CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
1Q18 January - February

BRAND NAME
Not applicable

GENERIC NAME
Benznidazole

MANUFACTURER
Exeltis USA, Inc.

DATE OF APPROVAL
August 29, 2017

PRODUCT LAUNCH DATE
Unknown at this time. Currently, the product may be obtained from the Centers for Disease Control and Prevention (CDC) via the existing investigational new drug (IND) protocol (https://www.cdc.gov/laboratory/drugservice/formulary.html).

REVIEW TYPE
☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)[1]
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 was 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.

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OFF LABEL USES[2]

- Neonates: Safety and efficacy have not been established.
- Infants: Safety and efficacy have not been established; however, doses up to 7.5 mg/kg/day have been used off-label.
- Children younger than 2 years: Safety and efficacy have not been established; however, doses up to 7.5 mg/kg/day PO have been used off-label.
- Adolescents: Safety and efficacy have not been established; however, doses up to 7 mg/kg/day PO have been used off-label.
- Adults: Safety and efficacy have not been established; however, doses up to 7 mg/kg/day PO have been used off-label.
- Geriatric: Safety and efficacy have not been established; however, doses up to 7 mg/kg/day PO have been used off-label.

CLINICAL EFFICACY[3, 4, 5]

- **Disease description:** Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi (T. cruzi)*. Vectorborne transmission is limited to areas of North America, Central America, and South America. Other infection routes include transfusion, organ and bone marrow transplantation, and congenital transmission. Infection is lifelong in the absence of effective treatment. The most important consequence of infection is cardiomyopathy, which occurs in 20 to 30% of infected persons.
- **Diagnostic tests *(versus screening tests):*** Diagnostic tests include visualization of circulating *T. cruzi* trypomastigotes on microscopy if acute infection and two positive serologic tests using different antigens (e.g., whole-parasite lysate and recombinant antigens) and techniques (e.g., indirect fluorescent antibody and enzyme immunoassay) showing Immunoglobulin G antibodies to *T. cruzi* if chronic infection.
- **Treatment:** Nifurtimox and benznidazole are the only two drugs with proven efficacy and are currently available from the CDC under investigational protocols. Benznidazole, a nitroimidazole derivative, is considered first-line treatment on the basis of a better side-effect profile than nifurtimox, as well as a more extensive efficacy evidence base. Studies have suggested that the earlier in life children are treated, the higher the rate of negative seroconversion. Over the past 15 years, treatment of chronically infected adults has increased, including those with early cardiomyopathy [see BENEFIT trial]. Observational studies have also confirmed that women treated before pregnancy are significantly less likely than untreated women to transmit the infection to their offspring.
- **Monitoring:** Conventional serologic markers respond very slowly after treatment. The time to negative seroconversion is measured in years to decades and is said to be inversely proportional to the pretreatment duration of infection (for which age is often used as the proxy). Follow-up assays are technically challenging and are not currently available for clinical use.

Consultations should be sought through the Parasitic Diseases Public Inquiries line (404-718-4745, or parasites@cdc.gov), the CDC Drug Service (404-639-3670), or the CDC Emergency Operations Center (770-488-7100). Access varies outside the United States; questions can be addressed to the World Health Organization (www.who.int/chagas/home_treatment/en/).[6,7]

