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

CENTER FOR MEDICARE

Agenda

ICD-10 Coordination and Maintenance Committee Meeting
Department of Health and Human Services
Centers for Medicare & Medicaid Services
Virtual Meeting
ICD-10-PCS Topics
September 14, 2021

CMS is continuing to modify the approach for presenting the new technology add-on payment (NTAP) related ICD-10-PCS procedure code requests that involve the administration of a therapeutic agent. 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 ICD-10-PCS procedure code classification. CMS will initially only display those meeting materials associated with the NTAP related ICD-10-PCS procedure code requests that involve the administration of a therapeutic agent.

1. Administration of Fostamatinib — Pages 10-12
2. Administration of broad consortium microbiota-based live biotherapeutic suspension — Pages 13-16

The slide presentations for these procedure code topics are available at: https://www.cms.gov/Medicare/Coding/ICD10/C-and-M-Meeting-Materials.

CMS will solicit public comments regarding any clinical questions or coding options included for these two procedure code topics in advance of the meeting continuing through the end of the public comment period. The deadline to submit comments for topics being considered for April 1, 2022 implementation is October 15, 2021 and the deadline to submit comments for topics being considered for an October 1, 2022 implementation is November 15, 2021. Members of the public should send any questions or comments to the CMS mailbox at: ICDProcedureCodeRequest@cms.hhs.gov by the designated deadlines.

CMS intends to post a question and answer document in advance of the meeting to address any clinical or coding questions that members of the public may have submitted. Following the conclusion of the meeting, 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 during the meeting that CMS was not able to address or that were submitted after the meeting.

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 will continue to be presented during the virtual meeting on September 14, 2021, consistent with the standard meeting process.

Instructions to join the virtual meeting on September 14, 2021 are as follows:

Zoom Webinar and Dial-In Information

- This meeting will be conducted via Zoom Webinar. The URL to join the Zoom Webinar, the password, and the call-in numbers are the same for both days of the meeting. Meeting details for each day are as follows.
- Day 1: September 14, 2021: The meeting will begin promptly at 9:00 AM ET and will end at 5:00 PM ET. Lunch will be held from 12:30 PM to 1:30 PM.
- Day 2: September 15, 2021: The meeting will begin promptly at 9:00 AM ET and will end at 5:00 PM ET. Lunch will be held from 12:30 PM to 1:30 PM.

To minimize feedback to the maximum extent possible, join the meeting using only **ONE** of the options listed below.

Option 1: Remote participants (attendees wishing to both view slides and ask questions during the Q&A portions of the meeting) must join the Zoom Webinar via the web. To join this Zoom Webinar conference from a PC, MAC, iPad, iPhone or Android device as well as, connect to the audio portion of the conference:

Click the following URL:
https://cms.zoomgov.com/s/1611807597?pwd=dnB1TWxkRW1HbDRWUytzTURrcUZaQT09
Passcode: 649118

Option 2: Dial-in access is available for listen-only participants. Listen-only participants are participants who wish to only listen to the meeting and do not wish to comment or ask questions during the Q&A portions of the meeting.

1. From your phone, dial U.S.*: 669-254-5252 or 646-828-7666 or 833-568-8864 (Toll Free)
2. Enter the webinar ID: 161 180 7597

*If dialing in from outside of the U.S., visit https://cms.zoomgov.com/u/abTTQHnQHa for a list of Zoom International Dial-in Numbers.

Option 3: To join this Zoom Webinar conference from an H.323/SIP room system:

1. From your room system, dial 161.199.138.10 (US West) or 161.199.136.10 (US East)
2. Enter the webinar ID: 161 180 7597
   Passcode: 649118

   SIP: 1611807597 @sip.zoomgov.com
   Passcode: 649118

Those participating in the Zoom Webinar may ask questions during the Q&A portions of the meeting using the "Raise Your Hand" feature. If time does not permit you to comment or ask a question during the Q&A session, you may submit comments and questions at any time using the "Q&A" feature. All comments and questions submitted using the "Q&A" feature, along with CMS' responses to them, will be posted as soon as possible after the meeting in the "Downloads" section of the CMS web page located at: https://www.cms.gov/Medicare/Coding/ICD10/C-and-M-Meeting-Materials. Remaining questions may be submitted via the CMS ICD-10 Procedure Code Request mailbox at ICDProcedureCodeRequest@cms.hhs.gov.

