DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, Maryland 21244-1850

CENTER FOR MEDICARE

ICD-10 Coordination and Maintenance Committee Meeting
March 19, 2024
ICD-10-PCS Therapeutic Agent Topics

Consistent with the requirements of section 1886(d)(5)(K)(iii) of the Social Security Act, applicants submitted requests to create a unique procedure code to describe the administration of a therapeutic agent, such as the option to create a new code in Section X within the International Classification of Diseases, 10th Revision, Procedure Coding System (ICD-10-PCS). CMS is soliciting public comments on the proposed coding options and any clinical questions for the nine procedure code topics associated with new technology add-on payment (NTAP)-related ICD-10-PCS procedure code requests that involve the administration of a therapeutic agent. The deadline to submit comments for topics being considered for an October 1, 2024 implementation is April 19, 2024. Members of the public should send any questions or comments to CMS' ICD-10-PCS mailbox at: ICDProcedureCodeRequest@cms.hhs.gov.

Prior to the March 19, 2024 virtual meeting, CMS will post a question and answer document on our website at https://www.cms.gov/medicare/coding-billing/icd-10-codes/icd-10-coordination-maintenance-committee-materials to address clinical or coding questions that members of the public have submitted related to the nine therapeutic agents. At a later date, CMS will post an updated question and answer document to address any additional clinical or coding questions that members of the public may have submitted by the April 19, 2024 deadline.

CMS will not be presenting the nine NTAP-related ICD-10-PCS procedure code requests that involve the administration of a therapeutic agent at the March 19, 2024 virtual meeting. CMS will present the NTAP-related ICD-10-PCS procedure code requests that do not involve the administration of a therapeutic agent and all non-NTAP-related procedure code requests during the virtual meeting on March 19, 2024.

Comments on all procedure code proposals should be sent to the following email address: ICDProcedureCodeRequest@cms.hhs.gov

Instructions for Joining the ICD-10 Coordination and Maintenance Committee Meetings Govdelivery Subscriber List

To sign up go to the CMS website:
https://public.govdelivery.com/accounts/USCMS/subscriber/new?topic_id=USCMS_124 20

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6. You should receive a SUCCESS message that states (your email address) has been successfully subscribed to ICD-10 Coordination and Maintenance
7. Click on the Finish button at bottom of screen.
8. You should now be on the Welcome Quick subscribe page. You can subscribe to receive information from a list of topics of your choice from our partner organizations by checking the boxes; unsubscribe by unchecking the boxes.
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NTAP-Related ICD-10-PCS Procedure Code Requests That Involve Administration of a Therapeutic Agent

** Requestor has submitted a New Technology Add-on Payment (NTAP) application for FY 2025.*
***Requestor intends to submit a NTAP application for FY 2026 consideration.*

The slide presentations for these procedure code topics are available at: https://www.cms.gov/medicare/coding-billing/icd-10-codes/icd-10-coordination-maintenance-committee-materials.

Note: References may appear in either a topic background paper, the accompanying slide deck, or both.

ICD-10 TIMELINE

A timeline of important dates in the ICD-10 process is described below:

March 19-20, 2024	The ICD-10 Coordination and Maintenance Committee Meeting.
March 2024	Recordings and slide presentations of the March 19-20, 2024 ICD-10 Coordination and Maintenance Committee Meeting will be posted on the following web pages: **Diagnosis code portion of the recording and related materials–** https://www.cdc.gov/nchs/icd/icd10cm_maintenance.htm **Procedure code portion of the recording and related materials–** https://www.cms.gov/medicare/coding-billing/icd-10-codes/icd-10-coordination-maintenance-committee-materials
April 1, 2024	Any new or revised ICD-10 codes finalized from the September 2023 ICD-10 Coordination and Maintenance Committee meeting will be implemented on April 1, 2024.
April 19, 2024	**Deadline for receipt of public comments on proposed new codes and revisions discussed at the March 19-20, 2024 ICD-10 Coordination and Maintenance Committee Meeting being considered for implementation on October 1, 2024**.
April 2024	Notice of Proposed Rulemaking to be published in the Federal Register as mandated by the Omnibus Budget Reconciliation Act of 1986, Public Law 99-509 (Pub. L. 99-509). This notice will include references to the FY 2025 ICD-10-CM diagnosis and ICD-10-PCS procedure codes finalized to date. It will also include proposed revisions to the MS-DRG system based on ICD-10-CM/PCS codes on which the public may comment. The proposed rule can be accessed at: https://www.cms.gov/medicare/payment/prospective-payment-systems/acute-inpatient-pps
May 17, 2024	**Deadline for receipt of public comments on proposed new codes and revisions discussed at the March 19-20, 2024 ICD-10 Coordination and Maintenance Committee Meeting being considered for implementation on April 1, 2025.** **Deadline for receipt of public comments on proposed new diagnosis codes and revisions discussed at the March 19-20, 2024 ICD-10 Coordination and Maintenance Committee Meeting being considered for implementation on October 1, 2025**.

May/June 2024	Final addenda posted on web pages as follows: **Diagnosis addendum -** https://www.cdc.gov/nchs/icd/Comprehensive-Listing-of-ICD-10-CM-Files.htm **Procedure addendum -** https://www.cms.gov/medicare/coding-billing/icd-10-codes
June 7, 2024	**Deadline for requestors: Those members of the public requesting that topics be discussed at the September 10-11, 2024 ICD-10 Coordination and Maintenance Committee Meeting must have their requests submitted to CMS for procedures and NCHS for diagnoses.** Requestors should indicate if they are submitting their code request for consideration for an April 1, 2025 implementation date or an October 1, 2025 implementation date. The ICD-10 Coordination and Maintenance Committee will make efforts to accommodate the requested implementation date for each request submitted, however, the Committee will determine which requests will be presented for consideration for an April 1, 2025 implementation date or an October 1, 2025 implementation date.
July 2024	Federal Register notice for the September 10-11, 2024 ICD-10 Coordination and Maintenance Committee Meeting will be published. This will include the tentative agenda.
August 1, 2024	Hospital Inpatient Prospective Payment System final rule expected to be published in the Federal Register as mandated by Pub. L. 99-509. This rule will also include links to all the final codes to be implemented on October 1, 2024. This rule can be accessed at: https://www.cms.gov/medicare/payment/prospective-payment-systems/acute-inpatient-pps
August 2024	Tentative agenda for the Procedure portion of the September 10, 2024 ICD-10 Coordination and Maintenance Committee Meeting will be posted on the CMS webpage at – https://www.cms.gov/medicare/coding-billing/icd-10-codes/icd-10-coordination-maintenance-committee-materials Tentative agenda for the Diagnosis portion of the September 11, 2024 ICD-10 Coordination and Maintenance Committee Meeting will be posted on the NCHS webpage at - https://www.cdc.gov/nchs/icd/icd10cm_maintenance.htm

September 10-11, 2024	The September 2024 ICD-10 Coordination and Maintenance Committee Meeting is anticipated to be fully virtual by zoom and dial-in. Those who wish to attend must participate via Zoom Webinar or by dialing in.
September 2024	Recordings and slide presentations of the September 10-11, 2024 ICD-10 Coordination and Maintenance Committee Meeting will be posted on the following web pages: **Diagnosis code portion of the recording and related materials–** https://www.cdc.gov/nchs/icd/icd10cm_maintenance.htm **Procedure code portion of the recording and related materials–** https://www.cms.gov/medicare/coding-billing/icd-10-codes/icd-10-coordination-maintenance-committee-materials
October 1, 2024	New and revised ICD-10-CM and ICD-10-PCS codes go into effect along with MS-DRG changes. Final addenda available on web pages as follows: **Diagnosis addendum –** https://www.cdc.gov/nchs/icd/Comprehensive-Listing-of-ICD-10-CM-Files.htm **Procedure addendum –** https://www.cms.gov/medicare/coding-billing/icd-10-codes
October 11, 2024	**Deadline for receipt of public comments on proposed new codes discussed at the September 10-11, 2024 ICD-10 Coordination and Maintenance Committee Meeting being considered for implementation on April 1, 2025.**
November 2024	Any new ICD-10 codes that will be implemented on the following April 1 will be announced. Information on any new codes to be implemented April 1, 2025 will be posted on the following websites: https://www.cdc.gov/nchs/icd/Comprehensive-Listing-of-ICD-10-CM-Files.htm https://www.cms.gov/medicare/coding-billing/icd-10-codes/latest-news
November 13, 2024	**Deadline for receipt of public comments on proposed new codes and revisions discussed at the September 10-11, 2024 ICD-10 Coordination and Maintenance Committee Meeting being considered for implementation on October 1, 2025.**

Medicare Electronic Application Request Information System™ (MEARIS™)

CMS only accepts ICD-10-PCS code request applications submitted via MEARIS™. Requests submitted through the ICDProcedureCodeRequest mailbox will no longer be considered. Within MEARIS™, we have built in several resources to support requestors:

- Please refer to the "Resources" section for guidance regarding the request submission process at: https://mearis.cms.gov/public/resources.
- Technical support is available under "Useful Links" at the bottom of the MEARIS™ site
- Request related questions can be submitted to CMS using the form available under "Contact" at: https://mearis.cms.gov/public/resources?app=icd-10-pcs
- The time required for application request submission, including the time needed to gather relevant information as well as to complete the form may be extensive depending on the nature of the code request. Requestors are, therefore, encouraged to start in advance of the due date to ensure adequate time for submission.

ICD-10-PCS code request submissions are due no later than June 7, 2024 to be considered for the September 10-11, 2024 ICD-10 Coordination and Maintenance Committee Meeting.

Announcement of New Release

A new release of MEARIS™ became available on February 6, 2024 for ICD-10-PCS code request applications. This release enables the submission of information into MEARIS™ to automatically populate a draft background paper. Users will have the opportunity to review and edit the draft background paper that is generated based on the information entered into the system prior to submitting. Requests for new procedure codes must include both a background paper and an accompanying 508 compliant presentation slide deck. Requestors must also indicate if the code request is for consideration for an October 1 implementation date or an April 1 implementation date at the time of submission to be considered complete.

