Clinical Policy: Benznidazole

Reference Number: CP.PMN.90
Effective Date: 03.01.18
Last Review Date: 02.20
Line of Business: Commercial, 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 tests (a, b, or c):
   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* using different techniques (e.g., enzyme-linked immunoassay, indirect fluorescent antibody) and antigens (e.g., whole-parasite lysate, recombinant antigens) showing IgG antibodies to *T. cruzi*;
2. Prescribed by or in consultation with an infectious disease specialist;
3. Age 2 to ≤ 12 years;
4. Dose (weight-based) does not exceed 400 mg per day.

Approval duration: 60 days total

**If two commercial diagnostic IgG tests are unavailable, providers should consult their state health department for guidance; if results are discordant, a third assay may be needed. Chagas disease is a reportable disease in some states. Donor screening tests and Immunoglobulin M serology tests are not considered diagnostic tests.*

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member has not yet received 60 or more days of benznidazole therapy;
3. If request is for a dose increase, new dose does not exceed 400 mg per day.

Approval duration: 60 days total

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 60 days (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 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 – CP.CPA.09 for commercial, HIM.PHAR.21 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):
  - Benznidazole tablets are contraindicated in patients with a history of hypersensitivity reaction to benznidazole or other nitroimidazole derivatives. Reactions have included severe skin and soft tissue reactions.
  - Benznidazole tablets are contraindicated in 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 is contraindicated in patients 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

- Resources and Consultation
  - Centers for Disease Control and Prevention (CDC)
    1. Parasitic Diseases: 404-718-4745, https://www.cdc.gov/parasites/chagas/
       - 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.
    2. CDC Drug Service: 404-639-3670
    3. CDC Emergency Operations Center: 770-488-7100
  - World Health Organization (WHO)
    1. Outside the US: www.who.int/chagas/home_treatment/en/
  - American Society of Tropical Medicine and Hygiene
    1. 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)	# of 12.5 mg tablets	# of 100 mg tablets	Duration and Frequency of Therapy	400 mg/day
	< 15 kg	50 mg	4 tablets	½ tablet	PO BID approximately 12 hours apart for 60 days	
	15 kg to < 20 kg	62.5 mg	5 tablets			
	20 kg to < 30 kg	75 mg	6 tablets	¾ tablet		
	30 kg to < 40 kg	100 mg		1 tablet		
	40 kg to < 60 kg	150 mg		1 ½ tablets		
	≥ 60 kg	200 mg		2 tablets		

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.; August 2017. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209570lbl.pdf. Accessed November 6, 2019.
2. Benznidazole Drug Monograph. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: http://www.clinicalpharmacology-ip.com/.
3. 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.
4. 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.
5. Perez-Molina JA, Molina I. Chagas disease: Seminar. Lancet. June 30, 2017. http://dx.doi.org/10.1016/S0140-6736(17)31612-4.
6. Bern C. Chagas disease. N Engl J Med 2015; 373: 456-66. DOI: 10.1056/NEJMra1410150.
7. 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.
8. Formulary (Benznidazole, nifurtimox): Infectious Diseases Laboratory. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/laboratory/drugservice/formulary.html#tnifurtimox. Last updated May 18, 2018. Accessed November 7, 2018.
9. 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 April 30, 2019. Accessed November 6, 2019.

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, revised auth duration for Other diagnoses/indications to 60 days from 6 months; references reviewed and updated.	11.06.19	02.20

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.