Clinical Policy: Benznidazole

Reference Number: PA.CP.PMN.90
Effective Date: 10/2017
Last Review Date: 01/2024

Revision Log

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 (which may include office chart notes and lab results) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness 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 does not have Cockayne syndrome;
4. Member has not yet received 60 days of benznidazole therapy for the current infection;
5. 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 PA.PA.CP.PMN.53.

II. Continued Therapy

A. Chagas Disease (must meet all)**:**

1. Currently receiving medication via PA Health &Wellness benefit or member has met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies;
2. Member has not yet received 60 or more days of benznidazole therapy for 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 PA Health &Wellness benefit or member has met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies;
   Approval duration: Duration of request or 60 days(whichever is less); or
2. Refer to PA.PA.CP.PMN.53.

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 – PA.PA.CP.PMN.53 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):
  - Patients with a 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.
  - Patients with Cockayne syndrome. Severe irreversible hepatotoxicity/acute liver failure with fatal outcomes have been reported after initiation of metronidazole, another nitroimidazole drug, structurally related to benznidazole in patients with Cockayne syndrome.
- 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
      - 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 T	½ T	PO BID for 60 days	
	15 to < 20 kg	62.5 mg	5 T	---		
	20 to < 30 kg	75 mg	6 T	¾ T		
	30 to < 40 kg	100 mg	---	1 T		
	40 to < 60 kg	150 mg	---	1 ½ T		
	≥ 60 kg	200 mg	---	2 T		

VI. Product Availability

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

VII. References

1. Benznidazole Prescribing Information. Florham Park, NJ: Exeltis USA, Inc.; December 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209570s002lbl.pdf. Accessed October 23, 2023.

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 6, 2023.

Compendia, Guidelines, and Review Articles

5. Benznidazole Drug Monograph. Clinical Pharmacology [database online]. Elsevier; 2022. Updated periodically. Accessed November 6, 2023.
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.
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.
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.
14. Forsyth CJ, Manne-Goehler J, Bern C, et al. Recommendations for Screening and Diagnosis of Chagas Disease in the United States. The Journal of Infectious Diseases 2022; 225: 1601-1610.

Reviews, Revisions, and Approvals	Date
1Q 2019 annual review; references reviewed and updated.	01/2019
1Q 2020 annual review; aligned the maximum auth duration for Other diagnoses/indications to 60 days; references reviewed and updated.	01/2020
Age removed to allow use for any age; 60 days of therapy limitation added to initial criteria; clarification added to initial and continuation criteria that the 60-day limitation refers to the current infection; Appendix D and references reviewed and updated.	09/2020
1Q 2021 annual review: clarified 60 days of therapy limitation to benznidazole; references reviewed and updated.	01/2021
1Q 2022 annual review: no significant changes; references reviewed and reviewed.	01/2022
1Q 2023 annual review: updated contraindications to include Cockayne syndrome, added requirement that member does not have Cockayne syndrome due to irreversible and potentially fatal hepatotoxicity; references reviewed and updated.	01/2023
1Q 2024 annual review: no significant changes; references reviewed and reviewed.	01/2024