Introductions and Overview

- ICD-10 Coordination & Maintenance (C&M) Committee meeting is a public forum on ICD-10-CM & ICD-10-PCS code updates
- CMS & CDC Co-chair the meetings
  - CMS has lead responsibility on procedure issues
  - CDC has lead responsibility on diagnosis issues
- Coding proposals requested by the public are presented and public given opportunity to comment

Code Proposals

- ICD-10-PCS code proposals being considered for implementation on October 1, 2024
- No final decisions are made at the meeting
- CMS will describe options and recommendations to facilitate discussion
- Public can comment during the meeting and send written comments

Comments on Code Proposals

- Submit written comments by
  - April 19, 2024 for codes being considered for October 1, 2024 implementation
  - May 17, 2024 for codes being considered for April 1, 2025 or October 1, 2025 implementation
- Procedure comments to CMS: ICDProcedureCodeRequest@cms.hhs.gov
- Diagnosis comments to NCHS: nchsicd10cm@cdc.gov

Proposed and Final Rules

- April 2024 – Notice of Proposed Rulemaking, IPPS
  - Includes ICD-10-CM/PCS diagnosis and procedure updates approved prior to March 2024 C&M meeting

- August 2024 – Final rule with links to final codes to be implemented October 1, 2024
  - Includes any additional codes approved from March 19-20, 2024 C&M meeting
  - https://www.cms.gov/medicare/payment/prospective-payment-systems/acute-inpatient-pps

Addenda

- May/June 2024 – Final code updates and addenda posted
  - FY 2025 ICD-10-PCS (Procedures)
    https://www.cms.gov/medicare/coding-billing/icd-10-codes
  - FY 2025 ICD-10-CM (Diagnoses)
    https://www.cdc.gov/nchs/icd/Comprehensive-Listing-of-ICD-10-CM-Files.htm

Public Participation

- For this virtual meeting, the public may participate in the following ways:
  - Participate via Zoom Webinar
  - Listen to proceedings through free conference lines
  - Listen to recordings and view slide presentations
- CMS & CDC hope this provides greater opportunity for public participation

Written Comments

- No matter how you participate – please send written comments by
  - April 19, 2024 for codes being considered for October 1, 2024 implementation
  - May 17, 2024 for codes being considered for April 1, 2025 or October 1, 2025 implementation
  - Procedure comments to CMS: ICDProcedureCodeRequest@cms.hhs.gov
  - Diagnosis comments to NCHS: nchsicd10cm@cdc.gov

ICD-10-PCS Codes Implementation

- ICD-10-PCS codes discussed today under consideration for October 1, 2024 implementation

September 10-11, 2024 C&M Code Requests

- June 7, 2024 – Deadline for submitting topics for September 10-11, 2024 C&M meeting
  - Procedure requests to CMS: https://mearis.cms.gov
  - Diagnosis requests to NCHS: nchsicd10cm@cdc.gov

Topic # 01 – Administration of bentracimab

Issue: There are no unique ICD-10-PCS codes to describe the administration of bentracimab, an investigational monoclonal antibody fragment designed to reverse the antiplatelet activity of ticagrelor, an oral $P2Y_{12}$ inhibitor. An October 1, 2024 implementation date is being requested.

New Technology Application? Yes. The requestor intends to submit a New Technology Add-On Payment (NTAP) application for FY 2026 consideration.

Food & Drug Administration (FDA) Approval? No. A Biologics License Application (BLA) is projected to be submitted to the FDA in the first half of 2024 with a request for Priority Review. Bentracimab is under investigation and upon FDA approval would be the only $P2Y_{12}$ inhibitor reversal agent specific to ticagrelor[1], an oral $P2Y_{12}$ inhibitor that is marketed in the U.S. under the brand name Brilinta®.

Background: Ticagrelor (Brilinta®) is indicated to 1) reduce the risk of cardiovascular death, myocardial infarction (MI) and stroke in patients with acute coronary syndrome or a history of MI, 2) to reduce the risk of a first MI or stroke in patients with coronary artery disease at high risk for such events, and 3) to reduce the risk of stroke in patients with acute ischemic stroke. While the clinical benefit of ticagrelor is well established, there is a trade-off to clinical benefits, as antiplatelet therapy also increases risk and severity of major bleeding and of bleeding associated with surgery or invasive procedures.[2,3] Neither the specific agents that reverse the anticoagulation effect of direct-acting oral anticoagulants (DOAC) nor a blood coagulation factor replacement factor indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) can reverse $P2Y_{12}$ inhibitor antiplatelet effect. Further, the antiplatelet effects of ticagrelor cannot be reliably reversed with platelet transfusion.[1,4]

According to the ticagrelor prescribing information[1], there is no known treatment to reverse ticagrelor's antiplatelet effects, and ticagrelor is not expected to be dialyzable. If a non-deferrable surgery is indicated for a patient on ticagrelor antiplatelet therapy, the surgeon must either proceed while accepting the increased bleeding risk or postpone the procedure for several days while accepting the incrementally but steadily increasing thrombotic risks associated with delaying a clinically indicated procedure without antiplatelet protection.[2] All major guidelines recommend cessation of oral $P2Y_{12}$ receptor antagonists at least 3 to 5 days before surgery[5], which places the patient at interim risk for thrombotic complications. Significant patient risk factors for major bleeding in patients on ticagrelor antiplatelet therapy include advanced age, chronic kidney disease, and diabetes; all are also factors for ischemic risk.[6] Many other risk factors exist, including

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[1] Brilinta (ticagrelor), prescribing information. Astra Zeneca.
[2] Bhatt DL, et al. Bentracimab for ticagrelor reversal in patients undergoing urgent surgery. *NEJM Evidence;* DOI:10.1056/EVIDoa2100047, December 2021.
[3] Bhatt DL, et al. Antibody-based ticagrelor reversal agent in healthy volunteers. *N Engl J Med* 2019;380:1825-33. DOI:10.1056/NEJMoa1901778, March 2019.
[4] Teng J, et al. Effects of autologous platelet transfusion on platelet inhibition in ticagrelor-treated and clopidogrel-treated subjects. *J Thromb Haemost.* 2016;14:2342-2352.
[5] Valgimigli M, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J.* 2018;39 :213-260.
[6] Levine GN, et al. 2016 ACC/AHA Guideline Focused Update. *Circulation*. 2016 ;134 :e123-e155.

anemia, heart failure, and certain concomitant medications (including oral anticoagulant therapy, chronic steroid, and chronic NSAID), among others.[6] Unlike other $P2Y_{12}$ inhibitors, ticagrelor is a reversible inhibitor. Patients treated with ticagrelor who experience major bleeding or those who require surgery that cannot be delayed will be candidates for bentracimab to reverse the antiplatelet effect of ticagrelor.

Mechanism of Action
Bentracimab is a specific and selective recombinant human neutralizing antibody fragment (molecular weight 47.4 kDa) that binds to ticagrelor and its active metabolite with high affinity (K_D 20 pmol/L). The mechanism of action of ticagrelor is to occupy the $P2Y_{12}$ receptor on platelets; that receptor is the binding site for adenosine diphosphate, one of the human body's most potent activators of platelet activity. "Activated" platelets are required to generate a stable blood clot; while ticagrelor's occupation of that receptor helps prevent pathologic thrombosis, it also leads to impaired hemostasis when platelet activation is needed in the setting of bleeding. According to the requestor, bentracimab's unique mechanism of action provides immediate and sustained sequestering of active ticagrelor and its active metabolite to prevent inactivation of the $P2Y_{12}$ receptor, providing for rapid reversal of ticagrelor's antiplatelet effects within 5-10 minutes of intravenous infusion. The requestor reports that restoration of platelet function as measured by the $P2Y_{12}$ reaction units (PRU) and vasodilator-stimulated phosphoprotein (VASP) assays has been demonstrated *in vivo* in preclinical animal models and in humans in Phase 1, 2, and 3 clinical studies.

Inpatient Administration of bentracimab
Bentracimab is administered via IV infusion in either the inpatient or outpatient setting and is intended to provide immediate and sustained reversal of the antiplatelet activity of ticagrelor for 24 hours or a duration determined by the clinician. The following information summarizes the dosing and administration of bentracimab that will be submitted with the BLA.

- Dosage form and strength: Bentracimab is available in single-use 6 gram (g) dose glass vials (ready for infusion, no reconstitution needed). For each patient, the administration regimen will use 3 x 6 g dose vials.
- Administration regimen: Initiate treatment with an IV bolus of 6 g over 10 minutes (immediate reversal in 5 minutes); immediately follow with a loading infusion of 6 g over 4 hours (target rate of 25 mg/minute); then immediately follow with a maintenance infusion of 6 g over 12 additional hours.
- How supplied: Bentracimab will be packaged in cartons of 3 x 6 g dose vials (ready for infusion; no reconstitution needed). Store at 2-8ºC.

Results from the pre-specified interim analysis of the Phase 3, REVERSE-IT study[2] (NCT04286438) demonstrate clinically meaningful and potentially life-saving benefits of bentracimab for patients taking ticagrelor who are in need of non-deferrable surgery or an invasive procedure or who experience major bleeding. With immediate and sustained restoration of platelet function, it is anticipated that bentracimab will contribute to an improved, streamlined, and consistent patient care pathway and will relieve patients and physicians from making difficult choices between accepting the higher bleeding risk to perform non-deferrable procedures while taking ticagrelor and attempting to delay necessary invasive procedures with potential thrombotic risk after ticagrelor is discontinued. According to the requestor, given the rapid onset and offset of action of bentracimab, patients will be able to remain on ticagrelor for the benefit of platelet inhibition until surgery, risks associated with surgery will be mitigated, and physicians will be able

to restart oral antiplatelet therapy once hemostasis is reached, as needed for individual patients. In addition, the requestor stated that if bentracimab becomes a new standard of care, the benefit-risk profile in ticagrelor-treated patients will be enhanced by supporting adequate hemostasis and improvement in management of major bleeding or by improved risk mitigation in non-deferrable surgery or invasive procedure when ticagrelor washout is not feasible or desirable**.**

Current Coding: There are no unique ICD-10-PCS codes to describe the administration of bentracimab. Facilities can report the intravenous administration of bentracimab using one of the following codes:

3E033GC	Introduction of other therapeutic substance into peripheral vein, percutaneous approach
3E043GC	Introduction of other therapeutic substance into central vein, percutaneous approach

Coding Options

Option 1. Do not create new ICD-10-PCS codes for the intravenous administration of bentracimab. Continue coding as listed in current coding.

Option 2. Create new codes in section X, New Technology, to identify the intravenous administration of bentracimab.

