

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209570Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BENZNIDAZOLE TABLETS safely and effectively. See full prescribing information for BENZNIDAZOLE TABLETS.

BENZNIDAZOLE tablets, for oral use

Initial U.S. Approval: 2017

INDICATIONS AND USAGE

Benznidazole Tablets, a nitroimidazole antimicrobial, is indicated in pediatric patients 2 to 12 years of age for the treatment of Chagas disease (American trypanosomiasis), caused by *Trypanosoma cruzi* (1).

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 (1, 14).

DOSAGE AND ADMINISTRATION

- Pediatric Patients 2 to 12 years of age: The total daily dose 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 (2.2).
- See Full Prescribing Information for important administration instructions (2.1, 2.3, 2.4).

DOSAGE FORMS AND STRENGTHS

- Tablets: 100 mg (functionally scored) (3).
- Tablets: 12.5 mg (3).

CONTRAINDICATIONS

- History of hypersensitivity reaction to benznidazole or other nitroimidazole derivatives (4.1).
- Disulfiram usage within the last two weeks (4.2).
- Alcoholic beverage consumption during and for at least three days after therapy (4.3).

WARNINGS AND PRECAUTIONS

- Potential Risk for Genotoxicity and Carcinogenicity (5.1).
- Embryo-Fetal Toxicity: Can cause fetal harm. Pregnancy testing is recommended for females of reproductive potential. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception (2.3, 5.2, 8.1, 8.3).
- Hypersensitivity skin reactions have been reported with benznidazole. In case of skin reactions, presenting with additional symptoms of systemic involvement such as lymphadenopathy, fever and/or purpura, discontinuation of treatment is recommended (5.3).
- Treatment with Benznidazole Tablets can potentially cause paresthesia or symptoms of peripheral neuropathy. In cases where neurological symptoms occur, immediate discontinuation of treatment is recommended (5.4).
- There have been hematological manifestations of bone marrow depression, such as neutropenia, thrombocytopenia, anemia, and leukopenia (5.5).

ADVERSE REACTIONS

Most common adverse reactions observed were abdominal pain, rash, decreased weight, headache, nausea, vomiting, neutropenia, urticaria, pruritus, eosinophilia, decreased appetite (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Exeltis USA, Inc. at 1-877-324-9349 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Breastfeeding is not recommended (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Administration Instructions
- 2.2 Recommended Dosage in Pediatric Patients (2 to 12 Years of Age)
- 2.3 Assessment Prior to Initiating Benznidazole Tablets
- 2.4 Preparation of Slurry as an Alternative Method of Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Hypersensitivity
- 4.2 Disulfiram
- 4.3 Alcohol and Products Containing Propylene Glycol

5 WARNINGS AND PRECAUTIONS

- 5.1 Potential for Genotoxicity and Carcinogenicity
- 5.2 Embryo-fetal Toxicity
- 5.3 Hypersensitivity Skin Reactions
- 5.4 Central and Peripheral Nervous System Effects
- 5.5 Hematological Manifestations of Bone Marrow Depression

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Disulfiram
- 7.2 Alcohol and Products Containing Propylene Glycol

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Benznidazole Tablets are indicated in pediatric patients 2 to 12 years of age for the treatment of Chagas disease (American trypanosomiasis) caused by *Trypanosoma 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* [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Benznidazole Tablets (12.5 mg and 100 mg) are for oral use and may be taken with or without food [see *Clinical Pharmacology (12.3)*].
- Benznidazole Tablets are dosed by body weight (kg) [see *Dosage and Administration (2.2)*].
- Benznidazole Tablets 100 mg 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 [see *Instructions for Use*].
- Benznidazole Tablets 12.5 mg and 100 mg can be made into slurry as an alternative method of administration [see *Dosage and Administration (2.4)*].

2.2 Recommended Dosage in Pediatric Patients (2 to 12 Years of Age)

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: Recommended Dosage of Benznidazole Tablets in Pediatric Patients (2 to 12 Years of Age)

Body Weight Range (kg)	Dose (mg)	Number of Benznidazole Tablets 12.5 mg	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	

2.3 Assessment Prior to Initiating Benznidazole Tablets

Obtain a pregnancy test in females of reproductive potential prior to therapy with Benznidazole Tablets [see *Use in Specific Populations (8.3)*].

2.4 Preparation of Slurry as an Alternative Method of Administration

A. Preparation of Slurry Using Benznidazole Tablets 12.5 mg for the Pediatric Population with Body Weight Less Than 30 kg

Benznidazole Tablets 12.5 mg may be made into slurry in a specified volume of water for the pediatric population with body weight less than 30 kg (see Table 2). The 12.5 mg tablet slurry is prepared by the following method:

Table 2: Preparation and Administration of Slurry Using Benznidazole Tablets 12.5 mg for the Pediatric Population with Body Weight of Less than 30 kg

- Place the prescribed dose of Benznidazole Tablets 12.5 mg into a cup. - Add the specified volume of water per number of 12.5 mg tablets as shown below.			
Body Weight Range (kg)	Dose (mg)	Number of Benznidazole Tablets 12.5 mg	Quantity of Water for Preparing the Slurry
Less than 15 kg	50 mg	4 tablets	40 mL
15 kg to less than 20 kg	62.5 mg	5 tablets	50 mL
20 kg to less than 30 kg	75 mg	6 tablets	60 mL
- Allow the tablets to disintegrate in the cup over a period of approximately 1-2 minutes. - Shake the contents of the cup gently to mix. - Drink the contents of the cup (slurry of tablets with water) immediately. - Rinse the cup with an additional 10 mL of water and drink the whole amount.			