<table>
<tr><th></th><th>Estani S, et al., 1998, Efficacy of Chemotherapy with Benznidazole in Children in the Indeterminate Phase of Chagas' Disease.[8]</th></tr>
<tr><td>Study Design</td><td>Trial 1: randomized, double-blind, placebo-controlled clinical field trial of benznidazole in the indeterminate phase of T. cruzi infection conducted in Argentina
<u>Inclusion criteria</u>
• Children 6 to 12 years of age with chronic indeterminate Chagas disease. The chronic indeterminate form of Chagas disease includes patients with serologic evidence of T. cruzi infection without symptoms of cardiac or gastrointestinal disease
• Patients with at least two positive conventional serologic tests for antibodies to T. cruzi. The conventional serologic tests used include indirect hemagglutination assay (IHA), immunofluorescence antibody assay (IFA), and/or enzyme-linked immunosorbent assay (ELISA) and were based on the detection of antibodies against T. cruzi parasites</td></tr>
<tr><td>N</td><td>106</td></tr>
<tr><td>Drug Regimen</td><td>Benznidazole (5 mg/kg/day for 60 days) or placebo</td></tr>
<tr><td>Primary Outcome(s)</td><td>Negative seroconversions after 4 years</td></tr>
<tr><td>Secondary Outcome(s)</td><td>• Antibody titers against T. cruzi, its trend during follow-up, and the relationship between antibody titers in each evaluation and baseline estimate
• Frequency of side effects, abnormal ECG, and the proportion of those with positive xenodiagnosis</td></tr>
<tr><td>Results</td><td>In both trials, benznidazole treatment resulted in a significantly higher percentage of seronegative patients by a nonconventional assay. Results at the end of follow-up are reported in the following table.[1]
<table>
<tr><th colspan="4">Nonconventional ELISA* Serologic Status at End-of-Follow-Up (mITT population**)</th></tr>
<tr><th></th><th>Benznidazole</th><th>Placebo</th><th>Difference (95% CI)†</th></tr>
<tr><td></td><td>N=40</td><td>N=37</td><td></td></tr>
<tr><td>Seronegative</td><td>24 (60.0%)</td><td>5 (13.5%)</td><td>46.5 (24.5, 64.4)</td></tr>
<tr><td>Seropositive</td><td>15</td><td>29</td><td></td></tr>
<tr><td>Missing</td><td>1</td><td>3</td><td></td></tr>
<tr><td colspan="4">*Enzyme-linked immunosorbent assay (F29 ELISA in Study Trial 1 and AT chemiluminescence-ELISA in Trial 2); the F29 and AT antigens represent antigens from the flagella of T. cruzi parasites.</td></tr>
</table></td></tr>
</table>

	**Modified intent to treat (mITT) population includes subjects who are positive for the assay at baseline. †Exact confidence intervals presented.
# Withdrew due to Lack of Efficacy	Not reported
# Withdrew due to Adverse Effects	Benznidazole was discontinued due to an adverse reaction in 5/55 (9%) patients. Some patients had more than one adverse reaction resulting in treatment discontinuation. The adverse reactions included abdominal pain, nausea, vomiting, rash, decreased appetite, headache, and increased transaminases.

	de Andrade, et al., 1996, Randomised Trial of Efficacy of Benznidazole in Treatment of Early *Trypanosoma cruzi* Infection.[9]
Study Design	Phase III, randomized, double-blind, placebo-controlled field trial of benznidazole in the early chronic phase of *T. cruzi* infection carried out from 1991 to 1995 in Brazil Inclusion criteria • Pediatric patients 7 to 12 years of age with chronic indeterminate Chagas disease and three positive conventional serologic tests for antibodies to *T. cruzi*. The conventional serologic tests include indirect IHA, IFA, and/or ELISA and were based on the detection of antibodies against *T. cruzi* parasites.
N	129
Drug Regimen	Benznidazole (7.5 mg/kg/day for 60 days) or placebo
Primary Outcome(s)	Negative seroconversions after 3 years
Secondary Outcome(s)	• A three-fold or greater reduction in antibody reciprocal titers assessed through repeated serological tests.
Results	In both trials, benznidazole treatment resulted in a significantly higher percentage of seronegative patients by a nonconventional assay. Results at the end of follow-up are reported in the following table.[1]

Nonconventional ELISA* Serologic Status at End-of-Follow-Up (mITT population)**

	N=64	N=65	
Seronegative	35 (54.7%)	3 (4.6%)	50.1 (35.8, 63.4)
Seropositive	23	51	
Missing	6	11	

	*Enzyme-linked immunosorbent assay (F29 ELISA in Study Trial 1 and AT chemiluminescence-ELISA in Trial 2); the F29 and AT antigens represent antigens from the flagella of *T. cruzi* parasites. **Modified intent to treat (mITT) population includes subjects who are positive for the assay at baseline. †Exact confidence intervals presented.
# Withdrew due to Lack of Efficacy	Not reported
# Withdrew due to Adverse Effects	One child was withdrawn due to a moderate papular rash during the treatment phase.