Section	**X** New Technology
Body System	**W** Anatomical Regions
Operation	**0** Introduction: Putting in or on a therapeutic, diagnostic, nutritional, physiological, or prophylactic substance except blood or blood products

Body Part	*Approach*	*Device / Substance / Technology*	*Qualifier*
3 Peripheral Vein **4** Central Vein	**3** Percutaneous	**ADD 3** Bentracimab, Ticagrelor Reversal Agent	**A** New Technology Group 10

CMS Recommendation: Option 2, as described above.

Interim Coding Advice: Continue using codes as listed in current coding.

Topic # 02 – Administration of cefepime-taniborbactam

Issue: There are no unique ICD-10-PCS codes to describe the administration of cefepime-taniborbactam. The requestor is seeking an October 1, 2024 implementation date.

New Technology Application? Yes. The requestor has submitted a New Technology Add-on Payment (NTAP) application for FY 2025 consideration.

Food & Drug Administration (FDA) Approval? No. A new drug application (NDA) for cefepime-taniborbactam is currently under review by the FDA. The NDA was submitted on June 22, 2023 with Qualified Infectious Disease Product (QIDP), Fast Track, and Priority Review designations, and is pending approval. The target Prescription Drug User Fee Act (PDUFA) date is February 22, 2024.

Background: In a recent report, the U.S. Centers for Disease Control and Prevention (CDC) reported that rates of antimicrobial resistance (AMR) have increased significantly in the U.S. among bacterial pathogens including those commonly causing complicated UTI (cUTI), pyelonephritis, and bacteremia. The report noted there are over 2.8 million AMR infections annually, directly related to over 35,000 deaths, which may be an underestimate. A Premier analysis estimates that in 2020 approximately 4 million (cUTI) inpatients were treated in a U.S. healthcare facility. Data analysis from 2014 and 2019 of U.S. urinary tract infection (UTI) patients determined that 4.4% of cases were carbapenem resistant (CR) and 24.5% of U.S. UTI patients were bacteremic with 1.7% of cases due to CR pathogens. The indication that 176,000 cases of CR cUTI and ~17,000 bacteremic CR cUTI patients warrants new interventions.

According to the requestor, Cefepime-taniborbactam is an investigational intravenous (IV) beta-lactam antibiotic/beta-lactamase inhibitor (BL/BLI) combination under development for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, melioidosis, and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP). Cefepime-taniborbactam has also demonstrated in vitro coverage against antibiotic resistant gram-negative bacteria, most notably extended spectrum beta-lactamase (ESBL)-expressing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and multidrug-resistant (MDR) *Pseudomonas aeruginosa* (MDR-PA), which can include carbapenem-resistant *P. aeruginosa* (CRPA).

Mechanism of Action
Cefepime inhibits bacterial cell wall synthesis by covalently binding penicillin-binding protein (PBP) enzymes responsible for the final step in transpeptidation during peptidoglycan wall synthesis. This binding causes defects in the bacterial cell wall leading to autolysis and bactericidal activity. The zwitterionic nature of cefepime provides the advantage of enhanced penetration of the gram-negative bacterial outer membrane relative to many other cephalosporins, thus more readily reaching its PBP targets before being inactivated by β-lactamases. Taniborbactam protects cefepime from hydrolysis by serine β-lactamases and metallo-β-lactamases, which are AMR mechanisms. It restores the activity of cefepime against many drug-resistant gram-negative pathogens, including *e*xtended-spectrum-β-lactamase-expressing (ESBL) Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and multidrug-resistant *P. aeruginosa* (MDR-PA) including carbapenem-resistant *P. aeruginosa* (CRPA). Taniborbactam on its own has no antibacterial activity. Cefepime-taniborbactam has demonstrated in vitro coverage against

antibiotic resistant gram-negative bacteria, most notably ESBL-E, CRE, and MDR-PA including some CRPA.

Inpatient Administration of Cefepime-Taniborbactam
Cefepime-taniborbactam is administered together by a health care professional via intravenous infusion to adult patients with cUTI, including pyelonephritis for 7 days. Patients with concurrent bacteremia could also receive cefepime-taniborbactam for up to 14 days. The therapy is supplied as one vial of cefepime and one vial of taniborbactam in a co-packaged presentation. The recommended dose of cefepime-taniborbactam is 2 g cefepime and 0.5 g taniborbactam administered together every 8 hours by intravenous infusion over 2 hours to adult patients with complicated urinary tract infections (cUTI), including pyelonephritis, and with or without concurrent bacteremia caused by susceptible gram-negative pathogens. Dosage adjustments are required for patients with estimate glomerular filtration rate (eGFR) less than 50 mL/min/1.73 m^2 and patients with eGFR greater than or equal to 120 mL/min/1.73 m^2.

Dosage Adjustment in Patients with Renal Impairment (eGFR <50 mL/min/1.73 m^2):
Dosage adjustment is recommended in patients with renal impairment who have an eGFR less than 50 mL/min/1.73 m^2. The recommended cefepime-taniborbactam dosage in adults with varying degrees of renal impairment is presented in Table 1. Monitor renal function in adult patients with changing renal function and adjust the dosage of cefepime-taniborbactam accordingly.

Dosage Adjustment in Patients with Augmented Renal Clearance (eGFR ≥120 mL/min/1.73 m^2):
For patients with eGFR greater than or equal to 120 mL/min/1.73 m2, cefepime-taniborbactam 2.5 g administered every 6 hours by IV infusion over 2 hours is recommended. Monitor renal function in adult patients with changing renal function and adjust the dosage of cefepime-taniborbactam accordingly.

Table 1: Dosage Table of Cefepime-Taniborbactam in Patients with Renal Impairment

eGFR* (mL/min/1.73 m^2	**Recommended Dosage Regimen for cefepime 2g and taniborbactam 0.5g****	**Dosing Interval**
30 to 49	2 g/0.5 g	q12h
20 to 29	1 g/0.25 g	q8h
15 to 19	1 g/0.25 g	q12h
5 to 14	Dose 1: 1 g/0.25 g Subsequent doses: 0.5 g/0.125 g	q24h
<5	Dose 1: 1 g/0.25 g Subsequent doses: 0.5 g/0.125 g	q48h

eGFR: Estimate Glomerular Filtration Rate
*As calculated using the Modified Diet in Renal Disease Formula
**All Doses of cefepime-taniborbactam administered over 2 hours
**The total duration of treatment is 7 days or up to 14 days for patients with concurrent bacteremia

According to the requestor, cefepime-taniborbactam's safety profile indicates the most common adverse effects exhibited were headache, diarrhea, constipation, and nausea.

Current Coding: There are no unique ICD-10-PCS codes to describe the administration of cefepime-taniborbactam. Facilities can report the intravenous administration of cefepime-taniborbactam using one of the following codes:

3E03329	Introduction of other anti-infective into peripheral vein, percutaneous approach
3E04329	Introduction of other anti-infective into central vein, percutaneous approach

Coding Options

Option 1. Do not create new ICD-10-PCS codes for the intravenous administration of cefepime-taniborbactam.

Option 2. Create new codes in section X, New Technology, to identify the intravenous administration of cefepime-taniborbactam.

Section	**X** New Technology
Body System	**W** Anatomical Regions
Operation	**0** Introduction: Putting in or on a therapeutic, diagnostic, nutritional, physiological, or prophylactic substance except blood or blood products

Body Part	*Approach*	*Device / Substance / Technology*	*Qualifier*
3 Peripheral Vein **4** Central Vein	**3** Percutaneous	**ADD 4** Cefepime-taniborbactam Anti-infective	**A** New Technology Group 10

CMS Recommendation: Option 2, as described above.

Interim Coding Advice: Continue using codes as listed in current coding.

Topic # 03 – Administration of ceftobiprole medocaril

Issue: There are no unique ICD-10-PCS codes to describe the administration of ceftobiprole medocaril. The requestor is seeking an October 1, 2024 implementation date.

New Technology Application? Yes. The requestor has submitted a New Technology Add-on Payment (NTAP) application for FY 2025 consideration.

Food & Drug Administration (FDA) Approval? No. The requestor submitted a New Drug Application (NDA) for ceftobiprole medocaril on October 3, 2023. The FDA has reviewed and accepted the ceftobiprole medocaril NDA for 3 indications: *Staphylococcus aureus* Bacteremia (SAB), including right sided infective endocarditis (RIE), Acute Bacterial Skin and Skin Structure Infections (ABSSSI), and Community Acquired Bacterial Pneumonia (CABP). The requestor received Qualified Infectious Disease Product (QIDP) priority review status for each of the three indications. The FDA set a Prescription Drug User Fee Act (PDUFA) action date of April 3, 2024.

Background: Antibiotic resistance poses a major threat to human health. Infections caused by antibiotic-resistant organisms, including Methicillin-resistant *Staphylococcus aureus* (MRSA), increase morbidity and mortality and increase hospital burden. The CDC estimates 2 million patients/year have infections due to drug-resistant bacteria[1]; resulting in 23,000 deaths annually in the U.S. MRSA contributes to a substantial portion of burden and is classified as a high-priority serious threat that is in urgent need of new treatment options. Additionally, there have been more than 100,000 deaths worldwide due to MRSA that are attributable to antibiotic resistance.

According to the requestor, ceftobiprole medocaril is an advanced generation intravenous bactericidal cephalosporin antibiotic for the treatment of challenging infections that are caused by Gram positive bacteria such as *Staphylococcus aureus*, including MRSA, *Streptococcus pneumoniae*, including *Penicillin-non-susceptible pneumococci* (PNSP) and *Enterococcus faecalis*, as well as non- extended spectrum beta-lactamase producing (non-ESBL) Enterobacterales. Ceftobiprole medocaril retains potent activity against clinically important and commonly encountered pathogens, such as Gram-positive and Gram-negative bacteria that are often resistant to other antibiotics. Ceftobiprole is the active moiety of the prodrug ceftobiprole medocaril, specifically developed and designed to treat these difficult, often resistant infections.

Mechanism of Action
Bactericidal activity is mediated through binding to multiple essential penicillin-binding proteins (PBPs) and inhibiting their transpeptidase activity, which is essential for the synthesis of the peptidoglycan layer of the bacterial cell wall, this inhibition leads to bacterial cell death. Ceftobiprole has a high affinity for *Staphylococcus aureus* PBPs 1 – 4, including PBP2a in methicillin resistant *Staphylococcus aureus,* and PBP2x and PBP2b in penicillin resistant *Streptococcus pneumoniae*. This differentiates ceftobiprole from almost all other beta-lactams that do not have activity against methicillin resistant *Staphylococcus aureus* (MRSA). Ceftobiprole is stable against *Staphylococcus aureus* PC-1 β-lactamases, and in Gram-negatives Class A TEM-1 β-lactamase, SHV-1 β-lactamase, the AmpC enzymes (unless expressed at high levels), and the SME-type carbapenem-hydrolyzing class A β-lactamases.

