BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

DIFICID® (fidaxomicin) oral
Generic Equivalent (if available)

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 prior authorization 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) and/or generic equivalent (if available) 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. Individual has a confirmed **OR** strongly suspected diagnosis of *Clostridium difficile*-associated diarrhea (CDAD)

4. Individual is **ONE** of the following:

a. **Adult** with initial or recurrent episodes of non-fulminant CDAD and meets **ONE** of the following:
   i. Has failure, contraindication per FDA label, intolerance, or is not a candidate for a standard 10-day course of oral vancomycin or a prolonged tapered/pulsed dose course of oral vancomycin
   ii. Has at least **ONE** of the following risk factors for recurrent CDAD:
      1. Individual is 65 years of age or older
      2. Episode is described as clinically severe CDI (see Definitions section)
      3. Infection is due to hypervirulent *Clostridioides difficile* strains (ribotypes 027, 078 or 244)
      4. Individual is immunocompromised (e.g., active hematologic malignancy, uses an antineoplastic or immunomodulating agent, uses corticosteroids, has received a solid organ transplant, is asplenic, or has an immunodeficiency condition, etc.)

b. **Child 6 month or older** with initial or recurrent episodes of mild or moderate non-fulminant CDAD that has failure, contraindication per FDA label, intolerance, or is not a candidate for oral vancomycin

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Requested agent is **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

Initial approval duration: 10 days

- **Criteria for continuation of coverage (renewal request):** Dificid (fidaxomicin) and/or generic equivalent (if available) 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 is **ONE** of the following:
   a. **Adult** experiencing recurrent episode (defined as reappearance of symptoms within 2-months of stopping previous therapy) of non-fulminant CDAD and has **ONE** of the following risk factors for recurrence of CDAD:
      i. Has failure, contraindication per FDA label, intolerance, or is not a candidate for a standard 10-day course of oral vancomycin or a prolonged tapered/pulsed dose course of oral vancomycin

ii. Has at least **ONE** of the following risk factors for recurrent CDAD:
    1. Individual is 65 years of age or older
    2. Episode is described as clinically severe CDI (see Definitions section)
    3. Infection is due to hypervirulent *Clostridioides difficile* strains (ribotypes 027, 078 or 244)
    4. Individual is immunocompromised (e.g., active hematologic malignancy, uses an antineoplastic or immunomodulating agent, uses corticosteroids, has received a solid organ transplant, is asplenic, or has an immunodeficiency condition, etc.)

b. **Child** experiencing recurrent episode (defined as reappearance of symptoms within 2-months of stopping previous therapy) of mild to moderate non-fulminant CDAD

3. Individual meets **ALL** other Initial Criteria as outlined above

4. Individual has been adherent with previous course of medication

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has not developed any significant adverse drug effects that may exclude continued use

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 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.

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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.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

***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

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

Standard-of-Care CDI Antibacterial Treatment for Adults:

Treatment of *Clostridioides* (formerly *Clostridium*) *difficile* Infection in **Adults**
Non-fulminant, non-severe disease: White blood cell count ≤15,000 cells/mL and serum creatinine <1.5 mg/dL
Initial episode: ▪ Fidaxomicin 200 mg orally twice daily for 10 days, **OR** ▪ Vancomycin 125 mg orally four times daily for 10 days ▪ If above agents are unavailable: o Metronidazole 500 mg orally three times daily for 10 to 14 days
Non-fulminant, severe disease: White blood cell count >15,000 cells/mL and/or serum creatinine ≥1.5 mg/dL
▪ Fidaxomicin 200 mg orally twice daily for 10 days, **OR** ▪ Vancomycin 125 mg orally four times daily for 10 days
Recurrent episodes: return of symptoms with a positive assay result after a period of symptom resolution that occurs within 8-weeks of the initial episode use an antibiotic regimen, in addition to adjunctive bezlotoxumab, if feasible
First recurrence (2nd episode): ▪ Fidaxomicin: o 200 mg orally twice daily for 10 days, **OR** o 200 mg orally twice daily for 5 days, followed by once every other day for 20 days ▪ Vancomycin in a tapered and pulsed 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 **Adjunctive treatment:** Bezlotoxumab 10 mg/kg intravenously, given once during administration of standard antibiotic regimen for individuals with prior infection within the last 6 months

