PHARMACY COVERAGE GUIDELINES

SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 07/16/15

LAST REVIEW DATE: 07/21/16

LAST CRITERIA REVISION DATE: 06/25/16

NEXT REVIEW DATE: 3rd QUARTER 2017

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.

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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.

A recent (2010) national guideline from the Society for Healthcare Epidemiology (SHEA) and Infectious Disease Society of America (IDSA) indicates oral Metronidazole as the drug of choice for the initial episode of mild-to-moderate CDI. The dosage is 500 mg orally 3 times per day for 10-14 days. Oral Vancomycin is the drug of choice for an initial episode of severe CDI. The dosage is 125 mg orally 4 times per day for 10-14 days.

Treatment of the first recurrence (second episode) of CDI is usually with the same treatment regimen that was used for the initial episode but should be modified by disease severity (mil-to-moderate, severe, or severe complicated). Metronidazole should not be used for the treatment of the second recurrence (third episode) or for chronic therapy because of possible neurotoxicity. Treatment of the second or later recurrence of CDI with oral Vancomycin therapy using a tapered and/or pulse regimen is the preferred next approach.

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.

Dificid® (fidaxomicin) is a macrolide antibiotic approved for the treatment of CDAD. It has few systemic side effects due to poor absorption through the gastrointestinal tract, has activity against *Clostridium difficile*, and has a lower rate of recurrence when compared with Vancomycin in the management of mild-to-moderately severe CDI. In clinical trials, Fidaxomicin was found to be non-inferior to Vancomycin in the primary efficacy endpoint, clinical cure defined as resolution of diarrhea, maintenance of resolution for the duration of therapy, and no further need for other *C. difficile* therapy. Recurrence rates in the studies were significantly lower in patients treated with Fidaxomicin. However, in a subgroup analysis, recurrence rates were NOT significantly lower in Fidaxomicin-treated patients who had the hypervirulent NAP1/BI/027 strain; a common strain isolated in majority of states within the United States and is more likely to cause complications and recurrence.

**Definitions:**

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

Disease Severity Classifications for _Clostridium difficile_ according to SHEA/IDSA Guidelines:
- Mild: White blood cell count <15,000 cells/µL, serum creatinine <1.5x pre-morbid level
- Moderate: White blood cell count <15,000 cells/µL, serum creatinine >1.5x pre-morbid level
- Severe: White blood cell count >15,000 cells/µL, serum creatinine >1.5x pre-morbid level
- Severe, complicated: Hypotension, shock, ileus, or megacolon

**Drug related events:**

**Ineffective / failure**
- Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

  A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

**Adverse Drug Event:** Allergic reaction / Hypersensitivity / Intolerance
- Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

  **Allergic reaction / hypersensitivity** – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

  If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

  **Intolerance** – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

**Contraindication**
- Use of a drug that is not recommended by the manufacturer or FDA labelling
DIFICID® (fidaxomicin) oral tablet (cont.)

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

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.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Dificid requires completion of the specific request form in its entirety. 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 will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Dificid is considered **medically necessary** with medical record documentation of **ALL** of the following:

  1. A confirmed OR strongly suspected diagnosis of **ONE** of the following:

     - Mild to moderate *Clostridium difficile*-associated diarrhea when oral Metronidazole cannot be used due to **ONE** of the following:
       - Failed current course
       - Experienced a significant adverse event with current course
       - Treatment is for a second recurrence (third episode) and there is concern for neurotoxicity
       - Has a contraindication to its use

     - Severe *Clostridium difficile*-associated diarrhea
DIFICID® (fidaxomicin) oral tablet (cont.)

- Dificid for all other indications not previously listed is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Toxin negative *Clostridium difficile*-associated diarrhea
- Use in other infections

<table>
<thead>
<tr>
<th>History:</th>
<th>Date:</th>
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<tbody>
<tr>
<td>Pharmacy and Therapeutics review</td>
<td>07-21-2016</td>
<td>Approved</td>
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<tr>
<td>Director Pharmacy Mgmt. review</td>
<td>06-25-2016</td>
<td>No criteria changes</td>
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<td>06-20-2015</td>
<td>Development</td>
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Criteria Revisions:
- Date: 07-21-2016 Activity: Approved
- Date: 06-25-2016 Activity: No criteria changes
- Date: 07-16-2015 Activity: Approved
- Date: 06-20-2015 Activity: Development

Resources:
FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<td>Dificid® is a macrolide antibacterial drug indicated in adults (≥18 years of age) for treatment of <em>Clostridium difficile</em>-associated diarrhea.</td>
<td>One 200 mg tablet orally twice daily for 10 days with or without food</td>
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DIFICID® (fidaxomicin) oral tablet (cont.)