Inpatient Administration of ceftobiprole medocaril
The proposed dosing for ceftobiprole medocaril is administered as a 500mg, 2-hour intravenous infusion three times a day (Q8h) for 5-14 days for CABP and ABSSSI. For SAB including cases of infective endocarditis, ceftobiprole is administered four times daily (Q6h) as a 2-hour infusion for the first 8 days followed by a three times daily infusion for the subsequent days up to a total of 42 days.

According to the requestor, ceftobiprole medocaril's safety profile is consistent with the cephalosporin drug classification. However, severe adverse effects are 2.8% less than comparators. Common side effects experienced with Ceftobiprole Medocaril therapy includes nausea, diarrhea, vomiting and headache.

Current Coding: There are no unique ICD-10-PCS codes to describe the administration of ceftobiprole medocaril. Facilities can report the administration of ceftobiprole medocaril with the following ICD-10-PCS codes:

3E03329 Introduction of other anti-infective into peripheral vein, percutaneous approach

3E04329 Introduction of other anti-infective into central vein, percutaneous approach

Coding Options

Option 1. Do not create new ICD-10-PCS codes for the intravenous administration of ceftobiprole medocaril.

Option 2. Create new codes in section X, New Technology, to identify the intravenous administration of ceftobiprole medocaril.

Section	**X** New Technology
Body System	**W** Anatomical Regions
Operation	**0** Introduction: Putting in or on a therapeutic, diagnostic, nutritional, physiological, or prophylactic substance except blood or blood products

Body Part	*Approach*	*Device / Substance / Technology*	*Qualifier*
3 Peripheral Vein **4** Central Vein	**3** Percutaneous	**ADD 5** Ceftobiprole Medocaril Anti-infective	**A** New Technology Group **10**

CMS Recommendation: Option 2, as described above.

Interim Coding Advice: Continue using codes as described in current coding.

Topic # 04 – Administration of obecabtagene autoleucel

Issue: There are no unique ICD-10-PCS codes to describe the administration of obecabtagene autoleucel (obe-cel), an autologous CD19 CAR T-cell investigational therapy for the treatment of adult patients with relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (B-ALL). An October 1, 2024 implementation date is being requested.

New Technology Application? Yes. The requestor intends to submit a New Technology Add-On Payment (NTAP) application for FY 2026 consideration.

Food & Drug Administration (FDA) Approval? No. The Biologics License Application (BLA) for obe-cel was submitted to the FDA on November 27, 2023.

Background: Acute Lymphocytic Leukemia (ALL) is classified as being either of B-cell or T-cell lineage. In adults, B-cell ALL accounts for approximately 82% of ALL cases.[1] B-cell ALL is a neoplastic disorder that originates from the clonal overgrowth of a single B lymphocyte progenitor that occurs in both children and adults. ALL is a serious and life-threatening disease and will progress rapidly if left untreated. The National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results Program)[2] reports the rate of new ALL cases were 1.8 per 100,000 per year with an estimated 6,540 new cases in 2023. Median overall survival (OS) is <1 year in adult R/R ALL, with deaths highest among people aged 65-74 years of age. Currently, allogeneic stem cell transplant (allo-SCT) is the only curative treatment for adult R/R ALL. However, older patients or those with overall poor health may not be eligible to receive an allo-SCT, as they may not be able to tolerate pre-transplant conditioning therapy. With current treatment options, up to 90% of adults with newly diagnosed ALL will enter complete remission; only 30-40% of these will achieve long-term remission.[3,4] Current T-cell therapies for adult patients with R/R ALL have limitations, including short duration of response (DOR), poor tolerability, and a need for consolidation with allo-SCT post-treatment.[5,6,7] Specifically, current CD19 CAR T-cell therapy induces increased rates of severe cytokine release syndrome (CRS) and high rates of severe immune effector cell-associated neurotoxicity syndrome (ICANS) with limited persistence of CAR T-cell activity and short duration of response.[8,9] Older patients or those with high tumor burden may not be eligible for CAR T therapies because of these treatment-related toxicities.[10] For adults with R/R ALL, new treatment options are needed to achieve high response rates and long-term remissions, with manageable safety and an improved patient journey.

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[1] Moorman AV, et al. *Blood* 2010;115(2):206-14.

[2] Surveillance, Epidemiology, and End Results (SEER) Program; Cancer Stat Facts: ALL. https://seer.cancer.gov/; accessed October 2023.

[3] American Cancer Society. https://www.cancer.org/cancer/acute-lymphocytic-leukemia/treating/typical-treatment.html (accessed January 2023).

[4] Sheykhhasan M, et al. *Cancer Gene Ther* 2022;29:1080–96

[5] Kantarjian H, et al. *N Engl J Med* 2017;376:836–47.

[6] Hadjivassileva T, et al. ZUMA-3 three-year follow-up [presented at EBMT-EHA 2023].

[7] Shah BD, et al. *Lancet* 2021;398:491–502.

[8] Hay KA, et al. *Blood* 2017; 130:2295–306.

[9] Hay KA. *Br J Haematol* 2018; 183:364–74.

[10] Roddie C, et al. J Clin Oncol 2023;41 (suppl 16):7000 [presented at ASCO 2023]

Mechanism of Action

Obe-cel is an autologous CD19 CAR T-cell investigational therapy with a unique mechanism of action designed to overcome the limitations in clinical activity and safety compared to current CD19 CAR T-cell therapies. Obe-cel specifically binds to and eliminates CD19-expressing B cells, including the cancerous blasts responsible for ALL.[11,12,13] Obe-cel has been purposely designed, with features such as a 4-1BB costimulatory domain and a unique CAT19 binder, to enhance T-cell expansion and persistence, and enable long-term DOR.[14,15,16] The novel CAT19 CAR is designed to have a fast target binding off-rate, a shorter half-life of interactions, and substantially lower affinity to CD19 than the FMC63 binder used in other CAR T-cell therapies. This unique design has the potential to minimize excessive activation of the CAR T-cells and thereby reduce toxicity and be less prone to T-cell exhaustion, which could enhance persistence and improve the ability of the CAR T-cells to engage in serial killing of target cancer cells. [17,18]

Inpatient Administration of obecabtagene autoleucel(obe-cel)

Obe-cel is produced from the patient's own T-cells, which are collected via leukapheresis and genetically modified to express a CD19 CAR. Obe-cel will be shipped and stored in vapor-phase liquid nitrogen shipping containers (below -150ºC) and will be thawed in a 37ºC water bath under sterile conditions prior to administration. Prior to receiving obe-cel treatment, patients receive pre-conditioning beginning Day -6 (fludarabine 30 mg/m^2 followed by cyclophosphamide 500 mg/m^2 on Days -6 and -5; then fludarabine 30mg/m^2on Days -4 and -3). Obe-cel is supplied as a cryopreserved autologous cell suspension packaged in three or more infusion bags overall containing a cell dispersion of the target dose of 410 x 10^6 CD19 CAR-positive viable T-cells:

- 10 x 10^6 CAR-positive viable T-cells in one 50 mL bag
- 100 x 10^6 CAR-positive viable T-cells in one or more 50 mL or 250 mL bags
- 300 x 10^6 CAR-positive viable T-cells in one or more 250 mL bags

The first-in-class tumor burden guided dosing of obe-cel is personalized to each patient based on the levels of disease present in their bone marrow. It was designed to minimize treatment-related toxicity associated with increased tumor burden. Obe-cel will be administered via two intravenous infusions (Day 1 and Day 10) using a syringe or gravity assisted infusion through a central or peripheral venous line over a few minutes (maximum 30 minutes from obe-cel being thawed to preserve cell viability). If there are multiple bags of obe-cel to be administered, one bag should be thawed and safely infused before the next bag is thawed. The first dose (Day 1) is determined by the patient's bone marrow disease burden within 7 days prior to lymphodepletion; the second dose (Day 10) is tailored for a total dose of 410 x 10^6 CAR T-cells.

- If the patient has <20% bone marrow blasts, the Day 1 dose is 100 x 10^6 CAR T-cells; the second dose (Day 10) is 310 x 10^6 CAR T-cells.
- If the patient's tumor burden is >20% bone marrow blasts, the Day 1 dose is 10 x 10^6 CAR T cells and the second dose (Day 10) is 400 x 10^6 CAR T-cells.

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[11] Scheuermann RH and Racila E. *Leuk Lymphoma* 1995;18:385–97.
[12] Roddie C, et al. J Clin Oncol 2021;39:3352–63.
[13] Maude SL, et al. *Blood* 2015;125:4017–23.
[14] Ghorashian S, et al. *Nat Med* 2019;25:1408–14
[15] Ying Z, et a. *Mol Ther Oncolytics* 2019;15:60-8.
[16] Roddie C, et al. *Blood* 2022;140 (suppl 1):7452–3 [presented at ASH 2022].
[17] Long AH, et al. *Nat Med* 2015;21:581–90.
[18] Tantalo DGM, et al. *J Immunother Cancer* 2021;9:e002555.

- Patients with Grade 2 CRS and/or Grade 1 ICANS following the first dose may receive the second dose on Day 10 (±2 days) only if CRS has resolved to Grade 1 or less and ICANS has completely resolved. If necessary, the infusion of the second dose may be postponed beyond Day 10 (±2 days) up to Day 21 to allow for the resolution of the adverse events.