CONTRAINDICATIONS[1]

- History of hypersensitivity reaction to benznidazole or other nitroimidazole derivatives. Reactions have included severe skin and soft tissue reactions.
- 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.
- Treatment during pregnancy or breast-feeding is generally not recommended; however, a case-by-case evaluation may be indicated.[1,4]

BLACK BOX WARNINGS[1]

Not Applicable

DRUG INTERACTIONS[1]

- Psychotic reactions have been reported in patients who are concurrently taking disulfiram and nitroimidazole agents (structurally related to benznidazole, but not with benznidazole).
- Abdominal cramps, nausea, vomiting, headaches, and flushing may occur if alcoholic beverages or products containing propylene glycol are consumed during or following therapy with nitroimidazole agents which are structurally related to benznidazole.

ADVERSE REACTIONS[1]

- Potential for genotoxicity, carcinogenicity, and mutagenicity
- Hypersensitivity skin reactions
- Central and peripheral nervous system effects
- Hematological manifestations of bone marrow depression

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DOSAGE AND ADMINISTRATION[1]

Benznidazole tablets (12.5 mg and 100 mg) are for oral use and may be taken with or without food. Benznidazole tablets are dosed by body weight (kg). Benznidazole 100 mg tablets are functionally scored tablets which can be split into one-half (50 mg) or one-quarter (25 mg) at the scored lines to provide doses less than 100 mg. Benznidazole 12.5 mg and 100 mg tablets can be made into slurry as an alternative method of administration. The total daily dose for pediatric patients 2 to 12 years of age is 5 mg/kg to 8 mg/kg orally administered in two divided doses separated by approximately 12 hours, for a duration of 60 days (see Table 1).

Table 1: Weight-Based Dosing of Benznidazole

Body Weight Range (kg)	Dose (mg)	Number of Benznidazole Tablets 12.5mg	Number of Benznidazole Tablets 100mg	Duration and Frequency of Therapy
Less than 15 kg	50 mg	4 tablets	½ tablet	Administered twice daily approximately 12 hours apart for 60 days.
15 kg to less than 20 kg	62.5 mg	5 tablets		
20 kg to less than 30 kg	75 mg	6 tablets	¾ tablet	
30 kg to less than 40 kg	100 mg		1 tablet	
40 kg to less than 60 kg	150 mg		1 ½ tablets	
Greater than or equal to 60 kg	200 mg		2 tablets	

PRODUCT AVAILABILITY[1]

Tablets:

- 100 mg (functionally scored twice as a cross on both sides)
- 12.5 mg (unscored)

THERAPEUTIC ALTERNATIVES[6,7]

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Nifurtimox	Nifurtimox is available through the CDC under investigational use; indications for distribution include patients with acute, subacute or early chronic Chagas disease. Cases may occur in laboratory workers, immigrants, and US citizens returning from travel to Latin America.	Contact Information: Drug Service, Division of Host Factors, Center for Infectious Disease (404) 639-3670, 8 AM to 4:30 PM EST Monday through Friday; for after hour or holiday emergencies, call (404) 639-2888.

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Utilization Management Recommendation
• There is not a significant potential for inappropriate use.

- It would be clinically appropriate to limit the quantity of benznidazole for 60 days.

Product Comparison

- Only available FDA-approved first or second line therapy for disease or condition (will not be scored).

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 October 17, 2017.
[2] Benznidazole Drug Monograph. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available at: http://www.clinicalpharmacology-ip.com/.
[3] Bern C. Chagas disease. N Engl J Med 2015;373:456-66. DOI: 10.1056/NEJMra1410150.
[4] 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.
[5] Perez-Molina JA, Molina I. Chagas disease: Seminar. Lancet. June 30, 2017. http://dx.doi.org/10.1016/S0140-6736(17)31612-4. Accessed October 2017.
[6] Formulary (Benznidazole, nifurtimox): Infectious Diseases Laboratory. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/dpdx/trypanosomiasisamerican/index.html. Last updated August 30, 2017. Accessed September 2017.
[7] 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 August 30, 2017. Accessed September 2017.
[8] 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.
[9] Sgambatti de Andrade, ALS, Zicker F, Mauricio de Oliveira. R, et al. Randomised trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection. 1996; Lancet 348: 1407-1413.