Second or subsequent recurrence (3rd or more episode): ▪ Fidaxomicin: o 200 mg orally twice daily for 10 days, **OR** o 200 mg orally twice daily for 5 days, followed by once every other day for 20 days ▪ Vancomycin in a tapered and pulsed 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 **Adjunctive treatment:** Bezlotoxumab 10 mg/kg intravenously, given once during administration of standard antibiotic regimen for individuals with prior infection within the last 6 months **Role of Fecal microbiota transplantation (FMT):** For individuals 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). Individual who is not a FMT candidate, management may include oral vancomycin suppressive therapy.
Fulminant disease: (previously referred to as severe, complicated *C. difficile* infection): Hypotension or shock, ileus, megacolon
▪ No ileus: Enteric vancomycin plus parenteral metronidazole: o Vancomycin 500 mg orally or via nasogastric tube four times daily, **AND** o Metronidazole 500 mg intravenously every 8 hours ▪ If ileus is present: use same approach as above but with additional considerations: o FMT administered rectally **OR** o Rectal vancomycin 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)
For individuals with non-fulminant disease, a fidaxomicin-based regimen is suggested over a vancomycin-based regimen. In addition, for individuals with non-fulminant recurrent disease and prior CDI in the last 6 months, adjunctive bezlotoxumab is suggested. Use of fidaxomicin or bezlotoxumab is based on a small benefit with respect to CDI recurrence rates (10 to 15% decrease). Consider prioritizing use of these agents for individuals at greatest risk for CDI recurrence (i.e., age ≥65 years, severe CDI, or immunosuppression). Vancomycin remains an acceptable agent for treatment of initial and recurrent CDI.

Standard-of-Care CDI Antibacterial Treatment for Children:

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 **OR** Fidaxomicin, dosed according to body weight: 4 to <7 kg (oral suspension): 80 mg orally twice daily for 10 days 7 to <9 kg (oral suspension): 120 mg orally twice daily for 10 days 9 to <12.5 kg (oral suspension): 160 mg orally twice daily for 10 days ≥12.5 kg (oral suspension): 200 mg orally twice daily for 10 days
Severe*	Vancomycin 40 mg/kg per day orally divided in 4 doses (maximum dose: 125 mg) for 10 days

Fulminant¶	Metronidazole 30 mg/kg per day IV divided in 3 doses (maximum dose: 500mg) **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: return of symptoms with a positive assay result after a period of symptom resolution that occurs within 8-weeks of the initial episode (typically within 1-3 weeks)	
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): 4 to <7 kg (oral suspension): 80 mg orally twice daily for 10 days 7 to <9 kg (oral suspension): 120 mg orally twice daily for 10 days 9 to <12.5 kg (oral suspension): 160 mg orally twice daily for 10 days ≥12.5 kg (oral suspension or tablets): 200 mg orally twice daily for 10days
*There is no consensus definition of severe C. difficile infection in children. The following criteria may be used to define severe disease: 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. ¶ Fulminant disease is characterized by hypotension, shock, ileus, or toxic megacolon	

Resources:

Dificid (fidaxomicin) product information, revised by Merck Sharp & Dohme LLC 06-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 31, 2024.

Johnson S, Lavergne V, Skinner AM, et al.: Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults. CID 2021:73 (1 September): e1029. Accessed June 01, 2023. Re-evaluated June 24, 2024.

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. Literature current through May 2024. Topic last updated March 19, 2024. Accessed June 23, 2024.

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