Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

P&T Date: 02/13/2025

Lantidra™ (donislecel-jujn)

HCPCS: J3590

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved age
   b. Diagnosis of Type 1 diabetes for ≥ 5 years
   c. Unable to reach target HbA1c despite intensive diabetes education and insulin management due to experiencing at least ONE of the following:
      i. Current repeated episodes of severe hypoglycemia, as defined by:
         a) The presence of hypoglycemia symptoms which required assistance of another person for intervention, AND
         b) Either a blood glucose level < 50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration
      ii. Hypoglycemia unawareness, as defined by the absence of adequate autonomic symptoms at glucose levels < 54 mg/dL, as reported by the patient
   d. Episodes of severe hypoglycemia and/or hypoglycemia unawareness persist despite intensive diabetes management that includes appropriate use of all modalities to reduce hypoglycemia, including continuous subcutaneous insulin infusion (i.e., an insulin pump) and continuous glucose monitoring
      i. Members who have failed to control hypoglycemia episodes and/or hypoglycemia unawareness utilizing non-integrated (i.e., self-managed) diabetes technologies must attempt management with an integrated system (i.e., automated insulin delivery system)
   e. Must be taken in combination with concomitant immunosuppressants
   f. Must not have had previous transplant
   g. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: 60 days
   c. Renewal Criteria: Independence from exogenous insulin has not been achieved within one year of infusion OR within one year after losing independence from exogenous insulin after a previous infusion

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- T1D affects nearly 1.9 million people in the united States. It is characterized by the autoimmune-mediated loss of insulin-producing β-cells within the islets of Langerhans in the pancreas and results in a complete deficiency of insulin, which can cause potentially life-threatening conditions like hyper and hypoglycemia, ketoacidosis, and dehydration.

- Of the total population with T1D in the United States, fewer than 80,000 are affected with a rare subset of T1D that is termed "brittle" diabetes. Brittle T1D is particularly difficult to treat as it is characterized by severe instability of blood glucose levels with frequent and unpredictable hypoglycemic episodes that often necessitate hospitalization. These patients have difficulty managing the amount of insulin needed to prevent hyperglycemia without causing frequent episodes of hypoglycemia. Their hypoglycemic episodes are often severe and may contribute to hypoglycemic unawareness, a hallmark of brittle T1D that can make the condition worse as the patient becomes unable to detect drops in blood sugar and may not be able to treat themselves to prevent blood glucose from further dropping. Hypoglycemia unawareness and severe hypoglycemia can lead to injuries resulting from loss of consciousness or seizures and can even be fatal.

- Secondary complications of diabetes like neuropathy, cardiovascular disease, and retinopathy can be common in brittle T1D due to lack of effective glucose control despite intensive insulin therapy, and these patients with difficult-to-treat diabetes exhibit a significant excess mortality.

- The most effective means of preventing or reducing symptoms and chronic complications of T1D is keeping blood glucose levels tightly controlled with insulin therapy. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2025) recommends that most individuals with T1D should be treated with multiple daily injections (MDI) of prandial and basal insulin, or continuous subcutaneous insulin infusion (i.e., an insulin pump). There is no consensus to guide choosing which form of insulin administration is best for a given individual; therefore, the choice of MDI or an insulin pump is based on the needs of the patient. MDI and insulin pump therapy are considered by the ADA to be intensive insulin therapy. Evidence supports intensive insulin therapy as providing the best combination of effectiveness and safety for people with T1D, and the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with MDI or an insulin pump reduced A1C and was associated with improved long-term outcomes.

- Intensive therapy has been associated with higher rates of severe hypoglycemia and hypoglycemia unawareness. The ADA recommends a target A1c goal for most nonpregnant adults of <7% without significant hypoglycemia, and that healthcare professionals consider de-intensifying therapy as appropriate to reduce hypoglycemia risks if this A1c target is too stringent and is limited by hypoglycemia.

- Level 1 hypoglycemia is defined as a measurable glucose concentration < 70 mg/dL but $\geq$ 54 mg/dL. Level 2 hypoglycemia is defined as blood glucose concentration < 54 mg/dL and is the threshold at which neuroglycopenic symptoms (e.g., warmth, weakness, difficulty thinking/confusion, tiredness/drowsiness) begin to occur and requires immediate action to resolve the event. Patients with level 2 hypoglycemia without adrenergic symptoms (e.g., sweating, hunger, tingling, shakiness, tachycardia, anxiety) or neuroglycopenic symptoms likely have hypoglycemia unawareness. Level 3 hypoglycemia is a severe event characterized by altered mental and/or physical functioning requiring assistance from another person for recover.

