BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

DIFICID® (fidaxomicin) oral
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/or 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.

Medical Necessity Requirements for DIFICID (fidaxomicin) and Fidaxomicin generic

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a Gastroenterologist, Pediatric Gastroenterologist, or Infectious Disease specialist, or in consultation with one of these specialists

Indication
- Clostridioides difficile associated diarrhea (CDAD) or Clostridioides difficile infection (CDI) is confirmed or strongly suspected

ORIGINAL EFFECTIVE DATE: 07/16/2015 | ARCHIVE DATE: | LAST REVIEW DATE: 08/21/2025 | LAST CRITERIA REVISION DATE: 08/21/2025

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Age Requirement
- 6 months of age or older

Baseline Clinical Evaluation
- For adults: initial or recurrent episodes of nonfulminant CDAD or CDI
- For child 6 months or older: initial or recurrent episodes of mild or moderate non fulminant CDAD/CDI who has failed, contraindication per FDA label, intolerance, or is not a candidate for oral vancomycin
- Not being used for infections other than Clostridioides difficile

Alternative Therapies
- For child 6 months or older: Failure, contraindication, intolerance, or is not a candidate for oral vancomycin

Brand Specific Criteria
- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the United States Food and Drug Administration (FDA) (see Definitions section)

Safety
- Does not have **ANY** of the following:
  - Life threatening or fulminant infection
  - Hypotension
  - Septic shock
  - Peritoneal signs
  - Significant dehydration
  - Toxic megacolon

Documentation Requirements
- A completed request form must be submitted, including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration:
- 10 days for nonfulminant disease
- **For recurrent episodes**: Individual must satisfy criteria as noted above
- Recurrent episodes are defined as 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 to 3 weeks) Individuals at greatest risk for recurrence include age ≥65 years, severe CDI, infection with hypervirulent strains, or immunosuppression

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Criteria for Off-Label Use Requests:

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:

Fidaxomicin (brand Dificid and generic) is a macrolide antibiotic approved for treatment of *Clostridioides (*formerly *Clostridium) difficile*-associated diarrhea (CDAD) in individuals 6 months of age and older for use of brand Dificid and individuals 18 years of age or older for use of generic fidaxomicin. 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.

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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. Recurrent CDI is defined by resolution of CDI symptoms while on appropriate therapy, followed by reappearance of symptoms within two months of discontinuing treatment.

Recurrence can represent either relapse or reinfection:
Relapse is a recurrence with the original isolate
Reinfection is a recurrence with a new isolate

Risk factors for recurrent CDAD/CDI:
- Individual is 65 years of age or older
- Episode is described as clinically severe CDAD/CDI
- Infection is due to hypervirulent strains of *Clostridioides difficile* (ribotypes 027, 078 or 244)
- 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.)

***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: [**Note:** defined based on expert opinion]

Non-severe	Leukocytosis with WBC count ≤ 15,000 cells/mL, serum creatinine < 1.5 mg/dL or a 50% rise over baseline creatinine level
Severe	Leukocytosis WBC count > 15,000 cells/mL, serum creatinine ≥ 1.5 mg/dL, or a ≥ 50% rise over baseline creatinine level
Fulminant	hypotension, shock, ileus, or megacolon

Disease Severity Classifications for *C. difficile* in children: [**Note:** There is no consensus definition of severe C. difficile infection in children. Determination of disease severity should be guided by clinician judgment]

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

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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, serum creatinine <1.5 mg/dL, or a ≥ 50% rise over baseline creatinine level
Initial (1st) episode of CDI: ▪ **Preferred**: 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: ○ Metronidazole 500 mg orally three times daily for 10 to 14 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 Individuals at greatest risk for CDI recurrence include age ≥65 years, severe CDI, or immunosuppression