In the pivotal FELIX trial, 94% of infused patients received both obe-cel infusions. In clinical studies, obe-cel has been administered in the inpatient setting; however, the requestor stated its clinical profile supports both hospital inpatient and hospital outpatient administration. According to the requestor, the pivotal FELIX study population represents the largest and most diverse patient population studied for R/R B-ALL with CAR T therapy, including a strong representation of Medicare-eligible patients: a total of 94 patients were treated ranging in age from 20-81 years of age; 48 of the 94 patients were 50 years of age or older, with 21 over 65 years of age. Thirty percent of patients identified as Hispanic, a population with a higher prevalence for B-ALL. Patients were heavily pre-treated with high disease burden at study entry: 29 (30.9%) had ≥3 prior lines of therapy. FELIX study results[19] suggest an improved safety and efficacy profile for obe-cel vs results reported for current standard of care for adult R/R B-ALL in FDA-approved product labels. Of the 94 patients infused with obe-cel, 76% achieved disease response (CR/Cri) (95% CI 66,84), p<0.0001, with a median DOR of 14.1 months (range 1.9 to 19 months) based on a median follow up of 9.5 months; only 13% of patients received subsequent allo-SCT post treatment and were censored from the DOR analysis. The most common Grade ≥3 treatment-emergent adverse events (TEAEs) were neutropenia (36.2%), thrombocytopenia (25.5%), febrile neutropenia (25.5%) and anemia (19.1%). One death (1/94; 1%) was considered obe-cel-related per investigatory assessment (hemophagocytic lymphohistiocytosis [HLH] and neutropenic sepsis). Low rates of ≥3 CRS and/or ICANS were observed. Across all 94 infused patients, CRS grade ≥3 was reported in 3 (3.2%) patients; ICANS grade ≥3 was reported in 7 (7.4%) patients. Tocilizumab and steroid was used to treat CRS in 56% and 17% of patients, respectively. Three (3%) patients required vasopressor for treatment of CRS. Six of the 7 patients (86%) with grade ≥3 ICANS were observed among patients with >75% bone marrow blasts at pre-conditioning.

Current Coding: There are no unique ICD-10-PCS codes to describe the administration of obecabtagene autoleucel. Facilities can report the intravenous administration of obecabtagene autoleucel using one of the following codes:

XW033C7 Introduction of autologous engineered chimeric antigen receptor t-cell immunotherapy into peripheral vein, percutaneous approach, new technology group 7

XW043C7 Introduction of autologous engineered chimeric antigen receptor t-cell immunotherapy into central vein, percutaneous approach, new technology group 7

Coding Options

Option 1. Do not create new ICD-10-PCS codes for the intravenous administration of obecabtagene autoleucel. Continue coding as listed in current coding.

[19] Roddie C, et al. presented at European Hematology Association 2023.

Option 2. Create new codes in section X, New Technology, to identify the intravenous administration of obecabtagene autoleucel.

Section	**X** New Technology
Body System	**W** Anatomical Regions
Operation	**0** Introduction: Putting in or on a therapeutic, diagnostic, nutritional, physiological, or prophylactic substance except blood or blood products

Body Part	*Approach*	*Device / Substance / Technology*	*Qualifier*
3 Peripheral Vein **4** Central Vein	**3** Percutaneous	**ADD 8** Obecabtagene Autoleucel	**A** New Technology Group **10**

CMS Recommendation: Option 2, as described above.

Interim Coding Advice: Continue using current codes as listed in current coding.

Topic # 05 – Administration of odronextamab

Issue: There are no unique ICD-10-PCS codes to describe the administration of odronextamab. The requestor is seeking an October 1, 2024 implementation date.

New Technology Application? Yes. The requestor has submitted a New Technology Add-on Payment (NTAP) application for FY 2025 consideration.

Food & Drug Administration (FDA) Approval? No. Odronextamab was granted Orphan Drug Designation, Fast Track Designation, and Priority Review by the FDA. The requestor submitted a Biologics License Application (BLA) to the FDA seeking approval to market odronextamab for the treatment of adult patients with relapsed or refractory follicular lymphoma (R/R FL) after at least two prior systemic therapies and for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) after at least two prior systemic therapies, including patients with or without prior CAR T therapy. FDA accepted the BLA filing on September 29, 2023. The anticipated Prescription Drug User Fee Act (PDUFA) date is March 31, 2024.

Background: Follicular Lymphoma (FL) is a heterogeneous clinicopathologic entity that includes tumors derived from germinal center B cells. It is the second most common subtype of non-Hodgkin lymphoma (NHL) and is the most common of the clinically indolent NHLs. In the United States as a whole, FL accounts for approximately 35 percent of NHLs and has an estimated incidence of 3.18 cases per 100,000 people. The median age of diagnosis is 64 years with a majority of the patients having advanced stage disease (Stage III/IV) at the time of diagnosis. The 5-year relative survival rate for FL is 90.6%. Approximately 20% of patients experience early disease progression within years of first line treatment (POD24), which is associated with poor outcomes. Despite current improvements in survival rates for FL patients, treating individuals with third line treatments is difficult. Patients with R/R FL face diminishing durability of response with each additional line of therapy. When disease progression is seen within 24 months of initiating first line therapy patients face a poor prognosis. Roughly, 20% of patients with third line treated FL achieve complete response with existing therapies. Studies have shown the median overall survival rate decreased with each line of therapy. The median overall survival not reached in the first line treatment decreased the rate to 11.67 years in the second line treatment and 3.31 years after the fifth line of treatment.

Conversely, diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL) accounting for approximately 25 percent of NHL cases with around 7 cases per 100,000 persons per year. DLBCL can be classified according to the cell of origin as germinal center B-cell-like (GCB), activated B-cell-like (ABC), or non-GCB DLBCL. The most common cytogenetic abnormalities in DLBCL involve the oncogenes B-cell-lymphoma 2 (BCL2), B-cell lymphoma 6 (BCL6), and myelocytomatosis (MYC), which are implicated in the development of high-grade B-cell lymphoma. First line treatments have a 59% complete response rate. However, patients who respond to first line therapy have a 5-year survival rate of 78%. The response and survival rates decrease with each subsequent line of therapy. Outcomes for patients with R/R DBCL are poor. The median overall survival rate after third line therapy is 7.7 months and decreases to 4.4 months after the fourth line of therapy.

According to the requestor, odronextamab is a novel, fully human CD20×CD3 bispecific antibody with an immunoglobulin G4 (IgG4)-based structure that is designed to simultaneously bind to two types of antigens, CD20 found on both healthy and cancerous B cells, and CD3 found on T cells. Simultaneous engagement of both arms of odronextamab results in the activation of immune system T cells, causing it to generate cytotoxic T cells that can destroy the targeted cells, including cancerous B cells. Odronextamab is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (R/R FL) after at least two prior systemic therapies and for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) after at least two prior systemic therapies, including patients with or without prior CAR T therapy.

Mechanism of Action
Odronextamab is a fully human CD20xCD3 bispecific antibody with an IgG4-based structure in B-cell non-Hodgkin lymphoma (B-NHL) created from Veloci-Bi® technology. CD20 is a highly regulated transmembrane protein confined to normal and malignant B cells. It is a well-validated target for B-cell malignancies because it is tightly restricted to the B cell lineage. Odronextamab is designed to simultaneously bind CD20 on cancer cells with CD3-expressing T cells, triggering T-cell-mediated cytotoxicity independent of T-cell-receptor recognition. The fully human design is intended to help reduce potential for immunogenicity and anti-drug antibodies, distinguishing it from the other CD20xCD3 bispecific antibodies in B-NHL, which are humanized IgG1-based bispecific antibodies. Furthermore, IgG4-based antibodies are referred to as "blocking antibodies" because of their reduced ability to elicit an inflammatory immune response.

Inpatient Administration of Odronextamab
Odronextamab is administered inpatient by a health care professional intravenously using a split and step-up dosing design. Cycle 1 for R/R DLBCL initial dose is 0.2 mg and by day 15 and 16 increases to 10 mg. During cycles 2 through 4 the dose is 160 mg. The maintenance dose is 320 mg and begins one week after the end of cycle 4, biweekly. Cycle 1 for R/R FL initial dose is 0.2 mg and increases to 10 mg by day 15 and 16. Cycles 2 through 4 the dose is 80 mg. The maintenance dose is 160 mg and begins one week after the end of cycle 4, biweekly. Maintenance will continue until disease progression, or an unacceptable toxicity occurs.

According to the requestor, Odronextamab's safety profile in patients with R/R FL experienced adverse effects such as pneumonia, progressive multifocal leukoencephalopathy, and systemic mycosis. Additionally, treatment was discontinued due to adverse effects less than 8% of the time. The safety profile in patients with R/R DLBCL includes pneumonia, COVID-19 and pseudomonal sepsis, with less than 8% of treatments being discontinued.

Current Coding: There are no unique ICD-10-PCS codes to describe the administration of odronextamab. Facilities can report the intravenous administration of odronextamab using one of the following codes:

3E03305	Introduction of other antineoplastic into peripheral vein, percutaneous approach
3E04305	Introduction of other antineoplastic into central vein, percutaneous approach

Coding Options

Option 1. Do not create new ICD-10-PCS codes for the intravenous administration of odronextamab. Continue coding as listed in current coding.

Option 2. Create new codes in section X, New Technology, to identify the intravenous administration of odronextamab.

Section	**X** New Technology
Body System	**W** Anatomical Regions
Operation	**0** Introduction: Putting in or on a therapeutic, diagnostic, nutritional, physiological, or prophylactic substance except blood or blood products

Body Part	*Approach*	*Device / Substance / Technology*	*Qualifier*
3 Peripheral Vein **4** Central Vein	**3** Percutaneous	**ADD 9** Odronextamab Antineoplastic	**A** New Technology Group 10

CMS Recommendation: Option 2, as described above.

Interim Coding Advice: Continue using codes as listed in current coding.

Topic # 06 – Administration of Orca-T Allogeneic T-cell Immunotherapy

Issue: There are no unique ICD-10-PCS codes to describe the administration of Orca-T, an allogeneic T-cell immunotherapy. An October 1, 2024 implementation date is being requested.

New Technology Application? Yes. The requestor intends to submit a New Technology Add-On Payment (NTAP) application for FY 2026 consideration.

Food & Drug Administration (FDA) Approval? No. On April 10, 2020 the FDA granted Orphan Drug designation (ODD) and on July 30, 2020 the FDA granted Regenerative Medicine Advanced Therapy (RMAT) designation to Orca-T. Orca Bio is currently enrolling in a registrational Phase 3 trial and will be seeking approval for a Biologics License Application (BLA).

Background: The incidences of acute leukemias and myelodysplastic syndrome (MDS) in the United States are 20,380 new cases per year and approximately 10,000 new cases per year respectively. Initial treatment options for acute leukemias and MDS is influenced by the severity of symptoms and risk classification, medical fitness, and pathologic features. In general, for medically fit patients, therapy includes induction chemotherapy, post-remission consolidation chemotherapy followed by maintenance therapy. For patients who receive a standard allo-transplant, nearly half die within 3 years due to relapse, Graft-versus-host disease (GvHD), infection, or organ failure. Patients with GvHD experience an increase in hospitalizations, drug utilization and mortality.

