

| Pharmacy Policy Bulletin: J-1342 Non-Preferred Metronidazole Products – Commercial and Healthcare Reform                                                                                                                  |                                                                                                                                                                                                   |
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| <b>Number:</b> J-1342                                                                                                                                                                                                     | <b>Category:</b> Prior Authorization                                                                                                                                                              |
| <b>Line(s) of Business:</b><br><input checked="" type="checkbox"/> Commercial<br><input checked="" type="checkbox"/> Healthcare Reform<br><input type="checkbox"/> Medicare                                               | <b>Benefit(s):</b><br><b>Commercial:</b><br><b>Prior Authorization (1.):</b><br>1. Other Managed Prior Authorization = Yes w/ Prior Authorization<br><br><b>Healthcare Reform:</b> Not Applicable |
| <b>Region(s):</b><br><input checked="" type="checkbox"/> All<br><input type="checkbox"/> Delaware<br><input type="checkbox"/> New York<br><input type="checkbox"/> Pennsylvania<br><input type="checkbox"/> West Virginia | <b>Additional Restriction(s):</b><br>None                                                                                                                                                         |
| <b>Version:</b> J-1342-002                                                                                                                                                                                                | <b>Original Date:</b> 12/06/2023                                                                                                                                                                  |
| <b>Effective Date:</b> 04/25/2025                                                                                                                                                                                         | <b>Review Date:</b> 04/09/2025                                                                                                                                                                    |

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| <b>Drugs Product(s):</b>           | <ul style="list-style-type: none"> <li>Likmez (metronidazole)</li> <li>metronidazole 125 mg tablet</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>FDA-Approved Indication(s):</b> | <ul style="list-style-type: none"> <li>Likmez (metronidazole)               <ul style="list-style-type: none"> <li>Trichomoniasis in adults</li> <li>Amebiasis in adults and pediatric patients</li> <li>Anaerobic bacterial infections in adults</li> </ul> </li> <li>metronidazole 125 mg               <ul style="list-style-type: none"> <li>Symptomatic Trichomoniasis</li> <li>Asymptomatic Trichomoniasis</li> <li>Treatment of Asymptomatic Sexual Partners (Trichomoniasis)</li> <li>Amebiasis</li> <li>Anaerobic Bacteria Infections</li> </ul> </li> </ul> |

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| <b>Background:</b> | <ul style="list-style-type: none"> <li>Although the exact mechanism of action is unknown, metronidazole is thought to enter bacterial cells by passive diffusion and interact with the DNA leading to DNA synthesis inhibition and DNA degradation which ultimately leads to bacterial cell death.</li> <li>Trichomoniasis is a common sexually transmitted disease caused by the protozoan parasite <i>trichomoniasis vaginalis</i>. However, only about 30% of patients will develop any symptoms, such as genital inflammation, painful urination, and vaginal/penile discharge. Without treatment, the infection could potentially last for many months or years. In 2018, the Centers for Disease Control and Prevention (CDC) estimates that there were more than 2 million trichomoniasis infections in the United States (U.S.). Asymptomatic sexual partners of treated patients should be treated simultaneously if the organism has been found to be present, in order to prevent reinfection of the partner. The decision as to whether to treat an asymptomatic male partner who has a negative culture or one for whom no culture has been attempted is an individual one. In making this decision, it should be noted that there is evidence that a woman may become reinfected if her sexual partner is not treated. Also, since there can be considerable difficulty in isolating the organism from the</li> </ul> |
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asymptomatic male carrier, negative smears and cultures cannot be relied upon in this regard. In any event, the sexual partner should be treated with metronidazole in cases of reinfection.