B. Preparation of Slurry Using Benznidazole Tablets 100 mg for the Pediatric Population with Body Weight (30 kg or greater)

Benznidazole Tablets 100 mg may be made into a slurry in a specified volume of water for the pediatric population with body weight of 30 kg or greater (see Table 3). The 100 mg tablet slurry is prepared as follows:

Table 3: Preparation and Administration of Slurry Using Benznidazole Tablets 100 mg for the Pediatric Population with Body Weight 30 kg or greater

- Place the prescribed dose of Benznidazole Tablets 100 mg tablets into a cup. - Add the specified volume of water per number of 100 mg tablets as shown below.			
Body Weight Range (kg)	Dose (mg)	Number of Benznidazole Tablets 100 mg	Quantity of Water for Preparing the Slurry
30 kg to less than 40 kg	100 mg	1 tablet	80 mL
40 kg to less than 60 kg	150 mg	1 ½ tablets	120 mL
Greater than or equal to 60 kg	200 mg	2 tablets	160 mL

- Allow the tablet(s) to disintegrate in the cup over a period of approximately 1- 2 minutes.
- Shake the contents of the cup gently to mix.
- Drink the contents of the cup (slurry of tablet(s) with water) immediately.
- Rinse the cup by adding **80 mL** of water and drink the whole amount. Repeat this rinse with **80 mL** of water and drink again.

3 DOSAGE FORMS AND STRENGTHS

Benznidazole Tablets are available as 100 mg and 12.5 mg tablets.

The 100 mg white tablets are round and functionally scored twice as a cross on both sides, debossed with “E” on one side of each quarter portion.

The 12.5 mg white tablets are round and unscored, debossed with “E” on one side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

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 [see *Adverse Reactions* (6.1)].

4.2 Disulfiram

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 [see *Drug Interactions* (7.1)].

4.3 Alcohol and Products Containing Propylene Glycol

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 [see *Drug Interactions* (7.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Genotoxicity and Carcinogenicity

Genotoxicity

Genotoxicity of benznidazole has been demonstrated in humans, in vitro in several bacterial species and mammalian cell systems, and in vivo in rodents [see *Nonclinical Toxicology* (13.1)].

A study evaluating the cytogenetic effect of benznidazole in pediatric patients ranging from 11 months to 11 years of age (the safety and effectiveness of Benznidazole Tablets in patients less than 2 years old has not been

established) with Chagas disease demonstrated a two-fold increase in chromosomal aberrations. In pediatric patients with Chagas disease who were treated with benznidazole, the median incidence of micronucleated interphase lymphocytes in 20 patients increased 2 fold compared to pre-dose values. In the same study, the mean incidence of chromosomal aberrations in 10 patients also increased 2 fold compared to pre-dose values.

Carcinogenicity

Carcinogenicity has been observed in mice and rats treated chronically with nitroimidazole agents which are structurally similar to benznidazole. Similar data have not been reported for benznidazole [see *Nonclinical Toxicology* (13.1)]. It is not known whether benznidazole is associated with carcinogenicity in humans.

5.2 Embryo-Fetal Toxicity

Based on findings from animal studies, Benznidazole Tablets can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, benznidazole administered orally to pregnant rats and rabbits during organogenesis was associated with fetal malformations at doses approximately 1-3 times the maximum recommended human dose (MRHD) in rats (anasarca, anophthalmia, and/or microphthalmia) and doses approximately 0.3-1 times the MRHD in rabbits (ventricular septal defect). In rats, reduced maternal weights and smaller litter sizes occurred at a dose approximately 3 times the MRHD. In rabbits, reduced maternal weight gain, and abortions in 2/20 females occurred at a dose approximately equal to the MHRD [see *Use in Specific Populations* (8.1)]. Advise pregnant women of the potential risk to a fetus. Pregnancy testing is recommended for females of reproductive potential [see *Dosage and Administration* (2.3)]. Advise females of reproductive potential to use effective contraception during treatment with Benznidazole Tablets and for 5 days after the last dose [see *Use in Specific Populations* (8.1, 8.3) and *Clinical Pharmacology* (12.3)].

5.3 Hypersensitivity Skin Reactions

Serious skin and subcutaneous disorders including acute generalized exanthematous pustulosis (AGEP), toxic epidermal necrolysis (TEN), erythema multiforme, and eosinophilic drug reaction have been reported with benznidazole. Discontinue treatment at the first evidence of these serious cutaneous reactions [see *Adverse Reactions* (6.2)].

Extensive skin reactions, such as rash (maculopapular, pruritic macules, eczema, pustules, erythematous, generalized, and allergic dermatitis, exfoliative dermatitis) have also been reported. Most cases occurred after approximately 10 days of treatment with benznidazole. Most rashes resolved with treatment discontinuation.

In case of skin reactions presenting with additional symptoms or signs of systemic involvement such as lymphadenopathy, fever and/or purpura, discontinuation of treatment is recommended.

5.4 Central and Peripheral Nervous System Effects

Treatment with Benznidazole Tablets can cause paresthesia or symptoms of peripheral neuropathy that may take several months to resolve. Headache and dizziness have been reported. In cases where neurological symptoms occur, immediate discontinuation of treatment is recommended. In most cases, symptoms occur late in the course of treatment.

5.5 Hematological Manifestations of Bone Marrow Depression

There have been reports of hematological manifestations of bone marrow depression, such as neutropenia, thrombocytopenia, anemia and leukopenia, which resolved after treatment discontinuation [see *Adverse*

Reactions (6.1)]. Patients with hematological manifestations of bone marrow depression must take Benznidazole Tablets only under strict medical supervision. Monitor complete blood count. Total and differential leukocyte counts are recommended before, during and after therapy.

6 ADVERSE REACTIONS

The following serious and otherwise important adverse reactions are discussed in greater detail in other sections of labeling:

- Potential for Genotoxicity, Carcinogenicity, and Mutagenicity [*see Warnings and Precautions (5.1)]*
- Hypersensitivity Skin Reactions [*see Warnings and Precautions (5.3)]*
- Central and Peripheral Nervous System Effects [*see Warnings and Precautions (5.4)]*
- Hematological Manifestations of Bone Marrow Depression [*see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Benznidazole was evaluated in two randomized, double-blind, placebo-controlled trials (Trial 1¹ and Trial 2²) and one uncontrolled trial (Trial 3³).

Trial 1 was conducted in pediatric patients 6 to 12 years of age with chronic indeterminate Chagas disease in Argentina. The chronic indeterminate form includes patients with serologic evidence of *T. cruzi* infection without symptoms of cardiac or gastrointestinal disease. A total of 106 patients were randomized to receive either benznidazole (5 mg/kg/day twice daily for 60 days; N= 55) or placebo (N=51) and followed for 4 years.

