Molina Clinical Policy
Pancreatic Cellular Replacement Therapy Lantidra (donislecel-jujn): Policy No. 441

Last Approval: 08/14/2024
Next Review Due By: August 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy covers Lantidra, an allogenic pancreatic islet cell therapy, for the treatment of adults with type I diabetes and recurrent episodes of severe hypoglycemia despite medical management.

Historically, pancreatic islet of Langerhans cell auto transplantation is a treatment used to preserve normal insulin function in select patients undergoing a total pancreatectomy, near-total pancreatectomy, or complete pancreatectomy for chronic pancreatitis. Recent advances in isolation and culture of the islets and peri transplant management have improved safety for patients (Rickels 2019). During islet cell transplantation, special enzymes are employed to remove islets from a resected pancreas. The islets are then purified and counted, diluted in plasma, and finally infused into the portal vein of the liver of the recipient. The types of islet transplant are autologous (self-donor), allogenic (human donor other than self or cadaver), or xenogeneic (animal source). Allogenic pancreatic islet cellular therapy was recently approved for the indication of Type I diabetes with episodes of severe hypoglycemia.

During allogenic pancreatic islet cellular transplantation, islet cells from a deceased donor are given percutaneously and infused via catheter which is advanced into the portal circulation. Historically immunosuppression was done with a regimen including steroids, however more recently steroid free regimens have been implemented allowing for better glycemic control (FDA 2009).

On June 28, 2023, the Food and Drug Administration approved Lantidra (donislecel-jujn) under a biologics licensing approval pathway. Lantidra is a cellular suspension of allogeneic pancreatic islets in buffered transplant media. The transplant medium does contain human serum albumin. Each dose is derived from the islets manufactured from the pancreas of a single deceased donor (Cell Trans, Inc). The primary mechanism of action of donislecel is believed to be secretion of insulin by infused (transplanted) beta-cells.

RELATED POLICIES

MCP-017 Pancreas Transplantation Procedures
MCP-440 Pancreatic Islet Cell Transplantation (Autologous)

COVERAGE POLICY

Allogenic Pancreatic Islet Cell Transplantation may be considered medically necessary in adults with Type I diabetes who meet **ALL** the following indications with relevant documentation:

1. Member has an active diagnosis of type 1 diabetes mellitus currently and has a history of type 1 diabetes mellitus for more than 5 years

2. Age 18 to 65

3. Previously undergone intensive insulin management (multiple daily injections or continuous insulin infusion with insulin pump/monitoring)

4. Member has significant episodes of hypoglycemia despite intensive insulin management defined as:
    a. Reduced awareness of hypoglycemia (absence of adequate autonomic response at capillary glucose level <54 mg/dL)
    b. At least one episode of severe hypoglycemia in the past 3 years in which the subject required the assistance of another person, and which was associated with either a blood glucose level < 50 mg/dL (2.8 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration

5. Insulin requirement ≤ 0.7 IU/kg/day

6. Body Mass Index ≤ 27 kg/m2

7. No history of previous transplant (not including prior dose of Lantidra islet transplant)

8. Not currently pregnant, breastfeeding, planning a pregnancy or unwilling to use effective contraception

9. Laboratory studies
    a. C-peptide response to glucagon stimulation, (any C-peptide < 0.3 ng/mL)
    b. Recent glycated hemoglobin (HbA1c) ≤ 12%
    c. Baseline Hemoglobin ≥ 12 gm/dL in women or ≥ 13 gm/dL in men
    d. Liver function tests completed and values ≤ 1.5 times the upper limit of normal
    e. Creatinine clearance ≥ 80 mL/min/1.73 m2 by 24-hour urine collection. If corrected creatinine clearance is < 80 and serum creatinine is < 1.2 mg/dl, then a nuclear renal scan is required to determine glomerular filtration rate.
    f. Serum creatinine consistently ≤ 1.5 mg/dL
    g. Urinary albumin excretion ≤ 300mg/24 hours)
    h. PT-INR ≤ 1.5.
    i. Negative pregnancy test (for women of childbearing age)