Orca-T is an allogeneic stem cell and T-cell immunotherapy biologic derived from a Human Leukocyte Antigen (HLA) matched donor and is being evaluated in a phase 3 study for the prevention of moderate-to-severe chronic GvHD or death in patients with acute leukemias and MDS following cytoreductive conditioning.

Mechanism of Action
The primary mechanism of action of Orca-T's hematopoietic stem progenitor cells is to reconstitute the blood and immune system of the recipient with that of a health, matched donor. Orca-T's goal is to safely and effectively build both a long-term and short-term immune system from a healthy matched donor inside of a patient while protecting the patient's tissue and organs from toxicities such as GvHD. The CD34+ cellular drug product of Orca-T acts to build a long-term immune system of a matched donor in the patient. The high precision regulatory Treg cellular drug product of Orca-T, a specialized CD4+ T-cell subset, acts to protect the patient's tissue and organs from any GvHD and other toxicities that result in non-relapse mortality. Treg cells are critical for establishing and maintaining self-tolerance from the immune system. The conventional Tcons cellular drug product of Orca-T acts to rapidly reconstitute the donor's immune system, mediating the graft-versus-leukemic effect, graft-versus-infection and the inflammatory responses, providing protection against infections by inserting a bridge immune system from a matched donor in the recipient undergoing cellular therapy. Stimulation of an inflammatory response against the recipient's solid organs such as liver, skin and gut can result in GvHD. GvHD is a potentially serious complication of allogeneic stem cell transplantation and is understood to be caused by the graft (allogeneic donor) T-cells reacting against host (recipient) organs.

Inpatient Administration of Orca-T
Orca-T is for allogeneic use only and infusions should be performed at room temperature. A leukodepleting filter and blood warmers should not be used. Central venous access is recommended for the infusion of Orca-T. After confirming the patient's identity matches the patient identifiers on each of the Orca-T cell therapy infusion bags, prime the tubing with normal saline prior to infusion. Infuse the entire contents of the Orca-T CD34+ infusion bag on Day 0 beginning by either gravity or a peristaltic pump at a rate of up to 5 mL/min and also infuse the entire contents of the Orca-T Treg infusion bag on Day 0 as soon as the CD34+ infusion bag has been infused. Infuse the Orca-T Treg infusion bag by either gravity or a peristaltic pump at a rate of up to 5 mL/min. Infuse the entire contents of the Orca-T Tcon infusion bag on Day +2 (48-72 hours) after the start of the CD34+ infusion bag. Infusion of the Orca-T Tcon infusion bag may be delayed up to Day +5. Begin infusion of Orca-T CD34+ and Treg infusion bags before the expiration time printed on the product label. The Orca-T Tcon infusion bag is thawed and diluted at the clinical site. Gently agitate each infusion bag to prevent cell clumping. Begin infusion of Tcon within 1 hour after thaw. Following infusion of Orca-T CD34+, Treg and Tcon infusion bags, patients should be monitored per institutional guidelines for patients who have received an allograft with vital signs recorded.

Vital signs checks (weight excluded) should be initiated within 30 minutes after the start of infusion for each Orca-T cellular product or the SoC control allograft. Vital sign checks should then be repeated every 30 ± 5 min until 2 hours after the start of infusion. Participants in the Orca-T group receive the CD34+ and Treg Drug Products sequentially on day 0. Once the Treg Drug Product is administered, the timing of vital signs checks should be based on the start of infusion of this drug product.

Current Coding: There are no unique ICD-10-PCS codes to describe the administration of Orca-T allogeneic T-cell immunotherapy. Facilities can report the intravenous administration of Orca-T immunotherapy using one of the following codes:

3E033GC	Introduction of other therapeutic substance into peripheral vein, percutaneous approach
3E043GC	Introduction of other therapeutic substance into central vein, percutaneous approach

Coding Options

Option 1. Do not create new ICD-10-PCS codes for the intravenous administration of Orca-T immunotherapy. Continue coding as listed in current coding.

Option 2. Create new codes in section X, New Technology, to identify the intravenous administration of Orca-T immunotherapy.

Section	**X** New Technology
Body System	**W** Anatomical Regions
Operation	**0** Introduction: Putting in or on a therapeutic, diagnostic, nutritional, physiological, or prophylactic substance except blood or blood products

Body Part	*Approach*	*Device / Substance / Technology*	*Qualifier*
3 Peripheral Vein **4** Central Vein	**3** Percutaneous	**ADD B** Orca-T Allogeneic T-cell Immunotherapy	**A** New Technology Group **10**

CMS Recommendation: Option 2, as described above.

Interim Coding Advice: Continue using codes as listed in current coding.

Topic # 07 – Administration of RP-L201 (marnetegragene autotemcel)

Issue: There are no unique ICD-10-PCS codes to describe the administration of RP-L201 (marnetegragene autotemcel), an autologous gene therapy. An October 1, 2024 implementation date is being requested.

New Technology Application? Yes. The requestor intends to submit a New Technology Add-on Payment (NTAP) application for FY 2026 consideration.

Food & Drug Administration (FDA) Approval? Marnetegragene autotemcel (RP-L201) was granted U.S. Orphan Drug designation in November 2016, Rare Pediatric designation in November 2018, Fast Track designation in December 2018, and Regenerative Medicine Advanced Therapy (RMAT) designation in March 2021, for the treatment of severe Leukocyte Adhesion Deficiency Type I (LAD-I). A Biologics License Application (BLA) for RP-L201 was submitted on August 1, 2023. The target Prescription Drug User Fee Act (PDUFA) date is June 30, 2024.

Background: Severe LAD-I is an extremely rare, pediatric disease caused by mutations in the *ITGB2* gene that encodes the CD18 protein, the common beta subunit of the β2 integrins, which is expressed on the surface of leukocytes and is crucial for neutrophil mediated responses to viral, bacterial, and fungal intrusion. Low neutrophil CD18 expression leads to a loss of immune response, resulting in recurrent severe infections. The global prevalence is approximately one case per every million individuals, of which >60% are categorized as severe based on well-established biomarkers.[1,2] Patients with severe LAD-I face mortality rates of 60-75% before reaching the age of 2, and those who surpass the age of 5 are rare.

Allogeneic hematopoietic stem cell transplant (HSCT) is the only current intervention for severe LAD-I capable of conferring long-term survival beyond early childhood years. However, complications are frequent and include high incidences of graft failure, graft-versus-host disease (GvHD), and resistant viral or fungal infections.[3,4] Furthermore, timely identification of a human leukocyte antigen (HLA)-matched donor is challenging and has been estimated to occur only in approximately 25-30% of cases.[5] Unmatched allogeneic HSCT is possible but is less effective. Overall, allogeneic HSCT requires rapid identification of a suitable donor and confers therapy associated risks including short-term mortality, chronic GvHD, and graft failure. According to the requestor, RP-L201 provides an efficacious treatment option that does not require a donor and was well-tolerated in 100% of documented patients treated in a clinical trial

[1] Cox D, Weathers D. Leukocyte adhesion deficiency type 1: an important consideration in the clinical differential diagnosis of prepubertal periodontitis. A case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;105:86–90.
[2] Almarza Novoa, Elena et al. Leukocyte adhesion deficiency-I: A comprehensive review of all published cases. *The journal of allergy and clinical immunology. In practice* vol. 6,4 (2018): 1418-1420.e10.
[3] Qasim et al. Allogeneic hematopoietic stem-cell transplantation for leukocyte adhesion deficiency. *Pediatrics*. 2009 Mar;123(3):836-40.
[4] Bakhtiar S, Salzmann-Manrique E, Blok H-J, Eikema D-J, Hazelaar S, Ayas M, et al. Allogeneic hematopoietic stem cell transplantation in leukocyte adhesion deficiency type I and III. *Blood Advances.* 2021;5:262-273.
[5] Acevedo, Mary Joseph et al. Outcomes of Related and Unrelated Donor Searches Among Patients with Primary Immunodeficiency Diseases Referred for Allogeneic Hematopoietic Cell Transplantation. *Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation* vol. 25,8 (2019): 1666-1673.

compared to current available treatment that does not confer the same outcomes. [6]

Description and Mechanism of Action
RP-L201 is an autologous gene therapy comprised of a patient's hematopoietic stem cells (autologous HSCs) that have been genetically modified ex vivo and then infused into the patient. Given the severity of LAD-I, RP-L201 treatment is administered as soon as possible after diagnosis. Patients receive anti-inflammatory therapy approximately 2 weeks prior to initiation of hematopoietic stem and progenitor cell (HSPC) mobilization and 1–2 weeks prior to infusion of RP-L201. Mobilization and selection of $CD34^+$ HSPCs from blood is followed by transduction with a lentiviral vector (LV) encoding for functional human CD18 *ITGB2* gene (Chim-CD18-WPRE LV), followed by cryopreservation of the transduced HSPCs.

If the amount of $CD34^+$ cells available for infusion is at least 2×10^6 viable $CD34^+$ cells/kg, patients receive myeloablative conditioning with I.V. busulfan over 4 days and receive an infusion of gene-corrected HSPCs 24–48 hours after the final busulfan dose. Patients are infused with RP-L201 in the inpatient setting and hospitalized until HSPC reconstitution is determined.

RP-L201 adds functional *ITGB2* genes into patients' hematopoietic stem cells (HSCs) through transduction of autologous $CD34^+$ cells with Chim-CD18-WPRE LV. The *ITGB2* gene encodes for the CD18 protein, which is expressed on leukocytes.

After RP-L201 infusion, gene-modified $CD34^+$ HSCs engraft in the bone marrow enabling hematopoiesis in which the *ITGB2* gene will be transcribed and translated to produce the therapeutic CD18 protein with a preferential expression in mature myeloid cells. Functional CD18 protein is essential for formation of a functional β2 integrin heterodimer on the surface of leukocytes. Leukocytes expressing this heterodimer can adhere to the endothelial cell surface via binding to an intercellular adhesion molecule (ICAM-1) which mediates extravasation to infectious and inflammatory sites in tissues. The transformed leukocytes allow patients' bodies to effectively fight infections, in contrast to the defective leukocytes in patients with LAD-I.

Inpatient Administration of RP-L201
All patients are infused with RP-L201 through the central vein in the inpatient setting after appropriate mobilization, apheresis and myeloablative conditioning. A single dose of RP-L201 is composed of one to two infusion bags which contain 0.3 to 20×10^6 $CD34^+$ cells/mL suspended in a cryopreservation solution. Each infusion bag contains approximately 30 mL of RP-L201. The minimum recommended dose of RP-L201 is 2×10^6 $CD34^+$ cells/kg.