Trial 2 was conducted in pediatric patients 7 to 12 years of age with chronic indeterminate Chagas disease in Brazil. A total of 129 patients were randomized to receive either benznidazole (7.5 mg/kg/day twice daily for 60 days; N = 64) or placebo (N = 65) and followed for 3 years.

Trial 3 was an uncontrolled study in pediatric patients 2 to 12 years of age with chronic indeterminate Chagas disease. A total of 37 pediatric patients with Chagas disease were enrolled in this safety and pharmacokinetics study. Patients were treated with benznidazole 5 to 8 mg/kg/day twice daily for 60 days.

Adverse Reactions Leading to Discontinuation

In Trial 1, 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 transaminases increased.

Common Adverse Reactions in Pediatric Patients

The most frequently reported adverse reactions in pediatric patients treated with benznidazole in Trial 1 were abdominal pain (25%), rash (16%), decreased weight (13%), and headache (7%). Table 4 lists adverse reactions occurring at a rate of 1% or greater in pediatric patients with Chagas disease aged 6 to 12 years of age in Trial 1.

Table 4: Adverse Reactions Occurring in Pediatric Patients with Chagas Disease aged 6 to 12 Years in Trial 1

Body System	Adverse Reaction	Benznidazole (N=55) N (%)	Placebo (N=51) N (%)
Gastrointestinal	Abdominal pain	14 (25)	4 (8)
	Weight decreased	7 (13)	1 (2)
	Nausea	3 (5)	1 (2)
	Vomiting	3 (5)	0
	Diarrhea	2 (4)	0
	Decreased appetite	3 (5)	0
Skin and subcutaneous tissue	Rash	9 (16)	0
Metabolism/Laboratory	Transaminases increased	3 (5)	0
Nervous system Disorders	Dizziness	2 (4)	2 (4)
	Peripheral neuropathy	1 (2)	0
	Tremor	1 (2)	0

In Trial 2, skin lesions were reported in 7 of 64 (11%) pediatric patients treated with benznidazole and in 2 of 65 patients receiving placebo. Adverse reactions reported in fewer than 5% of benznidazole-treated patients included nausea, anorexia, headache, abdominal pain and arthralgia.

In a subset of 19 pediatric patients 2 to 6 years of age treated with benznidazole in Trial 3, 6 patients (32%) had the following adverse reactions: rash, leukopenia, urticaria, eosinophilia, decreased appetite, and neutropenia. These adverse reactions were similar to those observed in the overall population of 37 patients.

6.2 Postmarketing Experience

The following adverse reactions have been identified during the use of other formulations of benznidazole outside of the United States. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 5: Adverse Reactions Reported in the Published Literature	
Body System	Adverse Reactions
Dermatological	• Maculo-papular cutaneous eruptions • Erythematous plaques • Rash, generalized • Rash, erythematous • Pruritic rash • Blistering eruptions • Peeling skin • Exfoliative dermatitis • Toxic epidermal necrolysis • AGEP • Erythema multiforme • Drug reaction with eosinophilia and systemic symptoms
Neurological (central and peripheral nervous system)	• Paresthesia • Hypoesthesia • Headaches • Insomnia • Convulsions • Inability to concentrate • Amnesia, temporary • Disorientation, temporary
Gastrointestinal	• Epigastric pain • Dry mouth • Ageusia
Hepatobiliary disorders	• Hepatitis • Toxic hepatitis
Skeletal Muscle	• Myalgia • Musculoskeletal pain • Migratory arthritis
General / Constitutional Symptoms	• Fever • Asthenia • Fatigue
Lymphatic	• Generalized edema • Eyelid edema • Edema in the extremities • Lymphadenopathy
Bone Marrow	• Thrombocytopenia • Granulocytopenia • Agranulocytosis
Metabolism / Laboratory	• Elevation of alkaline phosphatase • Elevation of bilirubin

7 DRUG INTERACTIONS

7.1 Disulfiram

Psychotic reactions have been reported in patients who are concurrently taking disulfiram and nitroimidazole agents (structurally related to benznidazole, but not with benznidazole). Benznidazole Tablets should not be given to patients who have taken disulfiram within the last two weeks [see *Contraindications* (4.2)].

7.2 Alcohol and Products Containing Propylene Glycol

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. Although no similar reactions have been reported with benznidazole, discontinue alcoholic beverage or products containing propylene glycol during and for at least 3 days after therapy with Benznidazole Tablets [see *Contraindications* (4.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, Benznidazole Tablets may cause fetal harm when administered to a pregnant woman. Published postmarketing reports on benznidazole use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes. There are risks to the fetus associated with Chagas Disease (see *Clinical Considerations*). In animal reproduction studies, benznidazole administered orally to pregnant rats and rabbits during organogenesis was associated with fetal malformations at doses approximately 1-3 times the MRHD in rats (anasarca, anophthalmia, and/or microphthalmia) and doses approximately 0.3-1.0 times the MRHD in rabbits (ventricular septal defect) (see *Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Published data from case-control and observational studies on chronic Chagas disease during pregnancy are inconsistent in their findings. Some studies showed an increased risk of pregnancy loss, prematurity and neonatal mortality in pregnant women who have chronic Chagas disease while other studies did not demonstrate these findings. Chronic Chagas disease is usually not life-threatening. Since pregnancy findings are inconsistent, treatment of chronic Chagas disease during pregnancy is not recommended due to risk of embryo-fetal toxicity from Benznidazole Tablets.

Acute symptomatic Chagas disease is rare in pregnant women; however, symptoms may be serious or life-threatening. There have been reports of pregnant women with life-threatening symptoms associated with acute Chagas disease who were treated with benznidazole. If a pregnant woman presents with acute symptomatic Chagas disease, the risks versus benefits of treatment with Benznidazole Tablets to the mother and the fetus should be evaluated on a case-by-case basis.

Data

Animal Data

In an embryo-fetal toxicity study in pregnant rats, an oral dose of benznidazole of 150 mg/kg/day during organogenesis (days 6-17 of gestation) was associated with maternal weight loss, reduced fetal weights, and smaller litter sizes. Benznidazole was also associated with a low incidence of fetal malformations including anasarca in one fetus at a dose of 50 mg/kg/day and anasarca and eye abnormalities (anophthalmia and microphthalmia) in 5 fetuses in 5 litters at a high dose of 150 mg/kg/day (approximately equivalent to 1 and 3 times, respectively, the MRHD based on whole body surface area comparisons). The No Observed Adverse Effect Level (NOAEL) dose for maternal toxicity in this study, 50 mg/kg/day, is approximately equal to the MRHD based on body surface area comparisons. The NOAEL dose for fetal toxicity was 15 mg/kg/day which is approximately equivalent to 0.3 times the MRHD based on whole body surface area comparisons.