- Amebiasis is an infection caused by the parasite *Entamoeba histolytica* and is more common in developing countries in areas with poor sanitation. The infection is mostly spread through fecal transmission of the infectious parasitic cysts. Only about 10-20% of patients will develop any symptoms such as diarrhea, gastric distress, and weight loss. In the U.S., amebiasis prevalence is low (4% prevalence reported in 2007) and is mostly seen in travelers and immigrants entering the country from endemic regions.
- Anaerobic bacterial infections are caused by anaerobes, which are bacteria that require little to no oxygen for growth. Examples of anaerobes include *Bacteroides*, *Prevotella*, *Clostridium*, and *Actinomyces* species that can cause a variety of infections including, but not limited to intra-abdominal infections, skin and soft tissue infections, and aspiration pneumonia. Some symptoms that can develop include abscess formation, foul odor, and diarrhea/colitis. A challenge faced by clinicians regarding anaerobic infections is the rise in antibiotic resistance. A study from 2001 to 2004 found that the mean incidence of anaerobic bacteremia was about 91 cases per year in the U.S.
- The 2021 CDC sexually transmitted infections guidelines recommend metronidazole as first line treatment for trichomoniasis and tinidazole as an alternative therapy option. Another option for the treatment of trichomoniasis in adults is secnidazole.
- The 2024 CDC Yellow Book recommends initial treatment of amebiasis with either metronidazole or tinidazole, followed by treatment with iodoquinol or paromomycin. Other options for treatment of amebiasis in adults or pediatrics include erythromycin, tetracycline, and chloroquine.
- Metronidazole is commonly used for treatment of a variety of anaerobic bacterial infections such as intra-abdominal infections, skin and soft tissue infections, and aspiration pneumonia as mentioned in IDSA practice guidelines for skin and soft tissue infections and pneumonia and in the 2017 Surgical Infection Society revised guidelines on the management of intra-abdominal infections. Other options for treatment of anaerobic infections in adults include clindamycin, penicillin/beta-lactamase inhibitor combinations, second generation cephalosporins, quinolones, and carbapenems.
- Likmez (metronidazole) suspension is a self-administered, oral antibiotic.
- Prior to the approval of Likmez, other dosage forms of metronidazole have been used for the treatment of trichomoniasis, amebiasis and anaerobic bacterial infections including tablets, capsules, and intravenous formulations. Metronidazole tablets can be crushed or split if they are immediate release formulations. Extended-release metronidazole oral formulations should not be crushed or broken. Guidelines do not specify which metronidazole formulation is preferred.
- ICD-10 Code: A41.4 "sepsis due to anaerobes" may apply to Likmez, however, given that there are several types of infections that fall under anaerobic bacterial infections, the prescriber must specify the diagnosis.
- Although the duration of therapy with Likmez will vary based on each member's individualized regimens based on the infection being treated, most durations will not exceed 7-10 days of treatment. However, anaerobic bacterial infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment. In the case of some types of joint infections, antibiotic therapy can last up to 12 weeks.
- Prescribing Considerations:
  - For patients with severe hepatic impairment, a dose reduction of 50% is recommended.

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|  | <ul style="list-style-type: none"> <li>○ Likmez is contraindicated for use in patients with prior history of hypersensitivity to metronidazole, disulfiram use within 2 weeks prior to metronidazole use, Cockayne syndrome and consumption of alcohol or products containing propylene glycol for at least three days after Likmez therapy.</li> </ul> |
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## Approval Criteria

### I. Likmez

#### A. Initial Authorization

When a benefit, coverage of Likmez may be approved when all of the following criteria are met **(1., 2., and 3.)**:

1. The member is 18 years of age or older if the diagnosis is for trichomoniasis or anaerobic bacterial infection.
2. The member has a diagnosis of one (1) of the following **(a., b., or c.)**:
  - a. Trichomoniasis (ICD-10: A59.9)
  - b. Amebiasis (ICD-10: A06.9)
  - c. Anaerobic bacterial infection (ICD-10: A41.4)
3. The member meets one (1) of the following **(a. or b.)**:
  - a. The member is unable to swallow or tolerate solid oral dosage forms (i.e., tablets, capsules).
  - b. The member has experienced therapeutic failure or intolerance to plan-preferred, generic metronidazole tablets (not including 125 mg tablets).