Current Coding: There are no unique ICD-10-PCS codes to describe the administration of RP-L201. Facilities can report the intravenous administration of RP-L201 with the following code:

30233C0	Transfusion of autologous hematopoietic stem/progenitor cells, genetically modified into peripheral vein, percutaneous approach

[6] Kohn, DB, Booth, C, Navarro, JS. et al. Gene Therapy for Leukocyte Adhesion Deficiency-I (LAD-I): A Phase I/II Clinical Trial to Evaluate the Safety and Efficacy of the Infusion of Autologous Hematopoietic Stem Cells Transduced With a Lentiviral Vector Encoding the *ITGB2* Gene. Presented at European Society of Gene & Cell Therapy Annual Meeting, Clinical Trials Session, October 12, 2022.

30243C0 Transfusion of autologous hematopoietic stem/progenitor cells, genetically modified into central vein, percutaneous approach

Coding Options

Option 1. Do not create new ICD-10-PCS codes for intravenous administration of marnetegragene autotemcel. Continue using the codes as listed in current coding.

Option 2. Create new codes in section X, New Technology, to identify the intravenous administration of marnetegragene autotemcel.

Section	**X** New Technology
Body System	**W** Anatomical Regions
Operation	**1** Transfusion: Putting in blood or blood products

Body Part	*Approach*	*Device / Substance / Technology*	*Qualifier*
3 Peripheral Vein **4** Central Vein	**3** Percutaneous	**ADD 7** Marnetegragene Autotemcel	**A** New Technology Group **10**

CMS Recommendation: Option 2, as described above.

Interim Coding Advice: Continue using codes as listed in current coding.

Topic # 08 – Administration of zanidatamab

Issue: There are no unique ICD-10-PCS codes to describe the administration of zanidatamab, an investigational human epidermal growth factor receptor 2 (*HER2*)-targeted bispecific antibody under evaluation for the treatment of adult patients with previously treated, locally advanced/metastatic *HER2*-positive biliary tract cancer (BTC). An October 1, 2024 implementation date is being requested.

New Technology Application? Yes. The requestor intends to submit a New Technology Add-On Payment (NTAP) application for FY 2026 consideration.

Food & Drug Administration (FDA) Approval? No. Results from phase IIb HERIZON-BTC-01 will form the basis for the Biologics License Application (BLA). The company initiated the zanidatamab BLA submission in 2023 for accelerated approval in previously treated, adult locally advanced (unresectable) /metastatic HER2-positive BTC and expects to complete the BLA in 1H 2024.

Background: BTC is a highly heterogeneous group of malignancies that affect both the small intrahepatic and large extrahepatic bile ducts (cholangiocarcinoma) or the gallbladder (gallbladder cancer, the most common form of BTC.[1] BTC was ranked as the fifth most common alimentary tract cancer in the U.S. in 2018, after colorectal, pancreatic, stomach, and liver cancers.[2] There are approximately 12,000 *HER2*-positive BTC cases annually[3] in the U.S., Europe, and Japan. Most patients with BTC present with incurable, locally advanced or metastatic disease and are ineligible for surgery.[4] The symptoms of BTC usually present in the later stages and are typically associated with a blockage in the bile duct.[5] The symptoms may include jaundice, itching, light-colored or greasy stool, dark urine, abdominal pain, loss of appetite or weight loss, fever, nausea, or vomiting and depend on whether the cancer is intrahepatic or extrahepatic.[5] In the first-line setting, patients can be treated with palliative cisplatin-gemcitabine or cisplatin-gemcitabine plus durvalumab, which results in improved overall survival (OS) compared with cisplatin-gemcitabine alone.[6] For patients with locally advanced/metastatic BTC who progress after first-line treatment, standard second-line and later-line treatments offer limited clinical benefit with overall response rate (ORR) of 5-15%[7,8] and median progression-free survival (mPFS) of 4.0 months.[7] *HER2* amplification/overexpression is observed in 20% of gallbladder cancer, 15% of extrahepatic cholangiocarcinoma, and 7% of intrahepatic cholanglocarcinoma.[1] There are no approved *HER2*-targeted therapies for BTC.

[1] Moeini A, et al. *JHEP Rep*. 2021;3(2):100226.
[2] Jiang Y, et al. *BMC Gastroenterol*. 2022;22(1):546.
[3] Incidence sources: Kantar reports; ToGA surveillance report; SEER, cancer.gov ; ClearView Analysis; GLOBOCAN; data on file. Europe represents major markets, U.K., France, Germany, Spain, Italy.
[4] Tella SH, et al. *Lancet Oncol*. 2020;21(1):e29–e41.
[5] American Cancer Society. Signs and Symptoms of Bile Duct Cancer. Accessed May 2023. Available from https://www.cancer.org/cancer/bile-duct-cancer/detection-diagnosis-staging/signs-symptoms.html.
[6] Harding JJ, et al. *Lancet Oncol*, published online 2 June 2023. DOI: https://doi.org/10.1016/S1470-2045(23)00242-5.
[7] Lamarca A, et al. *Lancel Oncol* 2021 ;22 :690-701.
[8] Yoo C et al. *Lancet Oncol* 2021 ;22 :1560-72.

Mechanism of Action
Zanidatamab is an investigational bispecific antibody that can simultaneously bind two non-overlapping epitopes of *HER2*, known as biparatopic binding.[9] Zanidatamab exerts its antitumor effects through multiple mechanisms of action including dual *HER2* signal blockade, increased binding and removal of *HER2* protein from the cell surface, complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis.[9] Zanidatamab is under evaluation for the treatment of patients with previously treated, locally advanced (unresectable)/metastatic, *HER2*-positive BTC. Continued development of zanidatamab is currently ongoing for the treatment of *HER2*-positive BTC in combination with standard first-line cisplatin-gemicitabine and for other *HER2*-expressing solid tumors, including in a phase III study for first-line treatment of gastroesophageal adenocarcinoma (GEA).

Zanidatamab has shown a manageable safety profile and encouraging antitumor activity in patients with *HER2*-expressing BTC in a Phase 1 trial.[10] Results from the global, multicenter, single-arm, phase IIb HERIZON-BTC-01 study(N=80, Cohort 1) have been recently reported[6,11], including rapid and durable responses: confirmed objective response rate (cORR) by independent central review of 41.3% with most responses identified at first disease assessment, mPFS of 5.5 months, and median duration of response (mDOR) of 12.9 months. According to the requestor, these results demonstrate meaningful clinical benefit with a manageable and tolerable safety profile and support the potential for zanidatamab as a future treatment option in *HER2*-positive BTC.

Inpatient Administration of zanidatamab
Zanidatamab will be supplied as a sterile, single-use, preservative-free, lyophilized powder in a glass vial containing 300 mg of drug product. In phase IIb HERIZON-BTC-01, zanidatamab was administered to patients at 20 mg/kg every 2 weeks (Q2W) on Days 1 and 15 of each 28-day cycle. Zanidatamab is administered by intravenous infusion in 0.9% normal saline over approximately 120 to 150 minutes during Cycle 1. In the HERIZON-BTC-01 study, if the first 2 doses were well tolerated by a given subject, the infusion duration for that subject could be decreased to 90 minutes. If the next 2 doses were well tolerated, the infusion duration could be further decreased to less than 90 minutes; however, the infusion rate was not to exceed 250 mL/hour. Zanidatamab is not to be administered as an intravenous push or bolus and is not to be mixed with other medications. The final zanidatamab dosing and administration instructions, including recommendations for potential dose modifications for zanidatamab-associated toxicity, will be provided in the FDA-approved label. In phase IIb HERIZON-BTC-01, the median duration of treatment was 5.6 months (0.5, 19.8+).[6,11] Zanidatamab will be administered in both the inpatient and outpatient treatment settings.

Between 15 September 2020 and 16 March 2022, 80 patients were enrolled in phase IIb HERIZON-BTC-01 cohort 1: median age 64 (32,79), 45 (56%) female and 35 (44%) male, 65% Asian, 89% Stage IV and 11% Stage III at baseline, with median of 1 (1,7) prior therapies in the locally advanced (unresectable)/metastatic setting. Treatment-related adverse events (TRAEs), any Grade, occurring in ≥10% of patients or Grade ≥3 in ≥2 patients were diarrhea (40%) and infusion-related reaction (35%), both predominantly low-grade and reversible.[6,11] Two TRAEs (decreased ejection fraction and non-infectious pneumonitis) led to zanidatamab discontinuation.[6,11] Three patients had TRAEs that led to dose reductions (1 grade 3 diarrhea, 1 grade 3 diarrhea and grade 3

[9] Weisser NE, et al. Nature Commun 2023; 14:1394.
[10] Merci-Bernstam F, et al. Lancet Oncol 2022 ;23 :1558-1570.
[11] Pant S, et al. J Clin Oncol 41, 2023 (suppl 16; abstr 4008).

nausea, and 1 grade 2 weight decreased).[6,11] No serious TRAEs occurred in more than 1 patient.[6,11] There were no Grade 4 TEAEs and no treatment-related deaths.[6,11] Seven patients were enrolled in Cohort 2 and did not reveal any responses nor unique safety signals.[11]

The median duration of HERIZON-BTC-01 follow-up was 12.4 months (7,24). cORR by independent central review was observed in 33 patients in cohort 1 (41.3%, 95% confidence interval [CI] 30.4-52.8).[6,11] Median time to first response was 1.8 months (range, 1.6-5.5)[6,11]. Median duration of response was 12.9 months (1.5,16.9+). mPFS was 5.5 months (0.3-18.5); OS data are not yet mature.[6,11]

Current Coding: There are no unique ICD-10-PCS codes to describe the administration of zanidatamab. Facilities can report the intravenous administration of zanidatamab using one of the following codes:

3E03305	Introduction of other antineoplastic into peripheral vein, percutaneous approach
3E04305	Introduction of other antineoplastic into central vein, percutaneous approach

Coding Options

Option 1. Do not create new ICD-10-PCS codes for the intravenous administration of zanidatamab. Continue coding as listed in current coding.

Option 2. Create new codes in section X, New Technology, to identify the intravenous administration of zanidatamab.

