



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES  
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 7/16/2015  
LAST REVIEW DATE: 8/19/2021  
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## DIFICID® (fidaxomicin) oral

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Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the [request form](#) in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to [Pharmacyprecert@azblue.com](mailto:Pharmacyprecert@azblue.com). **Incomplete forms or forms without the chart notes will be returned.**

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### Criteria:

- **Criteria for initial therapy:** Dificid (fidaxomicin) is considered **medically necessary** and will be approved when **ALL** of the following criteria are met:
1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Pediatric Gastroenterologist, or Infectious Disease
  2. Individual is 6 months of age or older
  3. A confirmed **OR** strongly suspected diagnosis of *Clostridium difficile*-associated diarrhea (CDAD)
  4. Individual is **ONE** of the following:
    - a. **Adult with initial non-severe episode, or initial severe episode, or recurrent episode of CDAD** that has failure, contraindication or intolerance to a standard 10-day course of oral vancomycin or a prolonged tapered/pulsed dose course of oral vancomycin
    - b. **Child 6 month or older with second or more recurrent episode of CDAD** that has failure, contraindication or intolerance to a prolonged tapered/pulsed dose course of oral vancomycin
  5. **NOT** being used for the treatment of infections other than *Clostridium difficile*
  6. Individual does not have **any** of the following:
    - a. Life-threatening/fulminant infection
    - b. Hypotension
    - c. Septic shock
    - d. Peritoneal signs
    - e. Significant dehydration
    - f. Toxic megacolon

**Initial approval duration:** 10 days

- **Criteria for continuation of coverage (renewal request):** Dificid (fidaxomicin) is considered **medically necessary** and will be approved when **ALL** of the following criteria are met:
1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Pediatric Gastroenterologist, or Infectious Disease
  2. Individual's condition has worsened
    - a. Worsening is defined as:
      - i. Recurrence (either a relapse or reinfection) of CDAD
  3. Individual has failure, contraindication, or intolerance to oral vancomycin
  4. Individual has been adherent with previous course the medication

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5. Individual has not developed any significant adverse drug effects that may exclude continued use
6. **NOT** being used for the treatment of infections other than *Clostridium difficile*
7. Individual does not have **any** of the following:
  - a. Life-threatening/fulminant infection
  - b. Hypotension
  - c. Septic shock
  - d. Peritoneal signs
  - e. Significant dehydration
  - f. Toxic megacolon

**Renewal duration:** 10 days

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:
1. **Off-Label Use of a Non-cancer Medications**
  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

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### **Description:**

Dificid (fidaxomicin) is a macrolide antibiotic approved for treatment of *Clostridioides* (formerly *Clostridium*) *difficile*-associated diarrhea (CDAD) in individuals 6 months of age and older. The safety and efficacy of fidaxomicin in pediatric patients less than 6 months of age has not been established.

*Clostridioides* (formerly *Clostridium*) *difficile* (*C. difficile*) is a spore forming, obligate anaerobic, gram-positive bacillus that is acquired from the environment or by the fecal-oral route. *C. difficile* is the most common cause of antimicrobial-associated diarrhea and is a common health care-associated pathogen. It is responsible for 15-25% of cases of nosocomial diarrhea and 20-30% of antibiotic-associated diarrhea. Clinical symptoms vary widely, from asymptomatic colonization to pseudomembranous colitis with bloody diarrhea, fever, severe abdominal pain, toxic megacolon, sepsis, bowel perforation and death. *C. difficile* infection (CDI) is defined by the presence of symptoms, usually diarrhea, and either a stool test positive for *C. difficile* toxins (toxigenic *C. difficile*) or colonoscopic or histopathologic findings revealing pseudomembranous colitis.

The ability of *C. difficile* to cause disease is due to exotoxins produced by the organism which cause inflammation and mucosal damage. Toxin negative *C. difficile* strains are considered nonpathogenic. Toxigenic (toxin positive) species are capable of producing toxin A, toxin B, and a binary (or a combination) toxin. Since 2003, a particularly hypervirulent strain of *C. difficile*, designated by its North American pulsed-field gel electrophoresis type 1 (NAP1), and by restriction endonuclease analysis type BI, and by its polymerase chain reaction ribotype 027 (NAP1/BI/027) has emerged and has become a major pathogen in the development of CDI.



