Clinical Policy: Benznidazole

Reference Number: CP.PMN.90
Effective Date: 03.01.18
Last Review Date: 02.25
Line of Business: HIM, 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 (including such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® 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 (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Chagas Disease (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line

of business: HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

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 policies – HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid 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 22, 2024.

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 October 31, 2024.
5. Clinical Care of Chagas Disease. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/chagas/hcp/clinical-care/index.html. Last updated February 2, 2024.

Compendia, Guidelines, and Review Articles

6. Benznidazole Drug Monograph. Clinical Pharmacology [database online]. Elsevier; 2022. Updated periodically. Available at: https://www.clinicalkey.com/pharmacology/. Accessed October 31, 2024.
7. 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.
8. 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.
9. 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.
10. 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
11. Perez-Molina JA, Molina I. Chagas disease. Lancet. 2018 Jan 6;391(10115):82-94.
12. Bern C. Chagas disease. N Engl J Med 2015; 373: 456-66. DOI: 10.1056/NEJMra1410150.
13. 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.
14. 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.
15. 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	P&T Approval Date
1Q 2020 annual review; no significant changes, revised auth duration for Other diagnoses/indications to 60 days from 6 months; references reviewed and updated.	11.06.19	02.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Age removed to allow use at 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.	09.01.20	11.20
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and reviewed.	12.07.20	02.21
1Q 2022 annual review: no significant changes; references reviewed and reviewed.	11.16.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.10.22	
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.	10.13.22	02.23
1Q 2024 annual review: removed Commercial line of business as criteria does not apply; references reviewed and reviewed.	10.23.23	02.24
1Q 2025 annual review: no significant changes; references reviewed and reviewed.	10.22.24	02.25

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to

applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.