

LAFEPE

Benznidazol 12,5 mg

Paediatric dosage form
of benznidazole

**NOW REGISTERED
IN BRAZIL**

Tangible Progress in Treating
Young Children with Chagas Disease



An easily dispersible,
simpler to administer,
safer, age-adapted
dosage for treatment
of **Chagas disease**
in patients up to
two years of age

PAEDIATRIC DOSAGE FORM OF BENZNIDAZOLE

LAFEPE BENZNIDAZOL 12,5 MG

IN BRIEF

An Improved Treatment Option

- Age-adapted, easy-to-use, affordable, and non-patented tablet, for the treatment of Chagas disease in infants and young children under 2 years of age (20 kg body weight).
- Contributes to improved dosing accuracy, safety, and adherence to treatment
- Granted registration by Brazil's National Health Surveillance Agency (ANVISA), with further endemic countries targeted for obtaining registration.

Main Advantages of the Paediatric Dosage Form of Benznidazole

- A single tablet allows coverage of a wide age range, up to 2 years old or body weight 20 kg
- Child-adapted dose of 12.5 mg per tablet
- Easily dispersible tablet to facilitate oral administration
- No need for tablet fractionation (except for low-birth weight babies <2.5 kg: half a tablet)
- Simple and reliable administration that does not require complex preparation and can therefore be administered at home, even during the long duration of treatment (twice daily for 60 days)

A Collaborative Partnership




- Result of a three-year collaborative partnership, starting in 2008, between DNDi and the Pernambuco State Pharmaceutical Laboratory (Laboratório Farmacêutico do Estado de Pernambuco; LAFEPE) of Brazil. LAFEPE is the second largest public laboratory in Brazil and the only producer of benznidazole in the world.

PRODUCT PROFILE

Key Drug Characteristics

- Paediatric-adapted dose (12.5 mg)
- Easily dispersible (disintegrated) single tablet

Dosing

Paediatric Dosage Form of Benznidazole Table of Doses	
Weight (kg)	Recommended dosage (5-10 mg/kg)
2.5 to < 5 kg	 Administer one tablet, 12.5 mg, twice daily for 60 days (total dose of 25 mg per day)
5 to < 10 kg	 Administer two tablets, 12.5 mg (25 mg), twice daily for 60 days (total dose of 50 mg per day)
10 to < 15 kg	 Administer three tablets, 12.5 mg (37.5 mg), twice daily for 60 days (total dose of 75 mg per day)

Clinical Development

In an expert consultation meeting held by DNDi in October 2006, consensus was reached for the development of a dispersible tablet formulation of benznidazole for paediatric patients.

To determine the appropriate paediatric tablet strength, the target paediatric therapeutic dose range for benznidazole was defined through a review of available paediatric dose recommendations from the WHO guidelines, national control programmes, and medical literature (Table 1).

The doses below were chosen based on efficacy/safety data in the observed age groups

Table 1: Benznidazole dose recommendations for Chagas infections	
Source	Age group
WHO – Chagas Control Technical Expert Group	Congenital infections: 5-10 mg/kg/d
WHO – model prescribing information	Children ≥12 years old: 5-7 mg/kg/d, children <12 years old: 10 mg/kg/d (no range provided)
Hoffman-La Roche package insert	Children ≥12 years old: 5-7 mg/kg/d, children <12 years old 10 mg/kg/d (no range provided)
Roche, Radanil® insert package	5-8 mg/kg/d bid PO for 60 d
Roche, Rochagan® insert package	5-7 mg/kg/d bid PO for 30-60 d Children <12 years old, especially with acute disease: up to 10 mg/kg/d for the initial 10-20 days of treatment
Brazilian Ministry of Health, Secretaria de Vigilância em Saúde	Adults: 5 mg/kg/d, children: 5-10 mg/kg/d 2 or 3 times/day PO for 60 d
Brazilian Ministry of Health, Secretaria de Vigilância em Saúde	Acute phase, congenital infection, immunocompromised patients and transplants: 8 mg/kg/d bid PO for 60 d
Consejo de Enfermedad de Chagas Mazza de la Sociedad Argentina de Cardiología	5 mg/kg/day for 30-60 d

Considering the target age group of infants under one year of age, for which dose accuracy represents the main challenge and an ideal regimen of a single tablet/intake (maximum of 2 tablets/day), with a single split, the 12.5 mg strength was the most appropriate, allowing coverage of a wide range of infant age and weight.

