BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

DIFICID® (fidaxomicin) oral

This Pharmacy Coverage Guideline (PCG):

- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope

- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance

- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Dificid (fidaxomicin) is considered ***medically necessary*** and will be approved when **ALL** 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 per FDA label, 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

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** the following criteria are met **(samples are not considered for continuation of therapy**):

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 with worsening defined as recurrence (either a relapse or reinfection) of CDAD.

3. Individual has failure, contraindication per FDA label, or intolerance to oral vancomycin.

4. Individual has been adherent with previous course the medication.

5. Individual has not developed any contraindications or other 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

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- 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 Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

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.

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.

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 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 ≤ 15,000 cells/mL, serum creatinine < 1.5 mg/dL
- Severe: Leukocytosis WBC count > 15,000 cells/mL, serum creatinine ≥ 1.5 mg/dL
- Fulminant: Hypotension, shock, ileus, or megacolon

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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 ≥ 15,000 cells/mL, elevated age-adjusted creatinine level, pseudomembranous colitis, serum creatinine ≥ 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

Treatment of *Clostridioides* (formerly *Clostridium*) *difficile* Infection (CDI) in Adults
Non-fulminant Disease:
Non-severe disease: Supportive clinical data: White blood cell count ≤15,000 cells/mL and serum creatinine <1.5 mg/dL **Severe disease:** Supportive clinical data: White blood cell count >15,000 cells/mL and/or serum creatinine ≥1.5 mg/dL
Initial episode: (For non-severe or severe disease) ▪ Vancomycin 125 mg orally four times daily for 10 days, **OR** ▪ Fidaxomicin 200 mg orally twice daily for 10 days ▪ For non-severe disease if above agents are unavailable: o Metronidazole 500 mg orally three times daily for 10-14 days
First recurrence (2nd episode): ▪ Vancomycin pulsed-prolonged tapered regimen: o 125 mg orally four times daily for 10 to 14 days, then o 125 mg orally twice daily for 7 days, then o 125 mg orally once daily for 7 days, then o 125 mg orally every 2 or 3 days for 2 to 8 weeks, **OR** ▪ Vancomycin 125 mg orally four times daily for 10 days **OR** ▪ Fidaxomicin 200 mg orally twice daily for 10 days **OR** ▪ Fidaxomicin 200 mg orally twice daily for 5 days, then once every other day for 20 days ▪ **Adjunctive treatment:** Bezlotoxumab 10 mg/kg intravenously, given once during administration of standard antibiotic regimen

Second or subsequent recurrence (3rd or more episode): ▪ Vancomycin pulsed-prolonged tapered regimen (outlined above), **OR** ▪ Vancomycin followed by rifaximin: o Vancomycin 125 mg orally four times per day for 10 days, then o Rifaximin 400 mg three times daily for 20 days, **OR** ▪ Fidaxomicin 200 mg orally twice daily for 10 days, **OR** ▪ Fidaxomicin 200 mg orally twice daily for 5 days, then once every other day for 20 days ▪ **Adjunctive treatment:** Bezlotoxumab 10 mg/kg intravenously, given once during administration of standard antibiotic regimen ▪ **Fecal microbiota transplantation (FMT):** For patients who have received appropriate antibiotic treatment for at least 3 CDI episodes (i.e., initial episode plus 2 recurrences), who subsequently present with a fourth or further CDI episode (third or subsequent recurrence),
Fulminant disease: (previously referred to as severe, complicated *C. difficile* infection) Supportive clinical data: Hypotension or shock, ileus, megacolon
If there is no ileus, enteric vancomycin plus parenteral metronidazole: ▪ Vancomycin 500 mg orally or via nasogastric tube four times daily, **AND** ▪ Metronidazole 500 mg intravenously every 8 hours If ileus is present, additional considerations include: ▪ 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) **OR** ▪ Fecal microbiota transplantation (FMT)

Treatment of *Clostridioides* (formerly *Clostridium*) *difficile* infection in children	
First episode:	
Mild or moderate	Vancomycin 40 mg/kg per day orally divided in 4 doses (maximum dose: 125 mg) for 10 days **OR** 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 cell count >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	Metronidazole 30 mg/kg per day IV divided in 3 doses (maximum dose: 500 mg), **PLUS** 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) **PLUS** 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
Recurrent episodes:	
First recurrence, mild or moderate	Repeat regimen used for first episode
Subsequent recurrence, mild or moderate	**Either** of the following: ▪ 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 ▪ 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

Resources:

Dificid (fidaxomicin) product information, revised by Merck Sharp & Dohme LLC 06-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 18, 2022.

Kelly CP, Lamont JT, Bakken JS. Clostridioides difficile infection in adults: Treatment and prevention. In: UpToDate, Calderwood SB, Bogorodskaya M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated on August 03, 2021. Accessed July 20, 2022.

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