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Strains with NAP1/BI/027 have increased toxin production, hypersporulation, and are resistance to fluoroquinolone antibiotics. This strain has been described as causing severe disease, including an increased incidence of symptomatic infection relative to colonization, recurrent disease, sepsis, toxic megacolon, bowel perforation, and mortality. It is the strain that has been found in a majority of states within the United States, all provinces of Canada, and numerous European countries. Other strains have also been isolated, but their role in human disease is not fully known.

Approximately 20-40% of individuals treated will experience a recurrence after cessation of therapy. Recurrence can represent either relapse or reinfection. Relapse is defined as recurrence with the original isolate. Reinfection is a recurrence with a new isolate. Recurrence of CDI is highest in the 7-14 days after completion of initial therapy. The risk of recurrence increases as the number of infections or reinfections increase. Failure of treatment is not defined by development of a recurrent episode. Treatment failure is defined as a course of therapy in which a patient has an inadequate response and has an unresolved CDI.

A recent (2017) national guideline from the Society for Healthcare Epidemiology (SHEA) and Infectious Disease Society of America (IDSA) states that either vancomycin or fidaxomicin for 10 days is recommended over metronidazole for an initial episode of CDI. In settings where access to vancomycin or fidaxomicin is limited, metronidazole for 10 days is recommended for an initial episode of non-severe CDI only. Avoid repeated or prolonged courses of metronidazole due to risk of cumulative and potentially irreversible neurotoxicity from metronidazole.

The guideline recommends that fulminant CDI should be treated with vancomycin administered orally as the regimen of choice. If ileus is present, vancomycin can also be administered per rectum. The vancomycin dosage is 500 mg orally 4 times per day and 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema. Intravenously administered metronidazole 500 mg every 8 hours should be administered together with oral or rectal vancomycin, particularly if ileus is present. Fulminant CDI was previously referred to as severe, complicated CDI, and it may be characterized by hypotension or shock, ileus, or megacolon.

For a first recurrence of CDI the guideline recommends treatment with oral vancomycin as a tapered and pulsed regimen rather than a second standard 10-day course of vancomycin **OR** treatment with a 10-day course of fidaxomicin rather than a standard 10-day course of vancomycin **OR** treatment with a standard 10-day course of vancomycin rather than a second course of metronidazole if metronidazole was used for the primary episode.

Options for patients with > 1 recurrence of CDI include oral vancomycin therapy using a tapered and pulsed regimen **OR** a standard course of oral vancomycin followed by rifaximin, or fidaxomicin. Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments. There are insufficient data at this time to recommend extending the length of anti-*C. difficile* treatment beyond the recommended treatment course or restarting an anti-*C. difficile* agent empirically for patients who require continued antibiotic therapy directed against the underlying infection or who require retreatment with antibiotics shortly after completion of CDI treatment, respectively.

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### **Definitions:**

**Clostridioides (formerly Clostridium) difficile (C. difficile) infection (CDI):** A bacterium causing symptoms ranging from diarrhea to more serious intestinal conditions such as colitis. CDI is one of the most common

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hospital-acquired infections and is an increasingly frequent cause of morbidity and mortality among older adult hospitalized individuals. *C. difficile* colonizes the human intestinal tract after the normal gut flora has been altered by antibiotic therapy and is the causative organism of antibiotic-associated pseudomembranous colitis.

**CDI recurrence:** The development of a new episode of diarrhea associated with a positive stool test for *Clostridioides difficile* (*C. difficile*) toxin following clinical cure of the initial CDI episode.