In an embryo-fetal study in pregnant rabbits, oral (gavage) administration of benznidazole during organogenesis (days 6 to 19 of gestation) at a high dose of 25 mg/kg/day was associated with maternal toxicity including reduced weight gain and food consumption and abortions in 2/20 females. Benznidazole was also associated with a low incidence of fetal abnormalities including ventricular septal defect in 2 fetuses in 2 litters at a dose of 7.5 mg/kg/day and in 1 fetus at a dose of 25 mg/kg/day (approximately equivalent to 0.3 and 1 times respectively the MRHD based on whole body surface area comparisons). The NOAEL values for maternal and fetal toxicity in this study were 7.5 and 2.5 mg/kg/day respectively, which are respectively equivalent to approximately 0.3 and 0.1 times the MRHD based on body surface area comparisons.

In a pre- postnatal study in rats, first generation (F₁) pups born to dams administered 15, 50, and 75 mg/kg/day benznidazole demonstrated normal pre-weaning behavior, physical and functional development, neurological findings, and reproductive parameters. However, cesarean section data for the pregnant first generation (F₁) females in the high-dose group included significantly higher pre-implantation loss and significantly lower mean values for corpora lutea counts, number of implantations, and number of live embryos. Also small testes and/or epididymides were observed in 1/20 and 2/20 first generation males in the mid- and high-dose groups respectively, and two of the affected animals failed to mate or induce pregnancy. However, the mean values for mating performance, fertility index, testes weight, testes and epididymides sperm counts, and epididymal sperm motility and progression were not altered in any of the F₁ males in benznidazole treatment groups. The number of live second generation (F₂) fetuses born to F₁ dams was reduced in the high-dose group. The NOAEL value was considered to be 50 mg/kg/day which is approximately equal to the MRHD based on body surface area comparisons.

8.2 Lactation

Risk Summary

Limited published literature based on breast milk sampling reports that benznidazole is present in human milk at infant doses of 5.5 to 17% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.3-2.79. There are no reports of adverse effects on the breastfed infant and no information on the effects of benznidazole on milk production. Because of the potential for serious adverse reactions, and transmission of Chagas disease, advise patients that breastfeeding is not recommended during treatment with Benznidazole Tablets.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential.

Contraception

Females

Benznidazole Tablets can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations* (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with Benznidazole Tablets and for 5 days after the final dose.

Infertility

Males

Based on findings in rodents, Benznidazole Tablets may impair fertility in males of reproductive potential. It is not known whether effects on fertility are reversible [see *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

The safety and effectiveness of Benznidazole Tablets have been established in pediatric patients 2 to 12 years of age for the treatment of Chagas disease. Use in pediatric patients 2 to 12 years of age was established in two adequate and well-controlled trials in pediatric patients 6 to 12 years old with additional safety and pharmacokinetic data from pediatric patients 2 to 6 years of age. [see *Dosage and Administration* (2.2), *Adverse Reactions* (6.1), *Clinical Studies* (14)].

Safety and effectiveness in pediatric patients below the age of 2 years and above the age of 12 years have not been established.

8.6 Hepatic Impairment

Use of Benznidazole Tablets has not been evaluated in patients with hepatic impairment.

8.7 Renal Impairment

Use of Benznidazole Tablets has not been evaluated in patients with renal impairment.

11 DESCRIPTION

Benznidazole Tablets contain benznidazole, a nitroimidazole antimicrobial. The chemical name of benznidazole is N-benzyl-2-(2-nitro-1H-imidazol-1-yl) acetamide. The empirical formula is $C_{12}H_{12}N_4O_3$ and the molecular weight is 260.246 g/mol. The structural formula is:

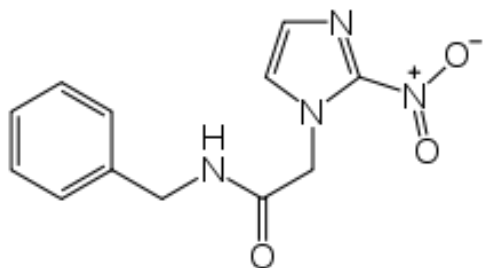


Figure 1: Benznidazole Structure

Benznidazole is a yellowish, practically crystalline powder that is practically insoluble in water, sparingly soluble in acetone and ethanol, and slightly soluble in methanol.

Benznidazole Tablets are white round tablets each containing 12.5 mg or 100 mg of benznidazole, for oral use. The 100 mg white tablets are round and functionally scored twice as a cross on both sides debossed with “E” on one side of each quarter portion. The 12.5 mg white tablets are round and unscored debossed with “E” on one side.

The inactive ingredients are as follows: magnesium stearate, NF; microcrystalline cellulose, NF; monohydrate lactose, NF; pre-gelatinized corn starch, NF; and sodium croscarmellose, NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Benznidazole is a nitroimidazole antimicrobial drug [see *Microbiology* (12.4)].

12.2 Pharmacodynamics

The pharmacodynamics of benznidazole is unknown.

12.3 Pharmacokinetics

Absorption

The absorption of benznidazole from three different 100 mg benznidazole preparations was comparable when administered as a single dose under fasting conditions in adult healthy volunteers (Table 6).

