

f. History of prior portal vein thrombosis, excluding thrombosis of 2nd or 3rd order portal vein branches

g. Active infection such as hepatitis C, hepatitis B, HIV, or tuberculosis

h. Malignancies (with the exception of adequately treated basal or squamous cell carcinoma of the skin)

7. Prescribed by a specialist who conducts islet cell transplantation such as an endocrinologist, hematologist, or hepatologist

8. The administration of donislecel (Lantidra) will not exceed 4,500 equivalent islet number (EIN) per kg patient body weight.

Approval duration: 1 year

Donislecel (Lantidra) is considered **experimental or investigational** for any other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Donislecel (Lantidra) is an allogeneic pancreatic islet cellular therapy indicated for the treatment of adults with DM Type 1 who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.
- The dosage form is a cellular suspension. Dosage strength depends on the total number of islets packaged for infusion, which is reported on the container label and associated documents.
- The recommended minimum dose is 5,000 equivalent islet number (EIN) per kg patient body weight for the initial infusion (transplant) and 4,500 EIN/kg for subsequent infusions, and the estimated tissue volume should not exceed 10 cc per transplant infusion.
- The second and third infusions may be performed if the patient does not achieve independence from exogenous insulin within one year of infusion or within one year after losing independence

from exogenous insulin after a previous infusion. There are no data regarding the effectiveness or safety for patients receiving more than three infusions total in a lifetime.

- The infusion is administered through the hepatic portal vein.
- Donislecel (Lantidra) is use in conjunction with concomitant immunosuppression and glucagon-like peptide-1 (GLP-1) receptor agonist therapy.
- Keep donislecel (Lantidra) in the insulated container at 15°C to 25°C no longer than 6 hours from time of product release. Dispose of any product not used within 6 hours.
- Do not irradiate the product or use leukodepleting filters.
- Each infusion uses one lot of donislecel (Lantidra) which consists of islets manufactured from the pancreas of a single deceased donor. Each dose of donislecel (Lantidra) is provided as two (2) infusion bags connected to each other via sterile connector. One bag contains donislecel (Lantidra) up to a maximum of 1 x 106 EIN in 400 mL of transplant media and the second bag (Rinse Bag) contains transplant media used to rinse the donislecel (Lantidra) bag and the infusion line.
- Prior to administration inspect the donislecel (Lantidra) infusion bag and the Rinse Bag for leaks and breaches of container integrity. Additionally, ensure the connector between the infusion bag and the Rinse Bag is secure and closed.
- Gently agitate the donislecel (Lantidra) infusion bag to ensure that the islets are suspended and to prevent clumping. Do not shake the bag, as this may damage the islets. Repeat gentle agitation periodically throughout the infusion process.
- Donislecel (Lantidra) should be infused by gravity flow over approximately 30 minutes at rates less than or equal to 25 mL/kg/h. However, the infusion rate may be reduced if the fluid load is not tolerated by the patient and discontinued in the event of an allergic reaction or if the patient develops a moderate to severe infusion reaction.
- Flush the infusion lines periodically to clear them.
- Do not administer donislecel (Lantidra) (islet cell product and rinse bag) through intravenous lines that contain any other medications or infusions other than physiological saline.
- It is recommended to monitor portal pressure, blood glucose levels, and for portal vein branch thrombosis during the infusion.

Dose Adjustments

- There is no evidence to support the use of donislecel (Lantidra) in patients with renal or hepatic disease.

Drug Availability

- Donislecel (Lantidra) (NDC 73539-001-01) is supplied as purified allogeneic islets of Langerhans suspended in buffered transplant medium containing sodium chloride, dextrose, minerals, amino acids, vitamins, and other compounds supplemented with HEPES (2-[4-(2-hydroxyethyl) piperazin-1-yl] ethanesulfonic acid; 10 mM final concentration) and human serum albumin (0.5% final concentration).
- Donislecel (Lantidra) is contained in one 1000 mL infusion bag filled with a supplied volume of 400 mL, containing not more than 10 cc of estimated packed islet tissue and not more than 1 x 106 EIN.

The 1000 mL infusion bag is aseptically connected to a smaller 750 mL Rinse Bag (NDC 73539-002-01) containing 200 mL of supplied volume of transplant media for use in rinsing the 1000 mL bag containing donislecel (Lantidra) and infusion line following infusion to assure complete transfer of islets to the patient.

- Additional product information, including islet number, is included on the Final Islet Product Certificate of Analysis and the container label.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Donislecel (Lantidra) is contraindicated in patients, including pregnancy, for whom immunosuppression is contraindicated.

Precautions/Warnings

- **Risks from Concomitant Immunosuppression:** Increased risk of severe infections including opportunistic infections, malignancy, and severe anemia. Monitor closely. Administer PCP and CMV prophylaxis.
- **Procedural Complications:** Liver laceration and hemorrhage have occurred. Monitor for bleeding, portal hypertension, and portal vein thrombosis during and immediately following infusion.
- **Increased Risk of Graft Rejection:** Patients with a positive T- and B-cell crossmatch between recipient serum and donor lymphocytes may be at increased risk for graft rejection.
- **Transmission of Donor-Derived Infections:** Monitor for signs of infection following infusion and treat accordingly.
- **Panel Reactive Antibodies (PRA):** Product administration may elevate PRA and negatively impact candidacy for renal transplant.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologicals (This code should only be used for drugs and biologicals that are approved by the FDA on or after January 1, 2004) (Hospital Outpatient Use ONLY)
J3590	Unclassified biologics

ICD-10 Diagnosis Codes That Support Medical Necessity

E10.8	Type 1 diabetes mellitus with unspecified complications
E10.9	Type 1 diabetes mellitus without complications

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

Islet Transplantation, 02-40000-21

OTHER:

None

REFERENCES:

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2. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2024. URL http://www.dynamed.com. Accessed 7/30/24.
3. FDA Cellular, Tissue, and Gene Therapies Advisory Committee Meeting. BLA 125734 Donislecel Applicant: CellTrans, Inc. Updated April 15, 2021. Accessed 8/4/23. https://www.fda.gov/media/147525/download
4. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 7/30/24.
5. Lantidra (donislecel) [package insert]. CellTrans, Inc., Chicago (IL): June 2023.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 08/14/24.

GUIDELINE UPDATE INFORMATION:

09/15/23	New Medical Coverage Guideline – Donislecel (Lantidra) as an allogeneic pancreatic islet cellular therapy for the treatment of adults with DM Type 1 who are unable to achieve the target HbA1c goal because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.
09/15/24	Review and revision of the guideline to update the position statement for conditions incompatible for transplant and removing the requirement for GLP-1 receptor agonist as concomitant therapy, adding billing code C9399, and updating references.