Recurrence can represent either relapse or reinfection:

- Relapse is a recurrence with the original isolate
- Reinfection is a recurrence with a new isolate

**C. difficile treatment failure:**

- An inadequate response with unresolved *C. difficile* infection
- Failure of treatment is not defined by development of a recurrent episode

**Disease Severity Classifications for C. difficile in adults:**

- Non-severe: Leukocytosis with WBC count  $\leq$  15,000 cells/mL, serum creatinine  $<$  1.5 mg/dL
- Severe: Leukocytosis WBC count  $>$  15,000 cells/mL, serum creatinine  $\geq$  1.5 mg/dL
- Fulminant: Hypotension, shock, ileus, or megacolon

**Disease Severity Classifications for C. difficile in children:**

Mild	afebrile, diarrhea (without systemic findings)
Moderate	fever, profuse diarrhea, abdominal pain
Severe	fever, profuse diarrhea, abdominal pain and tenderness, abdominal distention, leukocytosis with WBC count $\geq$ 15,000 cells/mL, elevated age-adjusted creatinine level, pseudomembranous colitis, serum creatinine $\geq$ 1.5 mg/dL
Fulminant	hypotension, shock, ileus, or megacolon

**Vancomycin oral regimens – Adults:**

- Standard 10-day course:
  - 125 mg QID
- Tapered/pulse dose:
  - 125 mg QID x 10–14 days then,
  - 125 mg BID x 7 days then,
  - 125 mg QD x 7 days then,
  - 125 mg every 2 or 3 days for 2–8 weeks
- Slow taper dose:
  - 125 mg every 6 hours X 1-2 weeks
  - 125 mg every 8 hours X 1 week
  - 125 mg every 12 hours X 1 week
  - 125 mg every 24 hours X 1 week
  - 125 mg every 48 hours X 1 week
  - 125 mg every 72 hours X 1 week

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<b>CID 2018; 66 (7):e1-e48: Clinical Practice Guidelines for <i>Clostridioides</i> (formerly <i>Clostridium</i>) <i>difficile</i> Infection in Adults</b>
<b>Non-severe disease:</b> Supportive clinical data: White blood cell count ≤15,000 cells/mL and serum creatinine <1.5 mg/dL
Initial episode: <ul style="list-style-type: none"> <li>▪ Vancomycin 125 mg orally four times daily for 10 days, <b>OR</b></li> <li>▪ Fidaxomicin 200 mg orally twice daily for 10 days</li> <li>▪ If above agents are unavailable: <ul style="list-style-type: none"> <li>○ Metronidazole 500 mg orally three times daily for 10 days</li> </ul> </li> </ul>
First recurrence (2 <sup>nd</sup> episode): <ul style="list-style-type: none"> <li>▪ If vancomycin was used for the initial episode: <ul style="list-style-type: none"> <li>○ Vancomycin pulsed-prolonged tapered regimen: <ul style="list-style-type: none"> <li>• 125 mg orally four times daily for 10 to 14 days, then</li> <li>• 125 mg orally twice daily for 7 days, then</li> <li>• 125 mg orally once daily for 7 days, then</li> <li>• 125 mg orally every 2 or 3 days for 2 to 8 weeks, <b>OR</b></li> </ul> </li> <li>○ Fidaxomicin 200 mg orally twice daily for 10 days</li> </ul> </li> <li>▪ If fidaxomicin or metronidazole was used for the initial episode: <ul style="list-style-type: none"> <li>○ Vancomycin 125 mg orally four times daily for 10 days</li> </ul> </li> </ul>
Second or subsequent recurrence (3 <sup>rd</sup> or more episode): <ul style="list-style-type: none"> <li>▪ Vancomycin pulsed-prolonged tapered regimen (outlined above), <b>OR</b></li> <li>▪ Fidaxomicin 200 mg orally twice daily for 10 days, <b>OR</b></li> <li>▪ Vancomycin followed by rifaximin: <ul style="list-style-type: none"> <li>○ Vancomycin 125 mg orally four times per day for 10 days, then</li> <li>○ Rifaximin 400 mg three times daily for 20 days, <b>OR</b></li> </ul> </li> <li>▪ Fecal microbiota transplantation</li> </ul>
<b>Severe disease:</b> Supportive clinical data: White blood cell count >15,000 cells/mL and/or serum creatinine ≥1.5 mg/dL
Initial episode: <ul style="list-style-type: none"> <li>▪ Vancomycin 125 mg orally four times daily for 10 days, <b>OR</b></li> <li>▪ Fidaxomicin 200 mg orally twice daily for 10 days</li> </ul>
Recurrences of severe disease to follow same recommendations Non-severe recurrences as above
<b>Fulminant disease:</b> (previously referred to as severe, complicated <i>C. difficile</i> infection) Supportive clinical data: Hypotension or shock, ileus, megacolon
Initial episode: <ul style="list-style-type: none"> <li>▪ Enteric vancomycin plus parenteral metronidazole: <ul style="list-style-type: none"> <li>○ Vancomycin 500 mg orally or via nasogastric tube four times daily, <b>AND</b></li> <li>○ Metronidazole 500 mg intravenously every 8 hours</li> </ul> </li> <li>▪ If ileus is present, additional considerations include: <ul style="list-style-type: none"> <li>○ Rectal vancomycin may be administered as a retention enema (500 mg in 100 mL normal saline per rectum; retained for as long as possible and re-administered every 6 hours)</li> <li>○ Fecal microbiota transplantation (FMT)</li> </ul> </li> </ul>
Recurrent episode: <ul style="list-style-type: none"> <li>▪ Use antibiotics as for initial fulminant episode above</li> <li>▪ Some favor FMT in the context of a first or second recurrence that presents as a fulminant episode</li> </ul>