Note: Proposals for diagnosis code topics will be led by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) and are scheduled to begin following completion of the CMS procedure code proposals on September 14, 2021. Remaining diagnosis code topics will continue to be presented on September 15, 2021. Please visit CDC's website for the Diagnosis agenda located at the following address: http://www.cdc.gov/nchs/icd/icd10cm_maintenance.htm.

Registration for the meeting:
Information on registering can be found at: https://www.eventbrite.com/e/icd-10-coordination-and-maintenance-committee-meeting-tickets-167332278349

***Please note that registration is not required to attend the Zoom Webinar. However, we are providing the ability to register on-line for those required to provide proof of attendance for continuing education purposes.**

Registration for the September 14-15, 2021 ICD-10 Coordination and Maintenance Committee Meeting opened on Monday, August 9, 2021, and will close on Thursday, September 9, 2021.

For questions about the registration process, please contact Mady Hue at 410-786-4510 or marilu.hue@cms.hhs.gov or Andrea Hazeley at 410-786-3543 or andrea.hazeley@cms.hhs.gov.

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

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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.
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ICD-10 TIMELINE

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

September 14-15, 2021	The September 2021 ICD-10 Coordination and Maintenance Committee Meeting is fully virtual by zoom and dial-in.
September 2021	Recordings and slide presentations of the September 14-15, 2021 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/ICD10/C-and-M-Meeting-Materials.html
October 1, 2021	New and revised ICD-10-CM and ICD-10-PCS codes go into effect along with MS-DRG changes. Final addendum available on web pages as follows: **Diagnosis addendum –** https://www.cdc.gov/nchs/icd/icd10cm.htm **Procedure addendum –** https://www.cms.gov/Medicare/Coding/ICD10/
October 15, 2021	**Deadline for receipt of public comments on proposed new codes discussed at the September 14-15, 2021 ICD-10 Coordination and Maintenance Committee Meeting being considered for implementation on April 1, 2022.**
November 2021	Any new ICD-10 codes required to capture new diseases or technology that will be implemented on the following April 1 will be announced. Information on any new codes to be implemented April 1, 2022 will be posted on the following websites: https://www.cdc.gov/nchs/icd/icd10cm.htm https://www.cms.gov/Medicare/Coding/ICD10/
November 15, 2021	**Deadline for receipt of public comments on proposed new codes and revisions discussed at the September 14-15, 2021 ICD-10 Coordination and Maintenance Committee Meeting being considered for implementation on October 1, 2022.**

December 3, 2021	**Deadline for requestors: Those members of the public requesting that topics be discussed at the March 8-9, 2022 ICD-10 Coordination and Maintenance Committee Meeting must have their requests submitted to CMS for procedures and to NCHS for diagnoses by this date.** **Requestors should indicate if they are submitting their code request for consideration for an October 1, 2022 implementation date, or an April 1, 2023 implementation date.**
January 2022	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 October 1, 2022 implementation date or an April 1, 2023 implementation date. Federal Register notice for the March 8-9, 2022 ICD-10 Coordination and Maintenance Committee Meeting will be published. This will include the tentative agenda.
February 2022	Tentative agenda for the Procedure portion of the March 8, 2022 ICD-10 Coordination and Maintenance Committee Meeting posted on CMS webpage as follows: https://www.cms.gov/Medicare/Coding/ICD10/C-and-M-Meeting-Materials.html Tentative agenda for the Diagnosis portion of the March 9, 2022 ICD-10 Coordination and Maintenance Committee Meeting posted on NCHS homepage as follows: https://www.cdc.gov/nchs/icd/icd10cm_maintenance.htm
February 1, 2022	**On-line registration opens for the March 8-9, 2022 ICD-10 Coordination and Maintenance Committee Meeting at:** https://www.cms.gov/apps/events/default.asp. Please note that this meeting will be conducted virtually and registration is not required to attend. However, we are providing the ability to register on-line for those required to provide proof of attendance for continuing education purposes. The on-line registration will be available through March 1, 2022.
March 8-9, 2022	ICD-10 Coordination and Maintenance Committee Meeting.
March 2022	Recordings and slide presentations of the March 8-9, 2022 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/ICD10/C-and-M-Meeting-Materials.html
April 1, 2022	Any new ICD-10 codes to capture new diseases or technology will be implemented on April 1, 2022.