The target paediatric patient population was defined through a review of paediatric treatment practices from endemic regions in Latin America. Anonymized data from different treatment centres in Latin America were compiled to confirm the weight and treatment dose range and to identify paediatric patient group(s) that pose a particular challenge to dosage accuracy.

Target dose recommendations were subsequently compared against the therapeutic dose range used in practice by clinical experts to confirm the therapeutic dose range that was to be used for the new paediatric dosage form of benznidazole across age and weight ranges of interest. In this assessment, it became evident that a significant proportion of children currently treated are being over-dosed and this proportion is greater in patients under 1 year of age. These results supported the conclusions of the highest medical need for a paediatric formulation among the infant population.

Clinical experts with programmatic experience subsequently discussed the optimal type of drug formulation needed by Chagas control programmes. Options for liquid solutions and dispersible tablets, need and acceptability of the use of tablet fractions, and other characteristics were discussed and used in the decision-making process to determine formulation type. While liquid/syrup formulations allow more accurate dosing and do not need dilution before intake, the production of a tablet is easier and is advantageous in terms of packaging, storage, and distribution costs. Dispersible tablets have advantages of both liquids and standard tablets. They allow the use of a minimal amount of non-toxic excipients, can be easily produced, are stable, low cost, and allow for a convenient, easy, and reliable administration in a treatment course of prolonged duration, administered at home.

SCIENTIFIC DATA

Table 2 summarizes the major efficacy trials of benznidazole in congenital Chagas infection.

Table 2. Summary of efficacy data from major clinical trials in children with congenital infection

Reference	Age (years)	Benznidazole			Nifurtimox			Design*	Follow-up (months) Lost in FU (%)	Efficacy measures†	
		n	Dose (mg/kg/d)	Time (days)	n	Dose (mg/kg/d)	Time (days)			Serologic test (% neg)	Parasitological test (% pos)
Russomando 1998	Congenital <2	6	7-10	60	-	-	-	nC nR nB	24m } 0%	(EIA, IFI) } 100%	(Hc,MH,PCR) } 0%
Blanco 2000	Congenital <1	3 -	5 -	30 -	- 29	- 10	- 60	C nR nB	24m } 6%	(EIA,HAI,IFI) } 94%	(MH) } 0%
Schijman 2003	Congenital <2	16 {	5-8 -	60 -	-	- 10-15	- 60	C nR nB	36m } 0%	(EIA,HAI) } 87%	(MH,PCR) } 0%
Chippaux (IRD) 2008 -2009	Congenital <1 (Control=non infected)	68 59 52	NT 5 7,5	- 60 30	-	-	-	C R B	10m 0% 2% 4%	(EIA,IC) 100% 91% 90%	(MH a 2m) 0% 0% 0%

Legend:

* Design: C (controlled: control or comparative group), nC (not controlled); R (randomized), nR (not randomized); B (blinded), nB (not blinded)

† Efficacy endpoints: IHA (Indirect Hemagglutination Assay), IFA (Immunofluorescence Assay), EIA (Enzyme Immune Assay), IC (Immunochromatography), MH (Microhematocrit), HC (Hemoculture), PCR (Polymerase Chain Reaction),

Source: IRD 2009

In the recommended doses, benznidazole is well tolerated. However, adverse reactions are frequent, often occurring in 25 to 30% of patients. In general, the tolerability is better in children than in adults. Clinical studies indicate differences in the frequency of occurrence of adverse reactions among children and adults.

In a study conducted in Bolivia in 111 newborns diagnosed with congenital infection at birth and treated with benznidazole (59 with the treatment regimen of 2.5 mg / kg twice daily for 60 days and 52 with regimen of 7.5 mg / kg once a day for 30 days), there were no reported adverse reactions (Chippaux 2009). Similar findings are reported in the study of Russomando et al. (1998) who did not identify any adverse reaction or toxicity monitoring of the six children treated with benznidazole (7 mg / kg per day, taken twice daily for 60 days).

In a cohort study with 95 children aged between 1 and 14, among which 64 treated with benznidazole, 5mg/kg/day, split in 2 doses daily for 30 days, Streiger et al. (2004) observed good treatment tolerability. There was discontinuation in two patients (2 / 53 or 3.8% of children who had at least a control post-treatment) due to benznidazole intolerance. In the group treated with benznidazole, the authors identified adverse events, such as vomiting, generalized erythema with edema and pruritus without specifying the degree of severity or frequency of occurrence.