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<b>Treatment of <i>Clostridioides</i> (formerly <i>Clostridium</i>) <i>difficile</i> infection in children</b>	
<b>First episode:</b>	
Mild or moderate	Vancomycin 40 mg/kg per day orally divided in 4 doses (maximum dose: 125 mg) for 10 days <b>OR</b> Metronidazole 30 mg/kg per day orally divided in 4 doses (maximum dose: 500 mg) for 10 days
Severe - Fever, profuse diarrhea, abdominal pain and tenderness, abdominal distention, white blood cellcount >15,000 cells/microL, elevated age-adjusted creatinine level, serum albumin <2.5 g/dL (25 g/L), and pseudomembranous colitis	Vancomycin 40 mg/kg per day orally divided in 4 doses (maximum dose: 125 mg) for 10 days
Fulminant - hypotension, shock, ileus, or toxic megacolon	Vancomycin 40 mg/kg per day orally divided in 4 doses (maximum dose: 500 mg) until clinical improvement and then (if applicable) decrease the maximum dose to 125 mg to complete 10 days
Fulminant and ileus	Metronidazole 30 mg/kg per day IV divided in 3 doses (maximum dose: 500 mg) <b>PLUS</b> Vancomycin 10 mg/kg per dose in normal saline (maximum dose: 500 mg in 100 mL normal saline) administered by retention enema 4 times per day; the volume of solution varies with age: 1 through 4 years: 50 mL 5 through 11 years: 75 mL ≥12 years: 100 mL
<b>Recurrent episodes:</b>	
First recurrence, mild or moderate	Repeat regimen used for first episode
Subsequent recurrence, mild or moderate	<b>Either</b> of the following: <ul style="list-style-type: none"> <li>▪ Pulsed-tapered vancomycin (maximum dose: 125 mg): 10 mg/kg orally 4 times daily for 10 to 14 days, followed by 10 mg/kg orally twice daily for 7 days, followed by 10 mg/kg orally once daily for 7 days, followed by 10 mg/kg orally every other day for 7 days, followed by 10 mg/kg orally every 3 days for 2 to 8 weeks</li> <li>▪ Fidaxomicin (maximum dose: 200 mg): 6 months to 5 years: 16 mg/kg per dose orally twice daily for 10 days ≥6 years: 200 mg per dose orally twice daily for 10 days</li> </ul>

**Resources:**

Dificid (fidaxomicin) product information, revised by Merck Sharp & Dohme Corp 02-2021. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed on July 08, 2021.



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Kelly CP, Lamont JT, Bakken JS. Clostridioides (formerly Clostridium) difficile infection in adults: Treatment and prevention. In: UpToDate, Calderwood SB, Baron EL (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at <http://uptodate.com>. Accessed on July 08, 2021.

Crews J. Clostridioides (formerly Clostridium) difficile infection in children: Treatment and outcome. In: UpToDate, Kaplan SL, Torrhia MM (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at <http://uptodate.com>. Accessed on July 08, 2021.

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