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 April 1, 2022 and October 1, 2022
- 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
  - October 15, 2021 for codes being considered for April 1, 2022 implementation
  - November 15, 2021 for codes being considered for October 1, 2022 implementation
- Procedure comments to CMS ICDProcedureCodeRequest@cms.hhs.gov
- Diagnosis comments to NCHS nchsicd10cm@cdc.gov

Proposed and Final Rules

- April 2021 – Notice of Proposed Rulemaking, IPPS
  - Includes ICD-10-CM/PCS diagnosis and procedure updates approved prior to March 2021 C&M meeting
- August 2021 – Final rule with links to final codes to be implemented October 1, 2021
  - Includes any additional codes approved from March 9-10, 2021 C&M meeting
  - https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS

Addendum

- May/June 2021 – Final code updates and addendum posted
  - FY 2022 ICD-10-PCS (Procedures) http://www.cms.gov/Medicare/Coding/ICD10/index.html
  - FY 2022 ICD-10-CM (Diagnoses) http://www.cdc.gov/nchs/icd/icd10cm.htm

Public Participation

- For this fully virtual meeting, the public may participate in the following ways:
  - Participate via Zoom Webinar.
  - Listen to proceedings through free conference lines
  - Listen to recordingsand 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
  - October 15, 2021 for codes being considered for April 1, 2022 implementation
  - November 15, 2021 for codes being considered for October 1, 2022 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 April 1, 2022 or October 1, 2022 implementation

March 8-9 2022 C&M Code Requests

- December 3, 2021 – Deadline for submitting topics for March 8-9, 2022 C&M meeting
  - Procedure requests to CMS ICDProcedureCodeRequest@cms.hhs.gov
  - Diagnosis requests to NCHS nchsicd10cm@cdc.gov

Administration of Fostamatinib

Issue: There are currently no unique ICD-10-PCS codes to describe the administration of fostamatinib.

New Technology Application? A request for Emergency Use Authorization (EUA) is under review by the U.S. Food and Drug Administration (FDA) for the treatment of hospitalized COVID-19 patients. If approved by the FDA under its COVID-19 EUA, fostamatinib will become eligible for the New COVID-19 Treatment Add-on Payment (NCTAP).[1] The NCTAP policy became effective November 2, 2020, and was established by CMS under the interim final rule for additional policy and regulatory revisions in response to the COVID-19 Public Health Emergency (PHE).

Food & Drug Administration (FDA) Approval? Fostamatinib is marketed in the U.S. as TAVALISSE (fostamatinib disodium hexahydrate) tablets, and is approved in the U.S., Europe, and Canada as a treatment for adult chronic immune thrombocytopenia (ITP). If EUA is granted for fostamatinib by the FDA, the commercially available formulation of TAVALISSE will be made available to hospitals for the treatment of hospitalized COVID-19 patients.