Table 6: Summary of Benznidazole Pharmacokinetic (PK) Parameters Following a Single Oral Dose of 100 mg Benznidazole Administered Under Fasting Conditions in Adult Healthy Volunteers

	Preparations for 100 mg Benznidazole Oral Dose		
	One Benznidazole 100 mg Tablets Taken Whole	Slurry prepared with one Benznidazole 100 mg Tablet	Slurry prepared with eight Benznidazole 12.5 mg Tablets
Parameter	Mean (SD)	Mean (SD)	Mean (SD)
C _{max} (mg/L)	2.4 (0.5)	2.4 (0.4)	2.4 (0.4)
T _{max} ^a (h)	2 (1 – 4)	2 (0.5 – 4)	2 (1 – 4.5)
AUC (mg*h/L)	43.5 (9.0)	41.8 (9.6)	44.1 (11.8)

^aT_{max} is presented as median (range)

Effect of Food

Benznidazole C_{max} and AUC were not affected by the administration of Benznidazole 100 mg tablet with a high-fat, high-caloric meal (approximately 1034 total kcal, 67 kcal from fat, 42 kcal from carbohydrates, 59 kcal from protein) compared with fasted conditions in adult healthy volunteers. Serum concentrations of benznidazole reached peak levels at 3.2 hours (1-10 hours) after administration of Benznidazole Tablets 100 mg tablet after a high-fat, high-caloric meal, and at 2.0 hours (0.5-4 hours) in fasted conditions [see *Dosage and Administration* (2.1)].

Distribution

Protein binding is reported to be approximately 44 to 60 %.

Elimination

The elimination half-life of benznidazole is approximately 13 hours in healthy volunteers following single dose.

Metabolism

Benznidazole metabolism pathway is unknown.

Excretion

Benznidazole and unknown metabolites are reported to be excreted in the urine and feces.

Specific Populations

The effect of sex, race, renal impairment, or hepatic impairment on the pharmacokinetics of benznidazole is unknown.

Drug Interaction Studies

In vitro studies showed that benznidazole is a P-gp substrate and does not notably induce Cytochrome P450 enzymes 1A2, 2B6, and 3A4 at concentrations up to 100 uM.

12.4 Microbiology

Mechanism of Action

Benznidazole inhibits the synthesis of DNA, RNA, and proteins within the *T. cruzi* parasite. Studies suggest that benznidazole is reduced by a Type I nitroreductase (NTR) enzyme of *T. cruzi* producing a series of short-lived intermediates that may promote damage to several macromolecules including DNA. In mammalian cells, however, benznidazole is metabolized by reduction of the nitro group to an amino group by a Type II NTR enzyme. The precise mechanism of action is not known.

Antimicrobial Activity

Benznidazole is active against all three stages, trypomastigotes, amastigotes, and epimastigotes, of *T. cruzi*. However, the sensitivity of *T. cruzi* strains to benznidazole, from different geographic regions, may vary.

Resistance

Studies *in vitro* and in mice infected with *T. cruzi* suggest a potential for development of resistance to benznidazole.

The mechanisms of drug resistance appear to be multifactorial. These mechanisms include decreased activity due to a mutation in the nitroreductase (*TcNTR*) gene. Other mechanisms include higher efflux activity due to over expression of *TcPGP₁* and *TcPGP₂* genes that encode p-glycoprotein as well as *TcABCG1* genes that encode ATP-binding cassette transporters. Also, some studies reported overexpression of other genes *TcFeSOD-A* and *TcCyP19* that encode superoxide dismutase and cyclophilin, respectively, which have diverse biological function and may help parasite survival. However, the clinical relevance of these findings is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Long-term carcinogenicity studies for benznidazole have not been performed.

Nitroimidazoles, which have similar chemical structures to benznidazole have been reported to be carcinogenic in mice and rats.

Genetic Toxicity

Genotoxicity of benznidazole has been demonstrated in vitro in several bacterial species and mammalian cell systems and in vivo in mammals.

Benznidazole was mutagenic in several strains of *S. typhimurium* (TA 100, 102 1535, 1537, 1538, 97, 98 99 53 and UTH8414), *E.coli*, and *K. pneumoniae*.

Benznidazole was genotoxic in several in vitro mammalian cell assays including a chromosome aberration assay in human lymphocytes and in sister chromatid exchange assays in human lymphocytes and in Human Hep G2 cells

In vivo, benznidazole was shown to be positive for genotoxicity in a mouse bone marrow micronucleus assay, in mouse and human red blood cell micronucleus assays, in a mouse abnormal sperm head assay and in a human peripheral blood lymphocyte assay. However in other micronucleus studies in mice and rats, oral doses of benznidazole did not cause a significant increase in the frequency of chromosomal aberrations in bone marrow cells or micronuclei in peripheral blood cells.

Impairment of Fertility

In a 6-month, chronic repeated-dosing study with Wistar rats, benznidazole was shown to produce dose-dependent testicular and epididymal atrophy at a dose of 30 mg/kg/day (approximately equivalent to 0.6 times the MRHD based on whole body surface area comparisons). Aspermia was also evident in affected rats, but fertility was not assessed in this study. The NOAEL value in this study was considered to be 10 mg/kg/day (5 mg/kg twice daily) in males which is approximately 0.2-times the MRHD based on body surface area comparison. In other literature reports, benznidazole has been shown to cause testicular atrophy and inhibit spermatogenesis in pubertal and adult rats and mice⁵⁻⁷.

In a female fertility study, oral (gavage) administration of benznidazole to female Wistar rats twice daily for a 2-week pre-mating period, during mating, and through day 7 of gestation was associated with transient lower body weight gain and food consumption. There was no benznidazole-related effect on mating performance or fertility and no adverse macroscopic or reproductive organ weight changes. However, benznidazole reproductive performance was associated with a higher post-implantation loss with lower live litter size at a dose of 150 mg/kg/day (equivalent to approximately 3 times the MRHD based on whole body surface area comparisons). The NOAEL value for this study was considered to be 50 mg/kg/day which is approximately equivalent to the MRHD based on whole body surface area comparison.

13.2 Animal Toxicology and/or Pharmacology

Single oral-dose toxicity studies in rats have established that benznidazole causes ultrastructural changes in the adrenal cortex, colon, esophagus, ovaries, and testis^{5, 8-11}. In these tissues, the changes were associated with the presence of nitro reductase activity, the production of reactive metabolites, and/or covalent binding of metabolites.

Neurotoxicity including brain axonal degeneration and Purkinje cell degeneration was observed with repeated-oral dosing in dogs without adverse changes in peripheral nerves¹²⁻¹⁴. Neurological signs included: apathy, hypertonia, hyperreflexia, ataxia, loss of balance, oscillatory movements of the trunk and head, strong contractions of the back and leg muscles, opisthotonus and nystagmus. Neurotoxicity was not observed in other test species, including mouse, rat, guinea pig, and rabbit.