10. No personal history of the following comorbidities:
    a. Stroke within past 6 months
    b. Cardiac disease:
        i. Recent myocardial infarction (<6 months), angiographic evidence of uncorrectable coronary artery disease, or evidence of ischemia on functional cardiac exam
        ii. Heart failure with New York Heart Association class II or greater symptoms
    c. Co-existing malignancy (except squamous or basal skin cancer – if these skin cancers exist they need to be removed prior to Lantidra therapy)
    d. Infectious disease complications that are uncontrolled pre transplant such as:
        i. Active infection
        ii. Chronic hepatitis (e.g., Hepatitis B, hepatitis C)
        iii. Human Immunodeficiency Virus
        iv. Tuberculosis
    a. Untreated proliferative retinopathy
    b. Factor V deficiency
    c. Addison's disease
    d. Hyperlipidemia (fasting cholesterol >130 mg/dL or fasting triglycerides >200 mg/dL)
    e. History of non-adherence to prescribed regimen
    f. Substance use disorder:
        i. Active including but not limited to cigarette smoking
        ii. Without evidence of meaningful risk reduction behaviors
    g. Gastrointestinal disease:
        i. Symptomatic cholecystolithiasis

ii. Symptomatic peptic ulcer disease
iii. Severe unremitting diarrhea, vomiting, or other gastrointestinal disorders that could interfere with medication absorption

h. Allergy to radiographic contrast material

11. No use of coumadin or other antiplatelet or anticoagulant therapy (except aspirin)
12. No use of any other antidiabetic medication other than insulin within 4 weeks of procedure
13. No Recent live attenuated vaccine within the past two months
14. Family history of Multiple Endocrine Neoplasia type 2 or medullary thyroid cancer

CONTINUATION OF THERAPY

Coverage of Lantidra is limited to an initial infusion of 5,000 equivalent islet number per kg (EIN/kg) given via infusion via the hepatic portal vein. Maximum of 1 x 10^6 EIN (10ml) per infusion. Infusion should be terminated if portal pressure remains >22 mm Hg for longer than 10 minutes.

Repeat second dose of 4,500 EIN/kg may be administered if independence from exogenous insulin is not achieved within 1 year of initial infusion or within 1 year after losing independence from exogenous insulin after a previous infusion. A third infusion may be administered using the same dose and criteria as the second dose if needed. There are no data for administration beyond 3 infusions and authorization for such will not be granted.

LIMITATIONS AND EXCLUSIONS

The following are **considered warnings/precautions:**

1. Prior portal vein thrombosis following infusion other than those limited to second or third order portal vein branches
2. Islet graft rejection risk in patients with a positive T and or B cell crossmatch
3. Panel reactive antibodies. Donislecel-jujn (Lantidra) administration may elevate panel reactive antibodies and negatively impact candidacy for future kidney transplant

The following are considered **experimental, investigational, or unproven** based on insufficient evidence:

1. Any indications other than those listed above
2. Repeat treatment beyond three infusions

PRESCRIBER REQUIREMENTS: Prescribed by, or in consultation with, an endocrinologist and at a treatment center skilled in islet cell transplantation.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Islet cell transplantation for select patients may allow patients freedom from insulin for some time. However according to studies, a limited number of allografts demonstrated sustained insulin independence. It was postulated that the immunosuppression regimen may have been an issue. Shapiro, et al note that advances in islet cell transplant and development of a glucocorticoid free transplant regimen may solve the difficult problem. To determine whether the appropriate patient scenario existed seven patients with type 1 diabetes and severe hypoglycemia with metabolic instability underwent islet cell transplantation at a single center. This islet transplantation protocol is now referred to as the University of Illinois protocol or UIC protocol, negates the need for steroids in the immunosuppression regimen. The results of the initial prospective phase ½ safety and reproducibility trial demonstrated significant decrease in the hypoglycemia measures across all groups as measured by the HYPO score (an index used to assess severity of hypoglycemia and glycemia lability in patients with type 1 diabetes post islet cell

transplant – see appendix for details). Combined treatment with etanercept and exenatide appeared to improve islet graft function and facilitate insulin independence (Gangemi 2008).