Section	**X** New Technology		
Body System	**W** Anatomical Regions		
Operation	**0** Introduction: Putting in or on a therapeutic, diagnostic, nutritional, physiological, or prophylactic substance except blood or blood products		
Body Part	*Approach*	*Device / Substance / Technology*	*Qualifier*
3 Peripheral Vein **4** Central Vein	**3** Percutaneous	**ADD C** Zanidatamab Antineoplastic	**A** New Technology Group **10**

CMS Recommendation: Option 2, as described above.

Interim Coding Advice: Continue using codes as listed in current coding.

Topic # 09 – Administration of Donislecel-jujn (Lantidra™)

Issue: There are no unique ICD-10-PCS codes to describe the administration of Donislecel-jujn (Lantidra™). An October 1, 2024 implementation date is being requested.

New Technology Application? Yes. The requestor has submitted a New Technology Add-on Payment (NTAP) application for FY 2025 consideration.

Food & Drug Administration (FDA) Approval? Yes. The FDA approved Donislecel-jujn (Lantidra™) on June 28, 2023. Donislecel-jujn is FDA approved as an allogeneic pancreatic islet cellular therapy indicated for the treatment of adults with Type 1 diabetes (T1D) who are unable to approach target HbA1c because of current, repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

Background: T1D is characterized by the autoimmune-mediated loss of insulin-producing β-cells within the islets of Langerhans in the pancreas and results in the complete deficiency of insulin, causing several potentially life-threatening conditions such as hyper- and hypoglycemia, ketoacidosis, and dehydration. Approximately 1.4 million Americans suffer from T1D.[1] A subset of this population suffers from hard-to-control diabetes, also known as brittle or labile diabetes. This is a particularly difficult form of T1D to treat and is characterized by severe instability of blood glucose levels with frequent and unpredictable episodes of hypoglycemia often requiring hospitalization.

According to the requestor, hypoglycemia unawareness is especially dangerous because the hypoglycemic individual will not know to take corrective action to prevent further deterioration. If left untreated, hypoglycemia may become severe, resulting in confusion, disorientation, loss of consciousness, or, in extreme cases of prolonged hypoglycemia, permanent brain damage or death.[2] Secondary complications, including neuropathy, cardiovascular disease, and retinopathy can be especially common in this hard-to-control form of T1D and there is a significant excess mortality in these patients despite intensive insulin therapy.[3]

Keeping blood glucose levels tightly controlled represents the most effective way to prevent or reduce both the symptoms and chronic complications of T1D.[4] For most T1D patients, insulin therapy is sufficient to manage blood glucose levels in a way that preserves an adequate quality of life. However, for hard-to-control T1D, insulin therapy, even in its most state-of-the-art and intensive form, often remains insufficient. Despite intensive insulin therapy and frequent blood sugar monitoring, these patients still suffer from debilitating symptoms and are left susceptible to numerous secondary complications of T1D. Furthermore, the risk of severe hypoglycemia

[1] Centers for Disease Control and Prevention: National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States., Atlanta, GA, USA (2020)
[2] Cryer, P.E., Davis, S.N., Shamoon, H.: Hypoglycemia in diabetes. Diabetes Care. 26, 1902– 12 (2003). hGps://doi.org/10.2337/diacare.26.6.1902
[3] Lind, M., Svensson, A.-M., Kosiborod, M., Gudbjörnsdovr, S., Pivodic, A., Wedel, H., Dahlqvist, S., Clements, M., Rosengren, A.: Glycemic control and excess mortality in type 1 diabetes. N Engl J Med. 371, 1972–82 (2014). hGps://doi.org/10.1056/NEJMoa1408214
[4] The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 329, 977–986 (1993)

increases with more intensive insulin regimens[5] and is further elevated in patients with hypoglycemia unawareness, with a reported 6-fold increase in the frequency of severe hypoglycemia in these patients.[6]

Over the past few years, advanced medical devices that combine blood sugar monitoring and insulin delivery have been developed. Closed-loop systems (also referred to as an "artificial pancreas") automate subcutaneous insulin delivery via a pump and have shown promise for reestablishing glycemic control in patients with T1D.[7][8][9] However, these products cannot adequately control blood sugar in all patients with brittle T1D, and severe hypoglycemia remains an ongoing and debilitating problem in these patients.[7] Furthermore, sudden death associated with severe hypoglycemia has been reported even with the use of these advanced sensor-pump devices.[10] Beyond intensive insulin therapy, whether by pump or manual administration, treatment for patients with hard-to-control T1D was limited to whole pancreas transplant, which carries with it both surgical and post-procedural risk and is not appropriate for all patients.[11]

The requestor states that Donislecel-jujn (Lantidra™) offers a safe and effective, minimally invasive alternative, as an allogeneic pancreatic islet cellular therapy indicated for the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. Donislecel-jujn (Lantidra™) consists of a suspension of allogeneic pancreatic islets 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).

Mechanism of Action

The active ingredient in Donislecel-jujn (Lantidra™) is allogeneic islets of Langerhans derived from a donor pancreas. Islets contain several types of endocrine (hormone-secreting) cells, including β-, α-, pancreatic peptide- (PP-), δ-, and ε-cells. Pancreatic islets regulate blood glucose levels through secretion of multiple hormones in response to increases and decreases in blood glucose. Endocrine cells within pancreatic islets release insulin, glucagon, somatostatin, pancreatic peptide, and ghrelin. Insulin stimulates glucose uptake by peripheral tissues; glucagon mobilizes

[5] Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes. 46, 271–86 (1997)

[6] Gold, A.E., MacLeod, K.M., Frier, B.M.: Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 17, (1994). hGps://doi.org/10.2337/diacare.17.7.697

[7] Brown, S.A., Kovatchev, B.P., Raghinaru, D., Lum, J.W., Buckingham, B.A., Kudva, Y.C.,Laffel, L.M., Levy, C.J., Pinsker, J.E., Wadwa, R.P., Dassau, E., Doyle, F.J., Anderson, S.M., Church, M.M., Dadlani, V., Ekhlaspour, L., Forlenza, G.P., Isganaitis, E., Lam, D.W., Kollman, C., Beck, R.W.: Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. New England Journal of Medicine. 381, (2019). hGps://doi.org/10.1056/NEJMoa1907863

[8] Kovatchev, B.: The artificial pancreas in 2017: The year of transition from research to clinical practice. Nat Rev Endocrinol. 14, 74–76 (2018). hGps://doi.org/10.1038/nrendo.2017.170

[9]Kovatchev, B.: A Century of Diabetes Technology: Signals, Models, and Artificial Pancreas Control. Trends Endocrinol Metab. 30, 432–444 (2019). hGps://doi.org/10.1016/j.tem.2019.04.008

[10] Nishihama, K., Eguchi, K., Maki, K., Okano, Y., Tanaka, S., Inoue, C., Uchida, A., Uemura, M., Suzuki, T., Yasuma, T., D'Alessandro-Gabazza, C.N., Gabazza, E.C., Yano, Y.: Sudden Death Associated with Severe Hypoglycemia in a Diabetic Patient During Sensor- Augmented Pump Therapy with the Predictive Low Glucose Management System. Am J Case Rep. 22, e928090 (2021). Gps://doi.org/10.12659/AJCR.928090

[11] Maffi, P., Secchi, A.: Islet Transplantation Alone Versus Solitary Pancreas Transplantation: an Outcome-Driven Choice? Curr Diab Rep. 19, 26 (2019). hGps://doi.org/10.1007/s11892-019-1145-2

glucose from the liver into circulation; somatostatin inhibits both α- and β-cell secretions; pancreatic peptide inhibits pancreatic exocrine secretion; and ghrelin inhibits insulin secretion. The primary mechanism of action of Donislecel-jujn (Lantidra™) is believed to be secretion of insulin by infused (transplanted) β- cells.

Inpatient Administration of Donislecel-jujn (Lantidra™) Allogeneic Pancreatic Islet Cellular Suspension
The proposed dosing for Donislecel-jujn (Lantidra™) is equal to Islet Equivalents (IE) per kilogram of a recipient's body weight (IE/kg). The recommended dosage is greater than or equal to 5,000 IE/kg for initial transplant; greater than or equal to 4,500 IE/kg for subsequent transplants. Patients receive a minimum of 1 infusion and a max of 3 infusions. 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.

Each dose of Donislecel-jujn (Lantidra™) is provided as two (2) infusion bags connected to each other via sterile connector. One bag contains Donislecel-jujn (Lantidra™) up to a maximum of 1 x 10^6 EIN in 400mL of transplant media and the second bag (Rinse Bag) contains transplant media (light yellow liquid only with no cellular aggregates present) used to rinse the Donislecel-jujn (Lantidra™) bag and the infusion line. Interventional radiologists and surgeons with expertise in islet cell infusion may administer the therapy in an interventional radiology suite or operating suite under controlled aseptic conditions. Donislecel-jujn (Lantidra™) is infused into the hepatic portal vein, via percutaneous or transvenous transhepatic access, or if these are not feasible, via laparoscopic or open surgical (mini laparotomy) access. Following transplant, the patient is monitored for graft function, immunosuppression levels, and safety in the hospital for a minimum of 24 hours.

According to the requestor, the islet transplantation procedure is minimally invasive, generally safe, and includes less procedural risk than whole pancreas transplantation. The primary risk is related to concomitant medications, especially immunosuppressants, and the long-term safety outcomes of Donislecel-jujn (Lantidra™) clinical trials (and the clinical trials of other allogeneic islet products) are consistent with what has been observed with chronic immunosuppressant use.

Current Coding: There are no unique ICD-10-PCS codes to describe the administration of donislecel-jujn. Facilities can report the intravenous portal vein administration of donislecel-jujn using the following code:

3E033U1	Introduction of nonautologous pancreatic islet cells into peripheral vein, percutaneous approach

Coding Options

Option 1. Do not create new ICD-10-PCS codes for the intravenous administration of donislecel-jujn. Continue coding as listed in current coding.

Option 2. Create new codes to identify in section X, New Technology, to identify the intravenous administration of donislecel-jujn.

Section	**X** New Technology
Body System	**W** Anatomical Regions
Operation	**0** Introduction: Putting in or on a therapeutic, diagnostic, nutritional, physiological, or prophylactic substance except blood or blood products

Body Part	*Approach*	*Device / Substance / Technology*	*Qualifier*
3 Peripheral Vein	**3** Percutaneous	**ADD D** Donislecel-jujn Allogeneic Pancreatic Islet Cellular Suspension	**A** New Technology Group **10**

CMS Recommendation: Option 2, as described above.

Interim Coding Advice: Continue using codes as listed in current coding.