14 CLINICAL STUDIES

The safety and effectiveness of benznidazole for the treatment of Chagas disease in patients 6 to 12 years of age was established in two adequate and well-controlled trials (Trial 1 and Trial 2) as described below.

Trial 1 was a randomized, double-blind, placebo-controlled trial in children 6 to 12 years of age with chronic indeterminate Chagas disease conducted in Argentina. The chronic indeterminate form of Chagas disease includes patients with serologic evidence of *T. cruzi* infection without symptoms of cardiac or gastrointestinal disease. A total of 106 patients were randomized to receive either benznidazole (5 mg/kg/day for 60 days) or placebo and followed for 4 years. Patients with at least two positive conventional serologic tests for antibodies to *T. cruzi* were included in the study. 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.

Trial 2 was a randomized, double-blind, placebo-controlled trial in pediatric patients 7 to 12 years of age with chronic indeterminate Chagas disease conducted in Brazil. A total of 129 patients were randomized to receive either benznidazole (7.5 mg/kg/day for 60 days) or placebo and followed for 3 years. Patients with three positive conventional serologic tests for antibodies to *T. cruzi* were included in the study. The conventional serologic tests include IHA, IFA, and/or ELISA and were based on the detection of antibodies against *T. cruzi* parasites.

Both trials measured antibodies by conventional and nonconventional assays. The nonconventional assays include F29-ELISA and AT- chemiluminescence-ELISA that are based on detection of anti-*T. cruzi* IgG antibodies against the recombinant antigens, F29 and AT from the flagella of *T. cruzi* parasites. 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.

Table 7. Nonconventional ELISA^a Serologic Status-at End-of-Follow-Up (mITT population^b)			
	Benznidazole	Placebo	Difference (95% CI)^c
Trial 1	N=40	N=37	
Seronegative	24 (60.0)	5 (13.5)	46.5 (24.5, 64.4)
Seropositive	15	29	
Missing	1	3	
Trial 2	N=64	N=65	
Seronegative	35 (54.7)	3 (4.6)	50.1 (35.8, 63.4)
Seropositive	23	51	
Missing	6	11	
^a 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 <i>T. cruzi</i> parasites. ^b Modified intent to treat (mITT) population includes subjects who are positive for the assay at baseline; ^c Exact confidence intervals presented.			

In Trial 1 using conventional ELISA, 4 of 53 (7.5%) benznidazole subjects and 2 of 50 (4.0%) placebo subjects seroconverted to negative by the end of follow-up (difference 3.5, 95% CI (-7.0, 14.9)). In Trial 2 using conventional ELISA, 4 of 64 (6.3%) of benznidazole subjects and 0 of 65 placebo subjects seroconverted to negative by the end of follow-up (difference 6.3, 95% CI (0.3, 15.2)).

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Benznidazole Tablets (12.5 mg or 100 mg) are supplied as follows:

- 100 mg white tablets, round and functionally scored twice as a cross on both sides. Each tablet is about 10 mm in diameter debossed with “E” on one side of each quarter portion.
- 12.5 mg white tablets, round and unscored. Each tablet is about 5 mm in diameter debossed with “E” on one side.

Benznidazole Tablets 100 mg are available in bottles of 100 tablets (NDC 0642-7464-10).

Benznidazole Tablets 12.5 mg are available in bottles of 100 tablets (NDC 0642-7463-12).

16.2 Storage and Handling

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Keep bottle tightly closed and protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that exposure to Benznidazole Tablets during pregnancy can result in fetal harm.

Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.2) and *Use in Specific Populations* (8.1)].

Advise females of reproductive potential to use effective contraception while taking Benznidazole Tablets and for 5 days after the last dose [see *Use in Specific Populations* (8.3)].

Lactation

Advise women not to breastfeed during treatment with Benznidazole Tablets [see *Use in Specific Populations* (8.2)].

Infertility

Advise males of reproductive potential that Benznidazole Tablets may impair fertility [see *Use in Specific Populations* (8.3) and *Nonclinical Toxicology* (13.1)].

Important Administration Instructions

Advise patients and parents/caregivers of pediatric patients taking Benznidazole Tablets that:

- Benznidazole Tablets 100 mg 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 Tablets 12.5 mg and 100 mg (whole or split) can be made into a slurry in a specified volume of water for the pediatric population [see *Dosage and Administration* (2.3)].

Hypersensitivity Skin Reactions

Advise patients that serious skin reactions can occur with Benznidazole Tablets. In case of skin reactions, presenting with additional symptoms of systemic involvement such as lymphadenopathy, fever and/or purpura, discontinuation of treatment is necessary.

Central and Peripheral Nervous System Effects

Advise patients that treatment can potentially cause paresthesia or symptoms of peripheral neuropathy. In cases where neurological symptoms occur, immediate discontinuation of treatment is recommended.

Hematological Manifestations of Bone Marrow Depression

Advise patients that there have been hematological manifestations of bone marrow depression, such as anemia and leukopenia, which are reversible, and normalized after treatment discontinuation.

Interaction with Alcohol

Advise patients to discontinue consumption of alcoholic beverages or products containing propylene glycol while taking Benznidazole Tablets and for at least three days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur.

Manufactured for Chemo Research, S.L.
Madrid, Spain

Manufactured by Laboratorios Liconsa S.A.
Guadalajara, Spain

Distributed by:



Exeltis USA, Inc.
Florham Park, NJ 07932

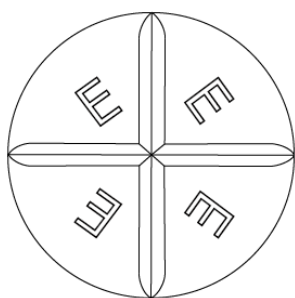
INSTRUCTIONS FOR USE
BENZNIDAZOLE
tablets, for oral use

Read this Instructions for Use before you start taking BENZNIDAZOLE and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

Note:

- Your doctor may need to change your dose of BENZNIDAZOLE during treatment as needed.
- BENZNIDAZOLE 100 mg tablets can be taken whole or broken at scored lines.
- BENZNIDAZOLE 100 mg tablets are marked with scored lines and may be broken at these scored lines to provide the following doses: 75 mg, 50 mg and 25 mg.