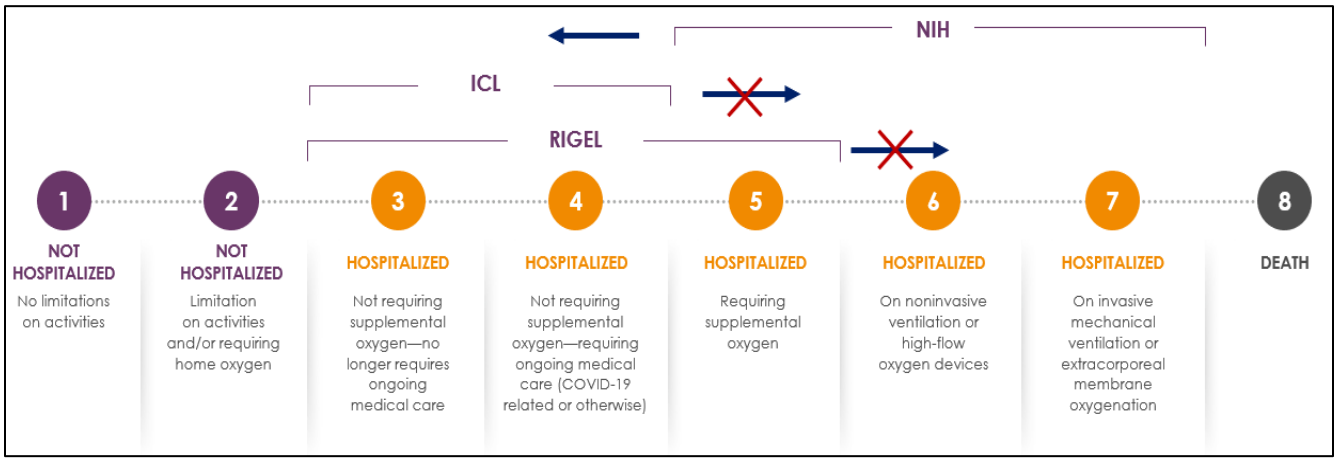
Background: COVID-19 is the infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). SARS-CoV-2 primarily infects the upper and lower respiratory tract and can lead to acute respiratory distress syndrome (ARDS). Additionally, some patients develop other organ dysfunction including myocardial injury, acute kidney injury, shock resulting in endothelial dysfunction and subsequently micro and macrovascular thrombosis.[2] Much of the underlying pathology of SARS-CoV-2 is thought to be secondary to a hyperinflammatory immune response associated with increased risk of thrombosis.[3]

Description and Mechanism of Action for Fostamatinib
Fostamatinib, an oral spleen tyrosine kinase (SYK) inhibitor, is under investigation for the treatment of hospitalized COVID-19 patients. SYK is involved in the intracellular signaling pathways of many different immune cells. According to the requestor, SYK inhibition may improve outcomes in patients with COVID-19 via inhibition of key Fc gamma receptor (FcγR) and c-type lectin receptor (CLR) mediated drivers of pathology, such as inflammatory cytokine release by monocytes and macrophages, production of neutrophil extracellular traps (NETs) by neutrophils, and platelet aggregation.[4,5,6] Fostamatinib has been shown to inhibit NETosis, a unique form of cell death that is associated with mortality in COVID-19 and differentiates fostamatinib from other immunomodulators in COVID-19 trials.[7] Furthermore, SYK inhibition in neutrophils and platelets may lead to decreased thromboinflammation, alleviating organ

[1] https://www.cms.gov/medicare/covid-19/new-covid-19-treatments-add-payment-nctap
[2] Rigel press release, July 14, 2020. https://www.rigel.com/investors/news-events/press-releases/
[3] Becker RC. COVID-19 Update: COVID-19 associated coagulopathy. Journal of Thrombosis and Thrombolysis May 15, 2020
[4] Hoepel W. et al. Anti-SARS-CoV-2 IgG from severely ill COVID-19 patients promotes macrophage hyper-inflammatory responses. bioRxiv July 13, 2020.
[5] Sung P-S and Hsieh S-L (2019) CLEC2 and CLEC5A: Pathogenic Host Factors in Acute Viral Infections. Front. Immunol. 10:2867.
[6] Behnen M. Immobilized Immune Complexes Induce Neutrophil Extracellular Trap Release by Human Neutrophil Granulocytes via Fcγ RIIIB and Mac-1. The Journal of Immunology July 2014.
[7] Strich JR, et al., Fostamatinib Inhibits Neutrophils Extracellular Traps Induced by COVID-19 Patient Plasma: A Potential Therapeutic. *Journal of Infectious Disease,* 2020.

dysfunction in critically ill patients with COVID-19.

World Health Organization (WHO) Ordinal Scale
A special WHO committee arrived at the ordinal scale that measures illness severity over time for a randomized multi-center adaptive trial to evaluate the efficacy and safety of investigational therapeutic agents in combination with standard of care (SOC) for the treatment of hospitalized patients with COVID-19. The 8-point ordinal scale is being used in fostamatinib clinical studies to assess hospitalized COVID-19 patients pre- and post-treatment with fostamatinib.