- The ADA recommends insulin-treated patients with hypoglycemia unawareness, one level 3 hypoglycemic event, or a pattern of unexplained level 2 hypoglycemia should be advised to raise glycemic targets to avoid hypoglycemia, to partially reverse hypoglycemia unawareness, and reduce risk of future episodes. Recurrent level 2 and/or level 3 hypoglycemia is considered an urgent medical issue that requires intervention with a treatment plan adjustment, behavioral intervention, and possibly the use of technology to assist in identifying and preventing the hypoglycemia.

- In recent years there have been significant advances in diabetes technology to aid in establishing tight glycemic control and minimizing hypoglycemia risk beyond optimizing the traditional self-administration of insulin and self-monitoring of blood glucose. The most commonly utilized diabetes technology includes continuous glucose monitoring (CGM) devices, insulin pumps, and automated insulin delivery (AID) systems. Per the ADA, the type(s) and selection of devices should be individualized based on a person's specific needs, preferences, and skill level.

- Monitoring blood glucose is integral to effective therapy to both monitor for and prevent hypoglycemia and hyperglycemia. Specific needs and goals are individualized to the patient and should guide decisions behind glucose monitoring, including consideration of continuous glucose monitoring (CGM) use. The 2025 Standards of Care recommend that people with diabetes should be offered any type of diabetes device (e.g., insulin pens, glucose meters, CGM or AID systems) and emphasize the need to start CGM early in T1D to promote early achievement of goals. Per the ADA, CGM should be offered for diabetes management in adults on intensive insulin therapy (i.e., MDI or insulin pump) who are capable of using the device safely, and choice of device is individualized to the patient. Sensor-augmented CGM and CGM-assisted pump therapy are available and provide alarm-based prevention of hypoglycemia. Evidence has shown that CGM appears useful in decreasing the time spent in hypoglycemic range in patients with impaired awareness.

- The ADA Standards recommend AID systems be offered for diabetes management to both children and adults with T1D who are capable of using the device safely, and the choice of device is based on the individual's circumstances, preferences, and needs. These devices increase and decrease insulin delivery based on sensor-derived glucose levels to mimic natural insulin delivery. AID systems consist of an insulin pump, a CGM device, and an algorithm for calculating insulin delivery. Basal insulin is adjusted in real time and some systems may also deliver automatic correction doses.

- For children and adults with T1D on MDI who are not able to use or who do not choose an AID system, the ADA recommends offering insulin pump therapy alone with or without sensor-augmented pump low glucose suspend feature and/or AID systems. Insulin pumps deliver rapid-acting insulin throughout the day to manage blood glucose levels and have a modest advantage for lowering A1c and reducing severe hyperglycemia rates in children and adults. Sensor-augmented pumps suspend insulin when glucose is low or are predicted to go low within the next half hour and offer an opportunity to reduce hypoglycemia. AID systems are preferred over nonautomated pumps and MDI in patients with T1D.

- The FDA describes AID systems (i.e., a CGM device linked to an insulin pump with the capability to automatically stop, reduce, or increase insulin infusion based on prespecified glucose thresholds) as "artificial pancreas device systems" (APDS). The components are designed to communicate together to automate maintenance of blood glucose concentrations at a specified range or target to minimize the incidence and severity of hypoglycemic and hyperglycemic events. There are different types of APDS that are approved for use and regulated by the FDA:

    - Sensor-augmented pump with low glucose suspend and sensor-augmented pumps with predictive low glucose management (e.g., suspend before low). When the device alarms, the user must take an action to assess their glucose level and resume the insulin infusion.

    - A control-to-range system, where insulin dosing is adjusted if glucose levels reach or approach predetermined higher and lower thresholds. Patients still need to monitor their blood glucose, set basal rates for their pump, and give premeal bolus insulin.

    - A control-to-target system which sets target glucose levels and tries to maintain them at all times. It is a fully automated system that only requires CGM calibration by the user.

    - A hybrid “closed-loop” system, which uses automated insulin delivery with continuous basal insulin delivery adjustments; however, mealtime requires the patient to enter their carbohydrates in order for the pump to determine the required bolus meal dose of insulin. A completely “closed-loop” system is not currently marketed in the United States.