First recurrence (2nd episode of CDI):
▪ If prior treatment was Vancomycin:
  ▪ Fidaxomicin:
  ○ 200 mg orally twice daily for 10 days, **OR**
  ○ 200 mg orally twice daily for 5 days, followed by once every other day for 20 days
▪ If prior treatment was Fidaxomicin:
  ▪ **Preferred**: Vancomycin in a tapered and pulsed regimen:
  ○ 125 mg orally four times daily for 10 to 14 days, then
  ○ 125 mg orally twice daily for 7 days, then
  ○ 125 mg orally once daily for 7 days, then
  ○ 125 mg orally every 2 or 3 days for 2 to 8 weeks, **OR**
  ▪ Alternative: Vancomycin 125 mg orally four times daily for 10 days

Second recurrence (3rd episode of CDI):
▪ **Preferred**: Fidaxomicin:
  ○ 200 mg orally twice daily for 10 days, **OR**
  ○ 200 mg orally twice daily for 5 days, followed by once every other day for 20 days
▪ Alternatives:
  ▪ Vancomycin in a tapered and pulsed regimen (as outlined above), **OR**
  ▪ Vancomycin followed by rifaximin:
  ○ Vancomycin 125 mg orally four times per day for 10 days, then
  ○ Rifaximin 400 mg three times daily for 20 days
▪ **Adjunctive treatment:** If fecal microbiota product (FMP) is available, give oral capsule (Vowst) or rectal suspension (Rebyota) several days after completion of CDI therapy. If FMP are not available, consider traditional fecal microbial therapy (FMT, a fecal slurry administered retrograde via enema or antegrade via loop colostomy into the intestinal tract)

Third and subsequent recurrences (4th and subsequent episodes of CDI):
▪ Fidaxomicin 200 mg orally twice daily for 5 days, followed by once every other day for 20 days **OR**
▪ Vancomycin in a tapered and pulsed regimen (as outlined above) **OR**
▪ Vancomycin followed by rifaximin:
  ▪ Vancomycin 125 mg orally four times per day for 10 days, then
  ▪ Rifaximin 400 mg three times daily for 20 days
▪ **Adjunctive treatment:** Following the antibiotic regimen, refer these patients for traditional FMT. If an FMP is available and was not administered during prior recurrences, it is reasonable to administer an FMP (e.g., rectal suspension [Rebyota], oral capsules [Vowst]) instead of traditional FMT after completion of CDI therapy

Fulminant disease: (previously referred to as severe, complicated *C. difficile* infection): Hypotension or shock, ileus, megacolon

- **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**: use same approach as above but with additional consideration:
  - Also administer rectal vancomycin 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) until ileus is resolved

- Individual who are improving should continue the treatment for 10 to 14 days. Once the individual improves clinically, IV metronidazole can be stopped, and the vancomycin dose can be reduced to the standard dose used in non-fulminant disease
- Individuals with severe or fulminant colitis and renal insufficiency (creatinine clearance <10 mL/minute) who are receiving a prolonged course (>10 days) of enteral vancomycin therapy, it is suggested to monitor serum vancomycin levels unless the patient is on dialysis
- Metronidazole should be avoided in individuals who are frail, age ≥65 years, or who develop CDI in association with inflammatory bowel disease. Caution is also warranted during pregnancy and lactation

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, according to weight (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 10 days
*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 09, 2025.

Fidaxomicin product information, revised by Teva Pharmaceuticals, Inc. 05-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 21, 2025.

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. Last Updated May 05, 2023. Accessed June 01, 2023. Re-evaluated May 29, 2025.

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 April 2025. Topic last updated May 21, 2025. Accessed May 29, 2025.

Nicholson MR. Clostridioides difficile infection in children: Treatment and outcome. In: UpToDate, Kaplan SL, Blake D (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2025. Topic last updated July 09, 2024. Accessed May 29, 2025.

Borody TJ, Ramrakha S. Fecal microbiotia transplantation for treatment of Clostridioides difficile infection: Treatment and outcome. In: UpToDate, Lamont JT, Meter C, Bogorodskaya M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2025. Topic last updated March 21, 2025. Accessed May 29, 2025.