Adapted from Ordinal Scale for Clinical Improvement, WHO 2020.

Inpatient Administration of Fostamatinib
Fostamatinib was administered to hospitalized COVID-19 patients in the Phase 2 clinical trial by a twice daily oral dose of 150 mg for 14 days plus SOC. The study protocol provided for dose reduction to 100 mg daily, if necessary, because of adverse events (AEs). The study protocol also specified that patients unable to swallow the oral tablets would receive dosing through enteral feeding. In the Phase 2 study, enteral feeding of fostamatinib was administered via nasogastric (NG) tube. No patients were administered fostamatinib via gastrostomy tube, although this method of enteral feeding would not be contraindicated. FDA review is underway; an approved fostamatinib EUA Fact Sheet for Healthcare Providers will not be available until EUA approval.

Fostamatinib will be available to hospitals immediately upon EUA approval as it has received full FDA approval and is commercially available under the brand name, TAVALISSE, for a non-COVID, chronic, outpatient indication: treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

While these 60-count commercially available SKUs will be available for access by the hospitals, the requestor is also working on the manufacturer of SKUs specific to use of fostamatinib under EUA:
- 150 mg tablets: bottles of 30 tablets for use under EUA (NDC 71332-002-05)
- 100 mg tablets, bottles of 30 tablets for use under EUA (NDC 71332-001-05)

Current Coding: There are no unique ICD-10-PCS codes to describe the administration of fostamatinib. Facilities can report the oral or enteral administration of fostamatinib using the following codes:

3E0DXGC	Introduction of other therapeutic substance into mouth and pharynx, external approach
3E0G7GC	Introduction of other therapeutic substance into upper G.I. via natural or artificial opening
3E0H7GC	Introduction of other therapeutic substance into lower G.I. via natural or artificial opening

Coding Options

Option 1. Do not create new ICD-10-PCS codes for the oral or enteral administration of fostamatinib. Continue coding as listed in current coding.

Option 2. Create new codes in section X, New Technology, to identify the oral or enteral administration of fostamatinib.

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*
D Mouth and Pharynx	**X** External	**ADD R** Fostamatinib	**7** New Technology Group 7
G Upper GI **H** Lower GI	**7** Via Natural or Artificial Opening	**ADD R** Fostamatinib	**7** New Technology Group 7

CMS Recommendation: Option 2, as described above.

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

Administration of Broad Consortium Microbiota-Based Live Biotherapeutic Suspension

Issue: There are no unique ICD-10-PCS codes to describe the rectal administration of RBX2660, a broad consortium microbiota-based live biotherapeutic suspension.

New Technology Application? Yes. The requester intends to submit a New Technology Add-on Payment (NTAP) application for FY 2023 consideration.

Food & Drug Administration (FDA) Approval? No. The FDA has granted RBX2660 the following designations: Fast Track status (2013), Breakthrough Therapy status (2015), and amended Orphan Drug status (2017). The requester will be seeking approval for a Biologics License Application (BLA).

Background: *C. difficile* is a bacterium that causes diarrhea and colitis, with complications ranging from dehydration and electrolyte imbalance to toxic megacolon, sepsis, and death.[1,2,3,4,5,6,7,8] *C. difficile* infection (CDI) is a common healthcare-associated infection and a significant cause of morbidity and mortality, especially among elderly, hospitalized patients.[1,2,9,10] Infection recurs in more than 1 in 3 patients (≤35%) treated for an initial episode of CDI and nearly 2 in 3 patients (≤65%) with multiple, prior recurrences.[1,11] The causes of recurrent CDI (rCDI) are not completely understood, although dysbiosis, which is a disruption of the gut's microbial community, is thought to play a major role. In addition to higher readmission rates, rCDI is associated with longer hospital stays, increased mortality, and fewer treatment options than an initial case of CDI.[2,12,13,14]

Standard-of-care antibiotic pharmacotherapy for initial and recurrent episodes of CDI is a predominant risk factor for dysbiosis and is associated with high rates of recurrence.[15,16] In addition

