BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 7/16/15**
SECTION: DRUGS	**LAST REVIEW DATE: 8/02/18**
	LAST CRITERIA REVISION DATE: 8/02/18
	ARCHIVE DATE:

DIFICID® (fidaxomicin) oral tablet

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.

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.

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. **Incomplete forms or forms without the chart notes will be returned.**

DIFICID® (fidaxomicin) oral tablet (cont.)

Criteria:

- **Criteria for initial therapy:** Dificid (fidaxomicin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual is 18 years of age or older

  2. A confirmed **OR** strongly suspected diagnosis of *Clostridium difficile*-associated diarrhea (CDAD)

  3. Treatment is for **ONE** of the following: initial episode of non-severe CDAD, initial episode of severe CDAD, first recurrence of CDAD, or second or subsequent recurrence of CDAD

  4. Individual has failure, contraindication or intolerance such that the individual is unable to use oral vancomycin
     - **For initial episode, non-severe CDAD**: A standard 10 day course of oral vancomycin
     - **For initial episode, severe CDAD**: A standard 10 day course of oral vancomycin
     - **For first recurrence of CDC**: A tapered/pulsed dose course of oral vancomycin
     - **For second or subsequent recurrence CDC**: A tapered/pulsed dose course of vancomycin

  5. For second or subsequent recurrence of CDAD: Dificid (fidaxomicin) will be used with standard 10 day course of oral vancomycin

  6. There are **NO** contraindications
     - Contraindications include:
       - Hypersensitivity to fidaxomicin

  7. **NOT** being used for the treatment of infections other than *Clostridium difficile*

  Initial approval duration: 20 tabs for 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's condition has worsened
     - Worsening is defined as:
       - Recurrence (either a relapse or reinfection) of CDAD

  2. Treatment for **ONE** of the following:
     - First recurrence CDAD with **BOTH** of the following:
       - Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use a tapered/pulsed dose course of oral vancomycin
     - Second or subsequent recurrence CDAD with **BOTH** of the following:
       - Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use a tapered/pulsed dose course of oral vancomycin
       - Dificid (fidaxomicin) will be used with standard 10 day course oral vancomycin

DIFICID® (fidaxomicin) oral tablet (cont.)

3. Individual has been adherent with previous course the medication

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section

5. **NOT** being used for the treatment of infections other than *Clostridium difficile*

Renewal duration: 20 tabs for 10 days

Description:

Dificid® (fidaxomicin) is a macrolide antibiotic approved for treatment of *Clostridium difficile*-associated diarrhea (CDAD) in adults 18 years of age and older. The safety and efficacy of fidaxomicin in pediatric patients has not been studied.

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. *Clostridium 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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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:

Clostridium 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 *Clostridium 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

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

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Disease Severity Classifications for *Clostridium difficile* according to SHEA/IDSA Guidelines:

- 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

Vancomycin oral regimens:

- 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

Resources:

Dificid. Package Insert. Revised by manufacturer 12/2015. Accessed 05-23-16, 07-08-17, 06-27-18.
Dificid. Package Insert. Revised by manufacturer 04/2014. Accessed 04-22-2015.

Gould CV, McDonald LC: Bench to bedside review: *Clostridium difficile* colitis. Critical Care 2008; 12 (1):203-210.

O'Connor JR, Johnson S, Gerding DN: *Clostridium difficile* infection caused by the epidemic BI/NAP1/027 strain. Gastroenterol 2009; (6):136:1913-1924.

Cohen SH, Gerding DN, Johnson S, et al.: Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 2010; 31(5):431-455.

Louie TJ, Miller MA, Mullane KM, et al.: Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection. NEJM 2011; 364(5):422-431.

Ghose C: *Clostridium difficile* infection in the twenty-first century. Emerging Microbes and Infection 2013; 2, e62;doi:10.1038/emi.2013.62

Schutze GE, Willoughby RE: *Clostridium difficile* Infection in Infants and Children. Pediatrics 2013; 131:196-200.
Surawicz CM, Brandt LJ, Binion DG, et al.: Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections. Am J Gastroenterol 2013; 108:478-498

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 the Society for Healthcare Epidemiology of America (SHEA). CID 2018; 66 (7):e1-e48

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.