Clinical Policy: Benznidazole
Reference Number: ERX.SPA.227
Effective Date: 03.01.18
Last Review Date: 02.21
Line of Business: Commercial, Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Benznidazole is a nitroimidazole antimicrobial.

FDA Approved Indication(s)
Benznidazole is indicated in pediatric patients 2 to 12 years of age for the treatment of Chagas disease (American trypanosomiasis), caused by Trypanosoma cruzi (T. cruzi).

This indication is approved under accelerated approval based on the number of treated patients who became Immunoglobulin G (IgG) antibody negative against the recombinant antigens of T. cruzi. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that benznidazole is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Chagas Disease (must meet all):
      1. Diagnosis of Chagas disease confirmed by one of the following (a, b, or c) (see Appendix D):
         a. Detection of circulating T. cruzi trypomastigotes on microscopy;
         b. Detection of T. cruzi DNA by polymerase chain reaction assay;
         c. Two positive diagnostic serologic tests showing IgG antibodies to T. cruzi and meeting both of the following (i and ii):
            i. The two tests use different techniques (e.g., enzyme-linked immunosorbent assay [ELISA], immunofluorescent antibody test [IFA]);
            ii. The two tests use different antigens (e.g., whole-parasite lysate, recombinant antigens);
      2. Prescribed by or in consultation with an infectious disease specialist;
      3. Member has not yet received 60 days of benznidazole therapy for the current infection;
      4. Dose (weight-based) does not exceed 400 mg per day (see Appendix D for off-label dosing requests).
   Approval duration: 60 days total

   B. Other diagnoses/indications
      1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
   A. Chagas Disease (must meet all):
      1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member has not yet received 60 days of benznidazole therapy for the current infection;
3. If request is for a dose increase, new dose (weight-based) does not exceed 400 mg per day
   (see Appendix D for off-label dosing requests).

   Approval duration: 60 days total

B. Other diagnoses/indications (must meet 1 or 2):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions
   and documentation supports positive response to therapy.
   Approval duration: Duration of request or 60 days (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III
   (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:
A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient
   documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or
   evidence of coverage documents.

IV. Appendices/General Information
Appendix A: Abbreviation/Acronym Key
CDC: Centers for Disease Control and Prevention
IgG: immunoglobulin G

T. cruzi: Trypanosoma cruzi
WHO: World Health Organization

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s):
  - History of hypersensitivity reaction to benznidazole or other nitroimidazole derivatives.
    Reactions have included severe skin and soft tissue reactions.
  - Patients who have taken disulfiram within the last two weeks. Psychotic reactions may occur
    in patients who are using benznidazole and disulfiram concurrently.
  - Consumption of alcoholic beverages or products containing propylene glycol during and for at
    least 3 days after therapy with benznidazole tablets. A disulfiram-like reaction (abdominal
    cramps, nausea, vomiting, headaches, and flushing) may occur due to the interaction
    between alcohol or propylene glycol and benznidazole.
- Boxed warning(s): none reported

Appendix D: General Information
- Diagnostic tests:
  - Laboratories offering testing for Chagas disease include ARUP Laboratories, Mayo Clinic
    Laboratories, and Quest Diagnostics. IgG serology is performed in the majority of cases.
    After obtaining initial serologic IgG test results, providers should consult their state health
    department and the CDC for guidance on serologic confirmation. If two results are discordant,
    a third assay may be needed. Donor screening tests and Immunoglobulin M (IgM) serology
    tests are not considered diagnostic tests.
- Off-label dosing requests for Chagas disease:
  - Dosing for populations outside FDA-approved age ranges or for longer than 60 days may be
    appropriate and should be reviewed on a case-by-case basis. See CDC consultation
    resources below for questions.
- State reporting requirements:
  - According to the CDC (https://www.cdc.gov/mmwr/volumes/67/wr/mm6726a2.htm), in 2017
    Chagas disease was reportable in six states: Arizona, Arkansas, Louisiana, Mississippi,
    Tennessee, and Texas.
V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
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<tbody>
<tr>
<td>Chagas disease</td>
<td></td>
<td>400 mg/day</td>
</tr>
<tr>
<td>Body Weight</td>
<td>Dose (mg)</td>
<td>Tablet # - 12.5 mg</td>
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<tr>
<td>Range (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 kg</td>
<td>50 mg</td>
<td>4 tablet</td>
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<tr>
<td>15 to &lt; 20 kg</td>
<td>62.5 mg</td>
<td>5 tablet</td>
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<tr>
<td>20 to &lt; 30 kg</td>
<td>75 mg</td>
<td>6 tablet</td>
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<td>30 to &lt; 40 kg</td>
<td>100 mg</td>
<td>1 tablet</td>
</tr>
<tr>
<td>40 to &lt; 60 kg</td>
<td>150 mg</td>
<td>1 ½ tablet</td>
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<tr>
<td>≥ 60 kg</td>
<td>200 mg</td>
<td>2 tablet</td>
</tr>
</tbody>
</table>

VI. Product Availability

Tablets: 12.5 mg (not scored), 100 mg (scored for halves or quarters)

VII. References


Pivotal Trials


Centers for Disease Control (CDC)


Compendia, Guidelines, and Review Articles


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>Policy created</td>
<td>10.17.17</td>
<td>02.18</td>
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<tr>
<td>1Q 2019 annual review: no significant changes, references reviewed and updated.</td>
<td>11.13.18</td>
<td>02.19</td>
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<tr>
<td>1Q 2020 annual review: no significant changes, references reviewed and updated.</td>
<td>11.06.19</td>
<td>02.20</td>
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<tr>
<td>Age removed to allow use at any age; 60 days of therapy limitation added to initial; clarification added to initial and continuation criteria that the 60-day limitation refers to the current infection; Appendix D and references reviewed and updated.</td>
<td>09.01.20</td>
<td>11.20</td>
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<tr>
<td>1Q 2021 annual review: no significant changes; references reviewed and updated.</td>
<td>12.07.20</td>
<td>02.21</td>
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**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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