- Beyond intensive insulin therapy and the use of the latest diabetes technologies, treatment for patients with difficult-to-treat brittle T1D is limited to whole pancreas transplant as a means of repairing β-cell function, but it carries both surgical and post-procedural risks and may not be appropriate for all T1D patients. Due to potential adverse effects of lifelong immunosuppression post-transplant, the 2025 ADA guidelines recommend reserving pancreas transplant for those with T1D undergoing simultaneous kidney transplant, following kidney transplant, or those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management.

- An alternative to whole pancreas transplantation is allogenic (donor-derived) islet cell transplantation, which is available in the United States as the FDA approved cell therapy Lantidra (donislecel-jujn). Islet cell transplantation has generally been reserved for patients with frequent and severe metabolic complications who have consistently failed to achieve glycemic control with intensive insulin management. Though it may be less-invasive than whole pancreas transplant, surgical and post-procedural risks do still exist and risks must be balanced against the potential benefit for each individual patient.

- The FDA approved Lantidra in June 2023 as the first FDA approved allogenic pancreatic islet cell therapy and the first-ever cellular therapy to treat T1D. Lantidra was approved to treat adults with T1D who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. Treatment with Lantidra requires use in conjunction with concomitant immunosuppression. Limitations of use to Lantidra are as follows:

    - When considering the risks associated with the infusion procedure and long-term immunosuppression, there is no evidence to show a benefit of administration of Lantidra in patients whose diabetes is well-controlled with insulin therapy or patients with hypoglycemic unawareness who are able to prevent current repeated severe hypoglycemic events (neuroglycopenia requiring active intervention from a third party) using intensive diabetes management (including insulin, devices, and education).

    - Repeated intraportal islet infusions are not recommended in patients who have experienced prior portal thrombosis, unless the thrombosis was limited to second- or third-order portal vein branches.

    - There is no evidence to support the safe and effective use of Lantidra in patients with liver disease, renal failure, or who have received a renal transplant.

- Approval was based on two prospective, open-label, single-arm studies (Phase I/II UIH-001 and Phase III UIH-002) in which a combined total of 30 adult patients with T1D and hypoglycemic unawareness received at least one infusion and a maximum of three infusions of Lantidra. Patients were required to have a diagnosis of T1D for more than 5 years complicated by reduced awareness of hypoglycemia and/or episodes of severe hypoglycemia that persisted despite intensive insulin management efforts. Severe hypoglycemia was defined as an event with symptoms compatible with hypoglycemia 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. Reduced hypoglycemia awareness was reported by the subject and defined by the absence of adequate autonomic symptoms at glucose values < 54 mg/dL. Subjects with a history of previous transplant were excluded from the trial.

- Of the 30 total participants, 11 received one infusion, 12 received two, and 7 received three. Of the 11 who did not receive a second infusion, 4 were insulin-independent, 3 did not have a donor, and 4 were intolerant to immunosuppression or withdrew from the trial within 6 months. All 7 who received a third infusion were insulin-independent. One subject was unable to geta third infusion due to infection.

- Insulin independence, defined as not requiring exogenous insulin to achieve adequate glycemic control, was one of the efficacy endpoints studied and was achieved by about 70% of subjects. Lantidra demonstrated a mean total duration of insulin independence of 5.1 years in study 1 (n = 10) and 3.2 years in study 2 (n = 20).

- In the pooled population, 5 patients had no days of insulin independence. For the remaining 25 who achieved insulin independence, 4 patients (13.3%) were insulin independent for < 1 year, 12 patients (36.7%) for one to five years, and 9 patients for > 5 years.

- The FDA in their evaluation of Lantidra prior to the April 2021 FDA Cellular, Tissue, and Gene Therapies Advisory Committee meeting considered durable insulin independence without evidence of hypoglycemia a stronger demonstration of clinical benefit compared to adequate glycemic control without serious hypoglycemia. Restoring insulin independence removes the risk of hypoglycemia from exogenous insulin; therefore, for those who have achieved insulin independence, there is a reasonable expectation that severe hypoglycemia would not occur.