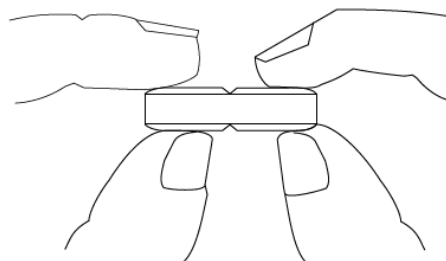
100 mg treatment (take the whole tablet)



full tablet top view



full tablet side view



full tablet side view
(with thumb and index finger)

How to break your BENZNIDAZOLE 100 mg tablet:

- Hold the tablet between your thumbs and index fingers close to the scored line (**See Figure 1**).
- Apply enough pressure to break the tablet at the scored line (**See Figure 2**).
- Only use a tablet that has been broken at the scored line (**See Figure 3**).
- **Do not** break the BENZNIDAZOLE 100 mg tablet in any other way.

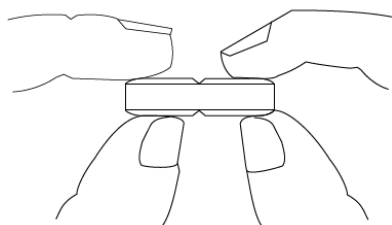


Figure 1

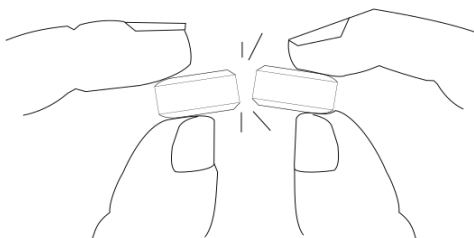


Figure 2

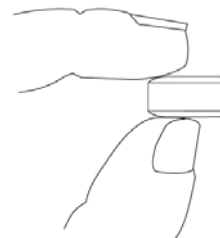
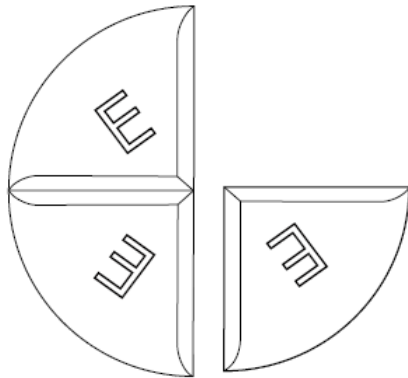


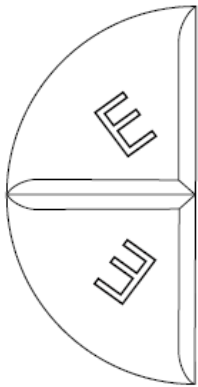
Figure 3

75 mg treatment (take one-half of the tablet and one-fourth of the tablet)

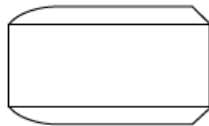


one-half tablet top view and
one-fourth tablet top view

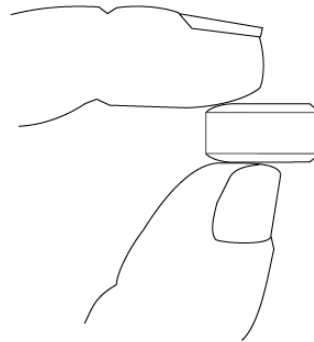
50 mg treatment (take one-half of the tablet)



one half-tablet top view

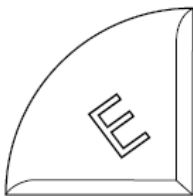


one half-tablet
side view



one half-tablet side view
(with thumb and index finger)

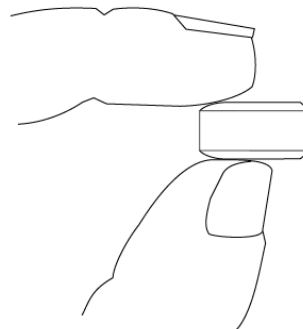
25 mg treatment (take one-fourth of the tablet)



one-fourth tablet top
view



one-fourth tablet
side view



one-fourth tablet side view
(with thumb and index finger)

How should I store BENZNIDAZOLE?

- Store BENZNIDAZOLE at room temperature 20° to 25°C (68°to 77°F).
- Keep BENZNIDAZOLE in the bottle that it comes in and keep the bottle tightly closed.
- Keep BENZNIDAZOLE away from moisture.

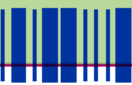
Keep BENZNIDAZOLE and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by: Laboratorios Liconsa S.A., Guadalajara, Spain