The Phase 3 clinical trial (NCT00679042) sponsored by CellTrans; Islet Transplantation in Type 1 Diabetic Patients Using the University of Illinois at Chicago (UIC) Protocol provided additional data. It was an open label unmasked interventional study aimed to increase access to biological treatment of diabetes with islet cell allotransplantation. The FDA reviewed an additional Phase 3 clinical trial (NCT03791567) Islet Transplantation in Type I Diabetic Patients Using the University of Illinois at Chicago (UIC) Protocol.

Twenty-one participants with type 1 diabetes enrolled in the study. Enrollment consisted of patients aged 21-67 with a median age of 47 years. Fifteen (71.4%) were females and 6 (28.6%) were males. All subjects received up to three transplantations of allogenic human islets along with the following medications: Basiliximab, Tacrolimus, Sirolimus, Etanercept, Exenatide. In one year, 2 patients withdrew from the study and 19 completed 1 year follow up. At 5 years only 5 patients completed follow up (6 ongoing, 1 died, 7 did not continue). The safety and efficacy goal primary endpoint were HbA1C $\leq$ 6.5% at the one year follow up and absence of severe hypoglycemic events from day 28 to 1 year after the first and last transplant. Additional primary endpoint was treatment emergent adverse events.

At 1 year after the first transplant only 8 (38.1%) participants met the primary endpoint. This number increased to 11 (52.4%) when measured at one year after the last transplant. Secondary measures included insulin independence at 1 year after the islet infusion. Participants were also monitored for additional secondary endpoints, fasting glucose measurements capillary (<140 mg/dl) greater than 3 times in a week and fasting plasma glucose levels <126 mg/dL. Additionally two-hour post prandial capillary glucose not exceeding 180 mg/dL more than once out of seven times in a week and evidence of endogenous insulin production (defined by C-peptide levels $\geq$ 0.5ng/mL) were monitored. Further, episodes and severity of hypoglycemia were monitored via the HYPO score as previously described by the Ryan hypoglycemic score (Ryan 2004).

All members had some type of adverse event, however the rate of serious transplant related adverse event was 11 (52.4%) and none leading to death or discontinuation. Treatment emergent adverse events were monitored for an average of a year following the last transplant. Ninety percent of subjects had at least one adverse reaction including those related to the procedure itself (liver laceration, hematoma, hemorrhage, and intra-abdominal bleeding) as well as elevation of portal pression. Additionally, subjects demonstrated effects of immunosuppression such as infection and malignancy.

National and Specialty Organizations

The **Organ Procurement and Transplant Network (OPTN):** The OPTN Policy on Allocation of Pancreas, Kidney Pancreas, and Islets addresses Islet Registration Status as follows: A transplant hospital may register an islet candidate on the waiting list with an active status if the candidate meets either of the following requirements:

1. Is insulin dependent
2. Has a hemoglobin A1c (HbA1c) value greater than 6.5%

The **American Diabetes Association (ADA):** The *ADA Standards of Medical Care in Diabetes* 2024 state the following:

1. For patients with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, human islet transplantation may be an option, but the approach remains experimental.
2. Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, people receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for people with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management.

SUPPLEMENTAL INFORMATION

HYPO Score: A composite hypoglycemic score (HYPO score) was devised based on the frequency, severity, and degree of unawareness of the hypoglycemia. HYPO score >1,047 is considered severe. Scores between 423 and

1,046 were indicative of subjects who had moderate problems with hypoglycemia, and a score of <423 indicated that hypoglycemia was unlikely to be a major clinical concern (Ryan 2004).