#### B. Reauthorization

When a benefit, reauthorization of Likmez may be approved when all of following criteria are met **(1., 2., and 3.)**:

1. The prescriber attests that the member has a repeat episode of one (1) of the following infections **(a., b., or c.)**:
  - a. Trichomoniasis (ICD-10: A59.9)
  - b. Amebiasis (ICD-10: A06.9)
  - c. Anaerobic bacterial infection (ICD-10: A41.4)
2. The prescriber attests that at least 4 weeks have passed since the member finished receiving the first course of treatment with Likmez if being treated specifically for a recurrent trichomoniasis infection.
3. The member meets one (1) of the following criteria **(a. or b.)**:
  - a. The member continues to have an inability to swallow solid oral dosage forms.
  - b. The member has experienced therapeutic failure or intolerance to plan-preferred, generic metronidazole tablets (not including 125 mg tablets).

### II. Metronidazole 125 mg tablets

#### A. Initial Authorization

When a benefit, coverage of metronidazole 125 mg tablets may be approved when all of the following criteria are met **(1., 2., and 3.)**:

1. The member is 18 years of age or older if the diagnosis is for trichomoniasis or anaerobic bacterial infection.
2. The member has a diagnosis of one (1) of the following **(a., b., or c.)**:
  - a. Trichomoniasis (ICD-10: A59.9)
  - b. Amebiasis (ICD-10: A06.9)
  - c. Anaerobic bacterial infection (ICD-10: A41.4)
3. The member has experienced therapeutic failure or intolerance to plan-preferred, generic metronidazole tablets (not including 125 mg tablets).

#### B. Reauthorization

When a benefit, reauthorization of metronidazole 125 mg tablets may be approved when all of following criteria are met **(1., 2., and 3.):**

- 1.** The prescriber attests that the member has a repeat episode of one (1) of the following infections **(a., b., or c.):**
  - a. Trichomoniasis (ICD-10: A59.9)
  - b. Amebiasis (ICD-10: A06.9)
  - c. Anaerobic bacterial infection (ICD-10: A41.4)
- 2.** The prescriber attests that at least 4 weeks have passed since the member finished receiving the first course of treatment with metronidazole 125 mg tablets if being treated specifically for a recurrent trichomoniasis infection.
- 3.** The member has experienced therapeutic failure or intolerance to plan-preferred, generic metronidazole tablets (not including 125 mg tablets).

- III.** An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

### Limitations of Coverage

- I.** Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.
- II.** For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

### Authorization Duration

#### Trichomoniasis

- Commercial and HCR Plans: If approved, up to a 7 day authorization may be granted.

#### Amebiasis

- Commercial and HCR Plans: If approved, up to a 10 day authorization may be granted.

#### Anaerobic Infections

- Commercial and HCR Plans: If approved, up to a 3 month authorization may be granted.

### Automatic Approval Criteria

None.

#### References:

1. Likmez [package insert]. Halifax, Nova Scotia: Appili Therapeutics; July 2024.
2. Metronidazole [package insert]. Southlake, TX: Method Pharmaceuticals LLC; January 2025.
3. Centers for Disease Control and Prevention. Trichomoniasis. Available at: <https://www.cdc.gov/std/trichomonas/stdfact-trichomoniasis.htm>. Accessed November 10, 2023.
4. Shirley D, Farr L, Watanabe K, et al. A Review of the Global Burden, New Diagnostics, and Current Therapeutics for Amebiasis. *Open Forum Infect Dis*. 2018;5:5(7)

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9. Metlay J, Waterer G, Long A et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Amer Jour Resp Crit Care Med*. 2019; 200(7):45-67.
10. StatPearls. Anaerobic Infections. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK482349/>. Accessed November 10, 2023.
11. Centers for Disease Control and Prevention. Amebiasis - CDC Yellow Book 2024. Available at: <https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/amebiasis>. Accessed February 6, 2025.
12. Le Vavasseur B, Zeller V. Antibiotic Therapy for Prosthetic Joint Infections: An Overview. *Antibiot (Basel)*. 2022;11(4):486.

*Pharmacy policies do not constitute medical advice, nor are they intended to govern physicians' prescribing or the practice of medicine. They are intended to reflect the plan's coverage and reimbursement guidelines. Coverage may vary for individual members, based on the terms of the benefit contract.*

*The plan retains the right to review and update its pharmacy policy at its sole discretion. These guidelines are the proprietary information of the plan. Any sale, copying or dissemination of the pharmacy policies is prohibited; however, limited copying of pharmacy policies is permitted for individual use.*