Issued: August 2017

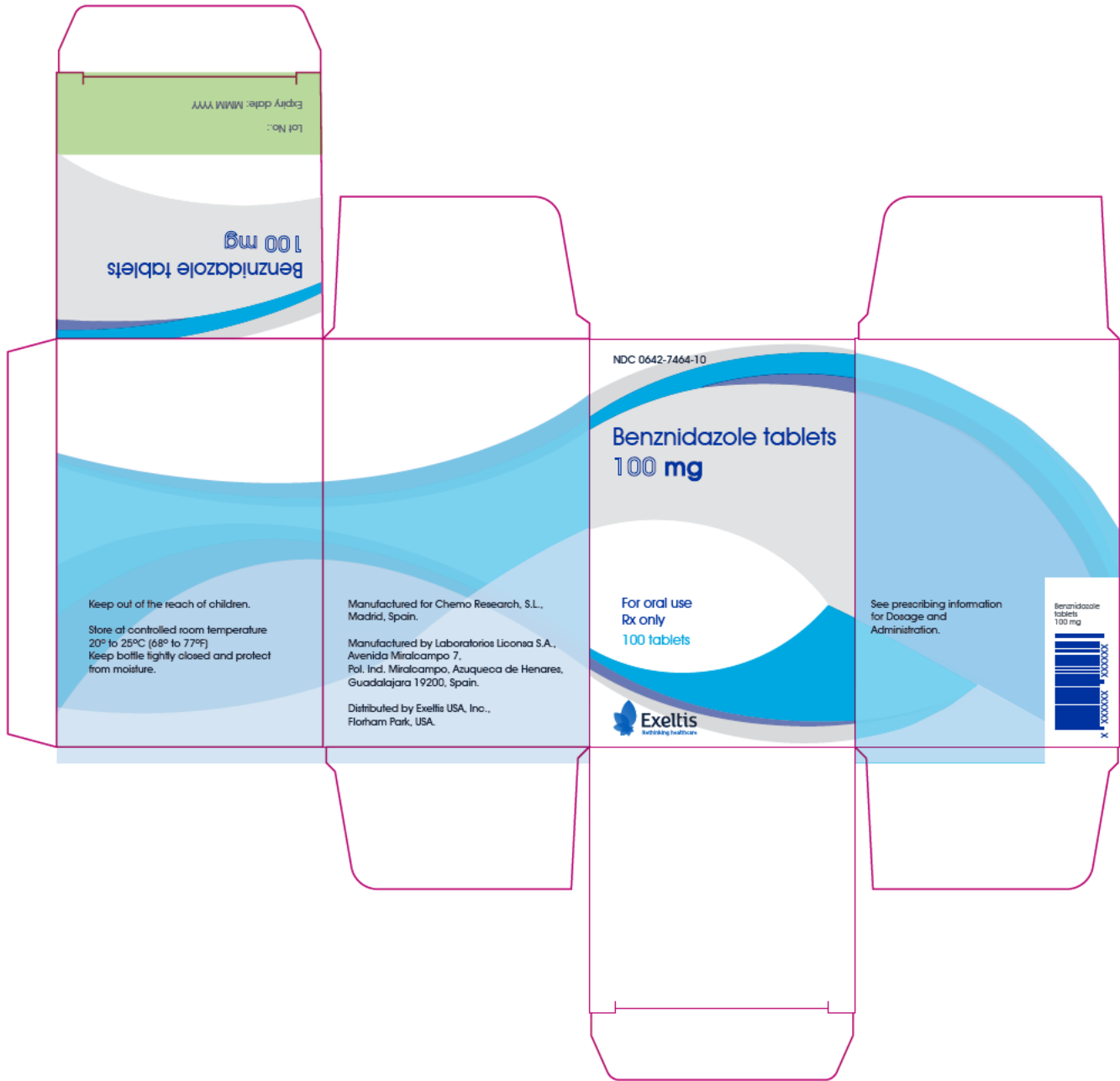
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	For oral use Rx only 100 tablets		

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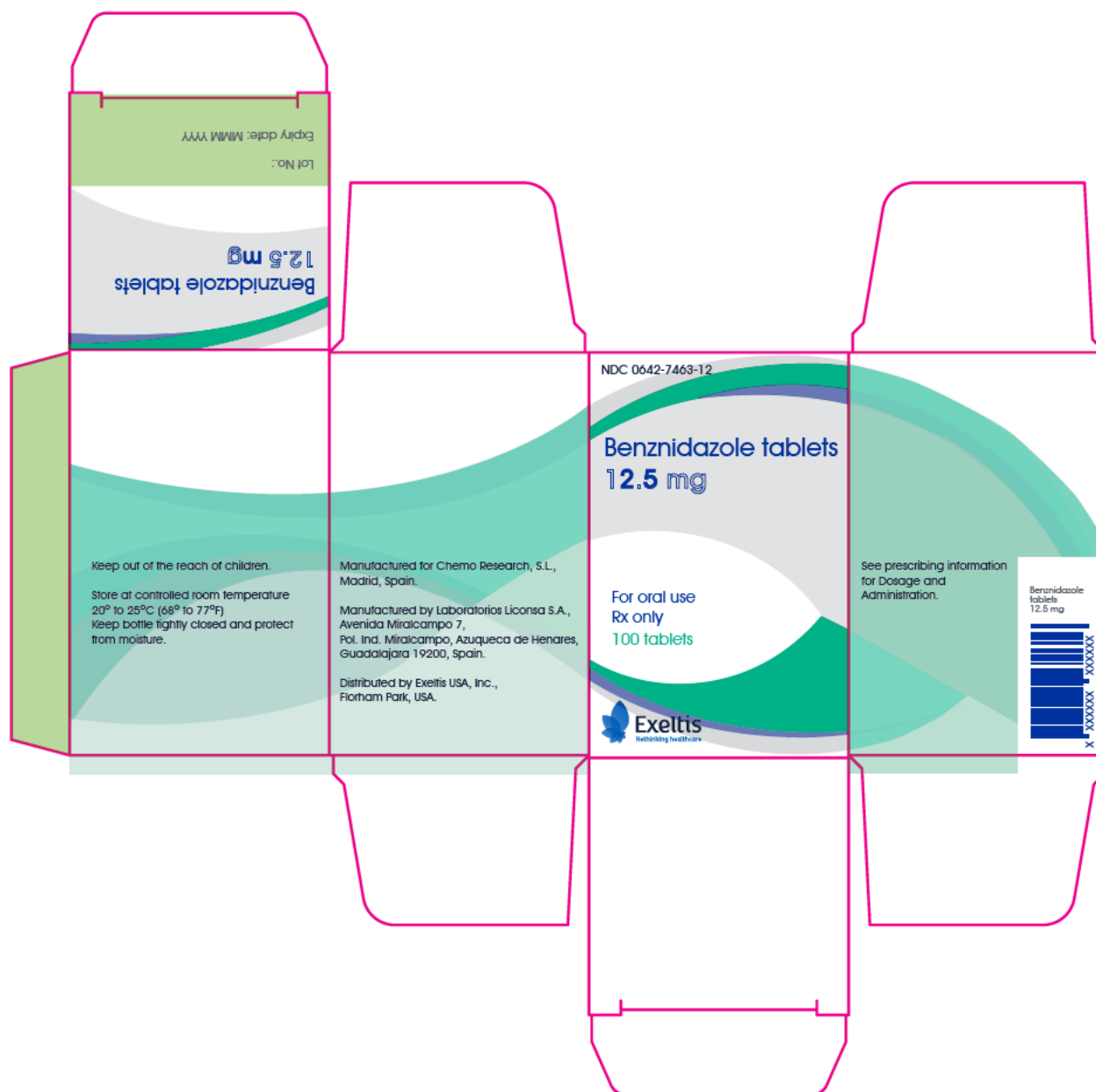
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