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Codes

CPT	Description
0584T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; percutaneous
0585T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; laparoscopic
0586T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; open
48554	Transplantation of pancreatic allograft
48556	Removal of transplanted pancreatic allograft

HCPCS (Healthcare Common Procedure Coding System) Codes

HCPCS	Description
C9399	Unclassified drugs or biologicals [when specified as Lantidra (donislecel-jujn)]
G0341	Percutaneous islet cell transplant, includes portal vein catheterization and infusion
G0342	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
G0343	Laparotomy for islet cell transplant, includes portal vein catheterization and infusion
S2102	Islet cell tissue transplant from pancreas; allogeneic
S2152	Solid organ(s), complete or segmental, single organ or combination of organs; deceased or living donor (s), procurement, transplantation, and related complications; including drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

08/14/2024 Policy reviewed, updated references, Reformatted indications, no changes to coverage criteria.
08/09/2023 New Policy. New FDA indication. IRO (Independent Review Organization) peer review by reviewer board certified in Transplant Hepatology July 2023.

REFERENCES

1. American Diabetes Association Professional Practice Committee. 6. Glycemic goal and hypoglycemia: Standards of Care in Diabetes-2024. Diabetes Care. 2024 Jan 1;47(Suppl 1):S158-S178. doi: 10.2337/dc24-S009. Erratum in: Diabetes Care. 2024 May 02;: PMID: 38078590; PMCID: PMC10725810
2. Approved Cellular and Gene Therapy Products | FDA [Internet]. United States Food and Drug Administration. [cited 2023Aug.1]. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.
3. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database: National coverage determination – islet cell transplantation in the context of a clinical trial (260.3.1). Effective October 1, 2004. Accessed June 10, 2024. https://www.cms.gov/medicare-coverage-database/search.aspx
4. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2021 July 27. Identifier NCT03791567, Islet Transplantation in Type I Diabetic Patients Using the University of Illinois at Chicago (UIC) Protocol. Available at: https://clinicaltrials.gov/ct2/show/NCT03791567. Accessed July 14, 2023.

5. Food and Drug Administration (FDA). Guidance document: Considerations for allogeneic pancreatic islet cell products (guidance for industry). Published September 2009. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-allogeneic-pancreatic-islet-cell-products
6. Gangemi A, Salehi P, Hatipoglu B, et al. Islet transplantation for brittle type 1 diabetes: the UIC protocol. Am J Transplant. 2008 Jun;8(6):1250-61. doi: 10.1111/j.1600-6143.2008.02234.x. Epub 2008 Apr 29. PMID: 18444920.
7. Organ Procurement and Transplantation Network (OPTN). Guidance. https://optn.transplant.hrsa.gov/professionals/by-topic/guidance/.
8. Organ Procurement and Transplant Network. OPTN Organ Procurement and Transplant Network Policies. Updated May 29, 2024. Accessed June 13, 2024. https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf
9. Robertson RP, Davis C, Larsen J, et al.; American Diabetes Association (ADA). Pancreas and islet transplantation in type 1 diabetes. Diabetes Care. 2006 Apr;29(4):935. doi: 10.2337/diacare.29.04.06.dc06-9908. PMID: 16567844.
10. Rickels MR, Robertson RP. Pancreatic Islet Transplantation in Humans: Recent Progress and Future Directions. Endocr Rev. 2019 Apr 1;40(2):631-668. doi: 10.1210/er.2018-00154. PMID: 30541144; PMCID: PMC6424003.
11. Robertson RP, Davis C, Larsen J, et al.; American Diabetes Association (ADA). Pancreas and islet transplantation in type 1 diabetes. Diabetes Care. 2006 Apr;29(4):935. doi: 10.2337/diacare.29.04.06.dc06-9908. PMID: 16567844.
12. Ryan EA, Shandro T, Green K, et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. Diabetes. 2004 Apr;53(4):955-62. doi: 10.2337/diabetes.53.4.955. PMID: 15047610.
13. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med. 2000 Jul 27;343(4):230-8. doi: 10.1056/NEJM200007273430401. PMID: 10911004.