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[1] Smits WK, Lyras D, Lacy DB, Wilcox MH, Kuijper EJ. *Clostridium difficile* infection. *Nat Rev Dis Primers*. 2016;2:16020.
[2] Arbel LT, Hsu E, McNally K. Cost-effectiveness of fecal microbiota transplantation in the treatment of recurrent *Clostridium difficile* infection: a literature review. *Cureus*. 2017;9(8):e1599.
[3] Yacyshyn B. Pathophysiology of *Clostridium difficile*-associated diarrhea. *Gastroenterol Hepatol (N Y).* 2016;12(9):558-560.
[4] Depestel DD, Aronoff DM. Epidemiology of *Clostridium difficile* infection. *J Pharm Pract*. 2013;26(5):464-475.
[5] Fernández-García L, Blasco L, López M, Tomás M. *Clostridium difficile* infection: pathogenesis, diagnosis, and treatment. In: Enany S, ed. *Clostridium difficile—A Comprehensive Overview*. InTech; 2017.
[6] Antharam VC, Li EC, Ishmael A, et al. Intestinal dysbiosis and depletion of butyrogenic bacteria in *Clostridium difficile* infection and nosocomial diarrhea. *J Clin Microbiol*. 2013;51(9):2884-2892.
[7] Ofosu A. *Clostridium difficile* infection: a review of current and emerging therapies. *Ann Gastroenterol.* 2016;29(2):147-154.
[8] Chandrasekaran R, Lacy DB. The role of toxins in *Clostridium difficile* infection. *FEMS Microbiol Rev*. 2017;41(6):723-750.
[9] Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States, 2019. US Department of Health and Human Services, CDC; 2019. Accessed May 10, 2021. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf
[10] Reveles KR, Lee GC, Boyd NK, Frei CR. The rise in *Clostridium difficile* infection incidence among hospitalized adults in the United States: 2001–2010. *Am J Infect Control*. 2014;42(10):1028-1032.
[11] Leffler DA, Lamont JT. *Clostridium difficile* infection. *N Engl J Med*. 2015;372(16):1539-1548.
[12] Olsen MA, Yan Y, Reske KA, Zilberberg MD, Dubberke ER. Recurrent *Clostridium difficile* infection is associated with increased mortality. *Clin Microbiol Infect*. 2015;21(2):164-170.
[13] Shah DN, Aitken SL, Barragan LF, et al. Economic burden of primary compared with recurrent *Clostridium difficile* infection in hospitalized patients: a prospective cohort study. *J Hosp Infect*. 2016;93(3):286-289.
[14] Zilberberg MD, Shorr AF, Jesdale WM, Tjia J, Lapane K. Recurrent *Clostridium difficile* infection among Medicare patients in nursing homes: a population-based cohort study. *Medicine (Baltimore)*. 2017;96(10):e6231.
[15] McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):e1-e48.
[16] Kelly CP. Can we identify patients at high risk of recurrent *Clostridium difficile* infection? *Clin Microbiol Infect*. 2012;18(Suppl 6):21-27.

to antibiotic treatment, dysbiosis may also be triggered by genetic predisposition, diet, stress, or other causes,[4,11] leaving the intestinal microenvironment susceptible to opportunistic bacterial infection, such as those caused by *C. difficile*.[17] Alternative treatments for rCDI such as fecal microbiota transplant (FMT) attempt to treat dysbiosis but have multiple limitations with safety and consistency.[11,18,19,20]

Description of RBX2660

RBX2660 is a nonantibiotic, live biotherapeutic intended to reduce the recurrence of CDI.[21] RBX2660 contains a broad consortium of diverse spore-forming and non-spore-forming bacteria, including *Bacteroides*, which closely mirror that of the healthy human gut microbiome.[22] The standardized donor protocol and quality control process for RBX2660 were established in collaboration with the FDA to reduce the risk of transmissible disease to recipients, including emerging threats such as COVID-19. Donors undergo regular, rigorous blood and stool screening. All donations are quarantined until the specimen passes screening and quality control testing. The donor testing protocol is part of the Chemistry, Manufacturing, and Controls information that will be included in the BLA for RBX2660 and will be reviewed by the FDA as part of the approval process.

