

## Clinical Policy: Benznidazole

Reference Number: ERX.SPA.227

Effective Date: 03.01.18

Last Review Date: 02.22

Line of Business: Commercial, Medicaid

[Revision Log](#)

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<sup>™</sup> 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.

- Consultation resources:
  - Centers for Disease Control and Prevention (CDC)
    - Parasitic Diseases: <https://www.cdc.gov/parasites/chagas/> - 404-718-4745 (hotline for healthcare providers), [chagas@cdc.gov](mailto:chagas@cdc.gov)
      - CDC recommended guidance document: Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review. JAMA 2007; 298:2171.
      - CDC Drug Service: 404-639-3670
      - CDC Parasitic Diseases Hotline for Healthcare Providers (for all non-malaria parasitic diseases) : 770-488-7100
  - World Health Organization (WHO)
    - Outside the US: <https://www.who.int/health-topics/chagas-disease>
  - American Society of Tropical Medicine and Hygiene
    - Directory of consultants: <http://www.astmh.org/education-resources/clinical-consultants-directory>

## V. Dosage and Administration

Indication	Dosing Regimen					Maximum Dose
Chagas disease	Body Weight Range (kg)	Dose (mg)	Tablet # - 12.5 mg	Tablet # - 100 mg	Duration / Frequency	400 mg/day
	< 15 kg	50 mg	4 tablet	½ tablet	PO BID for 60 days	
	15 to < 20 kg	62.5 mg	5 tablet	---		
	20 to < 30 kg	75 mg	6 tablet	¾ tablet		
	30 to < 40 kg	100 mg	---	1 tablet		
	40 to < 60 kg	150 mg	---	1 ½ tablet		
≥ 60 kg	200 mg	---	2 tablet			

## VI. Product Availability

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

## VII. References

1. Benznidazole Prescribing Information. Florham Park, NJ: Exeltis USA, Inc.; August 2017. Available at: [https://www.benznidazoletablets.com/assets/pdf/Prescribing\\_Information.pdf](https://www.benznidazoletablets.com/assets/pdf/Prescribing_Information.pdf). Accessed November 15, 2021 .

### Pivotal Trials

2. Estani SS, Segura EL, Ruiz AM, et al. Efficacy of chemotherapy with benznidazole in children in the indeterminate phase of Chagas disease. 1998; Am J Trop Med Hyg 59: 526-529.
3. Sgambatti de Andrade, ALS, Zicker F, Mauricio de Oliveira. R, et al. Randomized trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection. 1996; Lancet 348: 1407-1413.

### Centers for Disease Control (CDC)

4. American Trypanosomiasis. DPDx - Laboratory identification of parasitic diseases of public health concern. Centers for Disease Control and Prevention. Available at <https://www.cdc.gov/dpdx/trypanosomiasisamerican/index.html>. Last updated June 16, 2021. Accessed November 15, 2021 .

### Compendia, Guidelines, and Review Articles

5. Benznidazole Drug Monograph. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc. Updated periodically. Accessed November 15, 2021 .
6. Bern C, Messenger LA, Whitman JD, Maguire JH. Chagas Disease in the United States: a Public Health Approach. American Society for Microbiology. Clinical Microbiology Reviews. January 2020; 33(1): 1-42.
7. Guidelines for the diagnosis and treatment of Chagas disease. Joint publication of Pan-American Health Organization (PAHO) and World Health Organization (WHO), 2019, Washington D.C. Available at [https://iris.paho.org/bitstream/handle/10665.2/49653/9789275120439\\_eng.pdf](https://iris.paho.org/bitstream/handle/10665.2/49653/9789275120439_eng.pdf). Accessed December 7, 2020.

8. Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association. *Circulation*. Volume 138, Issue 12, 18 September 2018; Pages e169-e209. <https://doi.org/10.1161/CIR.0000000000000599>.
9. Crespillo-Andujar C, Chamorro-Tojeiro S, Norman F, et al. Toxicity of nifurtimox as second-line treatment after benznidazole intolerance in patients with chronic Chagas disease: when available options fail. *Clinical Microbiology and Infection* 24 (2018) 1344.e1e1344.e4. <https://doi.org/10.1016/j.cmi.2018.06.006>
10. Perez-Molina JA, Molina I. Chagas disease: Seminar. *Lancet*. June 30, 2017. [http://dx.doi.org/10.1016/S0140-6736\(17\)31612-4](http://dx.doi.org/10.1016/S0140-6736(17)31612-4).
11. Bern C. Chagas disease. *N Engl J Med* 2015; 373: 456-66. DOI: 10.1056/NEJMra1410150.
12. Perez-Molina JA, Sojo-Dorado J, Norman F, et al. Nifurtimox therapy for Chagas disease does not cause hypersensitivity reactions in patients with such previous adverse reactions during benznidazole treatment. *Acta Tropica* 127 (2013) 101–104.
13. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: A systematic review. *JAMA* 2007; 298:2171.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	10.17.17	02.18
1Q 2019 annual review: no significant changes, references reviewed and updated.	11.13.18	02.19
1Q 2020 annual review: no significant changes, references reviewed and updated.	11.06.19	02.20
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.	09.01.20	11.20
1Q 2021 annual review: no significant changes; references reviewed and updated.	12.07.20	02.21
1Q 2022 annual review: no significant changes; references reviewed and reviewed.	11.16.21	02.22

**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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