    - In UIH-001 and UIH-002, changes in severe hypoglycemic event (SHE) occurrence and A1c from baseline at 1 year post last transplant were evaluated as trial endpoints in addition to insulin independence; however, the FDA questioned clinical meaningfulness of the data on these endpoints. Most patients (25/30) did not have a documented SHE in the year prior to their first transplant so an absence in the year after would not represent a change. Additionally, 83% of patients across both trials experienced anemia as a side effect which can falsely lower A1c and affect endpoint interpretation; therefore, there are limitations in being able to demonstrate clinical meaningfulness of A1c improvement from baseline.

- Based on available Lantidra data, the duration of insulin independence cannot be predicted based on the total number of transplants achieved. Additionally, baseline SHE frequency is not predictive of the likelihood of a patient to achieve insulin independence post-Lantidra.

- Lantidra may be administered for up to a maximum of three infusions. To date, there are no data regarding the effectiveness or safety for patients receiving more than three infusions. Per the prescribing information, a second infusion 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. A third infusion may be performed using the same criteria as for the second infusion.

References:

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<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.4</td><td>Effective Date: 02/13/2025</td><td>Annual review of criteria performed, no changes were made</td></tr>
<tr><td>1.3</td><td>Effective Date: 02/08/2024</td><td>Annual review of criteria performed, no changes were made</td></tr>
<tr><td>1.2</td><td>Effective Date: 10/15/2023</td><td>UM medical management system update for MAPPO and BCNA
<table>
<tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr>
<tr><td>BCBS</td><td>Yes</td></tr>
<tr><td>BCN</td><td>Yes</td></tr>
<tr><td>MAPPO</td><td>Yes</td></tr>
<tr><td>BCNA</td><td>Yes</td></tr>
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<tr><td>1.1</td><td>Effective Date: 08/24/2023</td><td>UM medical management system update for BCBSM and BCN
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<tr><td>BCN</td><td>Yes</td></tr>
<tr><td>MAPPO</td><td>No</td></tr>
<tr><td>BCNA</td><td>No</td></tr>
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<tr><td>1.0</td><td>Effective Date: 08/10/2023</td><td>New Policy</td></tr>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*

Blue Cross Blue Shield/Blue Care Network of Michigan
Medication Authorization Request Form

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

This form is to be used by participating physicians to obtain coverage for **drugs covered under the medical benefit**. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

PATIENT INFORMATION	PHYSICIAN INFORMATION
Name	**Name**
ID Number	**Specialty**
D.O.B. ☐Male ☐Female	**Address**
Diagnosis	**City /State/Zip**
Drug Name	**Phone/Fax: P**: ( ) - **F**: ( ) -
Dose and Quantity	**NPI**
Directions	**Contact Person**
Date of Service(s)	**Contact Person Phone / Ext.**

STEP 1: DISEASE STATE INFORMATION

1. Is this request for: ☐ Initiation ☐ Continuation *Date patient started therapy:* _____
2. Administered by patient or a medical professional? ☐ patient (self) ☐ health care professional (physician, nurse, etc.)
3. Site of administration? ☐ Provider office/Home infusion ☐ Other: _____
   ☐ Hospital outpatient facility (go to #4) *Reason for Hospital Outpatient administration:* _____
   ☐ Hospital inpatient facility for Car-T therapy only (for example: Kymriah, Yescarta, or Tecartus) (go to #5)
4. Please specify location of administration if hospital outpatient infusion: _____
5. Please specify location of administration if hospital inpatient infusion: _____
6. Please provide the NPI number for the place of administration: _____
7. **Initiation AND Continuation of therapy:**
   a. What is the patient's diagnosis? _____
   b. What other medication has the patient received for their condition? Please list_____
      i. Please describe the response to previous therapies:
      _____
   c. Will the patient be receiving any other treatment for the listed condition while on this medication? Please list:
      _____
   d. Please list any labs values important for diagnosing or monitoring this patient's condition:
      _____
8. **Continuation of therapy:**
   a. Has the patient progressed while on this medication? ☐ yes ☐ no
   b. How has the patient's condition changed while on this medication?
      ☐ Improved: Please describe: _____
      ☐ Stable: please describe: _____
      ☐ Worsened; Please describe: _____
      ☐ Other; Please describe: _____

Chart notes are required for the processing of all requests. Please add any other supporting medical information necessary for our review **(required)**

Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name **Physician Signature** **Date**

Step 2: Checklist	☐ Form Completely Filled Out ☐ Provide chart notes	☐ Attach test results
Step 3: Submit	**By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979**	**By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320**

7/26/2018, 9/18/2018; 1/31/2020; 3/17/2020; 8/9/2021