Mechanism of Action

The exact mechanism of action for RBX2660 is not fully understood, but it is thought to involve restoration of the composition and diversity of the gut microbiome to suppress *C. difficile* outgrowth and rCDI.[22] Treatment success was associated with a shift of the gut microbiome from dysbiosis, characterized by decreased diversity, to a composition and diversity similar to those of healthy individuals.[22] RBX2660 administration was also associated with a shift in gut bile acid compositions to secondary bile acid predominance,[23] which has been associated with suppression of *C. difficile* outgrowth and rCDI in animal studies.

The safety and efficacy of RBX2660 were evaluated in 6 clinical trials involving more than 1,000 patients. Study participants received a minimum of 1 dose and a maximum of 4 total doses of RBX2660. Duration of follow-up ranged from 6 to 24 months. Treatment with RBX2660 has demonstrated the following:

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[17] Bien J, Palagani V, Bozko P. The intestinal microbiota dysbiosis and *Clostridium difficile* infection: is there a relationship with inflammatory bowel disease? *Therap Adv Gastroenterol*. 2013;6(1):53-68.

[18] Wilcox MH, Gerding DN, Poxton IR, et al; for the MODIFY I and MODIFY II investigators. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med*. 2017;376(4):305-317.

[19] Gerding DN, Kelly CP, Rahav G, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection in patients at increased risk for recurrence. *Clin Infect Dis*. 2018;67(5):649-656.

[20] Tariq R, Pardi SD, Bartlett MG, Khanna S. Low cure rates in controlled trials of fecal microbiota transplantation for recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. *Clin Infect Dis*. 2019;68(8):1351-1358.

[21] Ferring Pharmaceuticals Inc. Ferring and Rebiotix present landmark phase 3 data demonstrating superior efficacy of investigational RBX2660 versus placebo to reduce recurrence of *C. difficile* infection. May 21, 2021. Accessed June 9, 2021. https://www.ferring.com/ferring-and-rebiotix-present-landmark-phase-3-data-demonstrating-superior-efficacy-of-investigational-rbx2660-versus-placebo-to-reduce-recurrence-of-c-difficile-infection/

[22] Blount KF, Shannon WD, Deych E, Jones C. Restoration of bacterial microbiome composition and diversity among treatment responders in a phase 2 trial of RBX2660: an investigational microbiome restoration therapeutic. *Open Forum Infect Dis*. 2019;6(4):ofz095.

[23] Papazyan R. Rapid restoration of bile acid compositions after treatment with investigational microbiota-based therapeutic RBX2660 for recurrent *Clostrioides difficile* infection. Presented at: IDWeek 2020; October 21-25, 2020; virtual meeting.

- In a phase 3 trial, CDI-associated diarrhea remained absent at 8 weeks in 70.4% of patients treated with RBX2660 compared to 58.1% of patients treated with placebo[24]
- In a phase 2 open-label trial, 79.9% of patients were CDI recurrence-free at 8 weeks after RBX2660 treatment[25]
    - Of the patients evaluable for long-term follow-up:
        - 97.2% remained CDI recurrence-free at 6 and 12 months[26,27]
        - 91.6% remained CDI recurrence-free at 24 months[25]
- The biodiversity of the gut microbiome for patients treated with RBX2660 changed to become more similar to the composition of RBX2660[22]
- The microbiome of patients who received RBX2660 experienced more significant and longer-lasting shifts toward donor-like configurations compared to patients who received placebo[28,29]

A total of 188 adverse events (AEs) were reported in 28 participants in the open-label phase 2 PUNCH CD trial. Gastrointestinal (GI)-related AEs were the most common and included mild to moderate diarrhea (24.3%), flatulence (14.0%), abdominal pain/cramping (13.1%), and constipation (13.1%). AEs declined over time, with the majority (72.9%) occurring in the first 30 days. Over half (58.5%) of the AEs were related to CDI. None of the 20 serious AEs reported were related to RBX2660 or its administration; several were related to preexisting conditions.[30]
During the blinded portion of the phase 2b PUNCH CD2 trial, 379 AEs were reported in 82 (64.1%) participants. There were no differences in the number or rate of AEs among blinded treatment groups. The most common AEs were GI disorders. Of the serious AEs reported during the blinded and open-label portions of the study, 31.1% were related to CDI, and 77.8% were related to a preexisting condition. None were related to the rectal administration procedure.[31] Preliminary safety data including the rate of AEs in a phase 3 clinical trial are consistent with those found in phase 2 studies.[24]

Administration of RBX2660
RBX2660 is provided in a prepackaged, single-dose bag with a ready-to-use delivery system for rectal administration. Each dose contains ≥3 billion colony-forming units (CFUs) per 150 mL. The product is shipped frozen to the clinical site in a kit containing 1 bag of frozen RBX2660 and components for administration. RBX2660 must be thawed completely prior to use. To administer

[24] Lee C. Beyond FMT: a pragmatic approach to microbiome therapies: RBX2660 study. Presented at: Digestive Disease Week 2021; May 21-23, 2021; virtual meeting.
[25] Orenstein R, Mische S, Blount D, et al. A long-time coming: final 2-year analysis of efficacy, durability, and microbiome changes in a controlled open-label trial of investigational microbiota-based drug RBX2660 for recurrent *Clostridioides difficile* infections. IDWeek 2019 late breaker oral abstract LB5. *Open Forum Infect Dis*. 2019;6(Suppl 2):S994-S995.
[26] Garcia-Diaz J, Jones C, Karathia H, Fanelli B, Hasan NA, Blount K. Response to microbiota-based drug RBX2660 is associated with reduction in antimicrobial resistance genes in patients with recurrent *Clostridioides difficile* infections. Presented at: ASM Microbe 2019; June 20-24, 2019; San Francisco, CA.
[27] Jones C, Mische S, Blount K, Shannon B. Twelve-month durability of microbiota-based therapy RBX2660 for prevention of recurrent *Clostridium difficile* infection. IDWeek 2019 poster abstract 669. *Open Forum Infect Dis*. 2019;6(Suppl 2):S306.
[28] Kwak S, Choi J, Hink T, et al; CDC Prevention Epicenter Program. Impact of investigational microbiota therapeutic RBX2660 on the gut microbiome and resistome revealed by a placebo-controlled clinical trial. *Microbiome*. 2020;8(1):125.
[29] Langdon A, Schwartz DJ, Bulow C, et al; CDC Prevention Epicenter Program. Microbiota restoration reduces antibiotic-resistant bacteria gut colonization in patients with recurrent *Clostridioides difficile* infection from the open-label PUNCH CD study. *Genome Med*. 2021;13(1):28.
[30] Orenstein R, Dubberke E, Hardi R, et al. Safety and durability of RBX2660 (microbiota suspension) for recurrent *Clostridium difficile* infection: results of the PUNCH CD study. *Clin Infect Dis*. 2016;62(5):596-602.
[31] Dubberke ER, Lee CH, Orenstein R, Khanna S, Hecht G, Gerding DN. Results from a randomized, placebo-controlled clinical trial of a RBX2660-A microbiota-based drug for the prevention of recurrent *Clostridium difficile* infection. *Clin Infect Dis*. 2018;67(8):1198-1204.

RBX2660, the healthcare provider must insert a lubricated tube into the patient's rectum about 12 cm (5 inches). Once the product is fully instilled, the assembly should be removed, and the patient should remain in the administration position for at least 15 minutes. RBX2660 may be administered by a healthcare provider in multiple care settings including inpatient hospital, outpatient hospital clinics, and physician offices, without a requirement for bowel preparation, colonoscopy, or conscious sedation.

Current Coding: There are no unique ICD-10-PCS codes to describe the rectal administration of RBX2660. Facilities can report the rectal administration of RBX2660 with the following ICD-10-PCS code:

3E0H7GC Introduction of other therapeutic substance into lower GI, via natural or artificial opening

Coding Options

Option 1. Do not create new ICD-10-PCS codes for the rectal administration of RBX2660. Continue coding as listed in current coding.

Option 2. Create new codes in section X, New Technology, to identify the rectal administration of RBX2660.

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*
H Lower GI	**7** Via Natural or Artificial Opening	**ADD R** Broad consortium microbiota-based live biotherapeutic suspension	**8** New Technology Group 8

CMS Recommendation: Option 2.

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