Another recently published prospective cohort study, conducted between 2003 and 2007 in the Pediatric Hospital 'Ricardo Gutiérrez' in Buenos Aires (Argentina), Altcheh et al. described adverse events in 107 children aged between 10 days and 19 years (mean age 6.9 years), diagnosed with asymptomatic infection with *T. cruzi* treated with benznidazole, 5 mg/kg/day in two or three daily doses for 60 days, and followed up for of 3 years. A total of 62 adverse events related to treatment were observed in 44 children (41.1% of patients), mostly mild (80.6%) and moderate (16%). Only two adverse events (3.2%) were considered severe (generalized rash). In this cohort, 7 patients (6.5%) withdrew from treatment due to adverse events (1 gastrointestinal and 6 dermatological), 6 of whom were older than 7 years. Adverse events resulted in temporary interruption of treatment in 7 children (4 due to the appearance of rash, 2 with gastrointestinal discomfort, and 1 with headache), but all resumed and completed the treatment without any further interruption.

DISEASE BACKGROUND

Chagas disease (American trypanosomiasis) is a life-threatening, parasitic neglected tropical disease (NTD) endemic throughout Latin America. The people most affected by Chagas are often very poor, live in inadequate housing conditions, and/or have little access to healthcare.

Chagas Disease - AMERICAN TRYPANOSOMIASIS

21 endemic countries and worldwide impact due to global migration

WHAT IS THE ANNUAL IMPACT OF CHAGAS DISEASE?

100 million people at risk⁽¹⁾
Approximately 8 million cases⁽²⁾
12,000 deaths⁽³⁾

HOW IS CHAGAS DISEASE TRANSMITTED?

Caused by the kinetoplastid protozoan parasite *Trypanosoma cruzi*, Chagas disease is primarily transmitted by large, bloodsucking reduviid insects widely known as 'the kissing bugs' in endemic countries. Other routes of transmission include blood transfusion, organ transplantation, as well as congenital and oral routes through ingestion of contaminated food or beverage.

WHAT ARE THE SYMPTOMS?

The disease has two clinical phases:

- **Acute phase** (fatal for 2-8% of children⁽⁴⁾), often asymptomatic or unrecognized due to its non-specific symptoms, such as fever, malaise, generalized lymphadenopathy, and hepatosplenomegaly, which spontaneously resolve in 4-6 weeks.
- **Chronic phase** can be divided into two stages:
 - The chronic asymptomatic 'indeterminate' stage, during which patients can transmit the parasite to others, especially through vertical transmission, while showing no signs of the disease, and which may last decades after infection.
 - The chronic symptomatic stage, which develops in up to 30% of infected patients and most often involves the heart or gastrointestinal tract. Chagas disease is the leading cause of infectious heart disease (cardiomyopathy) in the region.

WHERE DOES CHAGAS DISEASE OCCUR?

Endemic in 21 countries across Latin America, but through population migration the disease has spread to Australia, North America, Japan, and Europe.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments have the highest efficacy in acute infection with limited evidence for efficacy in the chronic stages.

- **Benznidazole, nifurtimox** to treat acute and chronic phases:
 - Long treatment period (30-60 days)
 - Dose-dependent toxicity
 - High rate of patient non-compliance
 - No paediatric strengths

There is no treatment for chronic disease with target organ involvement.

WHAT ARE THE PATIENT TREATMENT NEEDS?

- A paediatric strength of benznidazole that is affordable and age-adapted.
- A new oral drug that is safe, efficacious, and adapted to the field, and ideally would work in both stages of the disease.



WHAT IS DND/ DOING TO ADDRESS UNMET TREATMENT NEEDS?

Short term: better use of existing treatments through the development of paediatric-strength benznidazole

Medium term:

- 1) Azoles:** clinical assessment of known compounds already in development against fungal infections. Specifically, clinical studies of E1224, in collaboration with Eisai are being conducted.
- 2) Development of new treatments** through combination therapy - in exploratory pre-clinical stage.

Long term: New drugs developed from promising compounds identified in discovery activities (such as GSK library of pyridones and cysteine protease inhibitors) and progressed through Chagas Lead Optimization Consortium.

By 2014, DNDi aims to deliver from its Chagas-specific portfolio

- 1 new paediatric-strength benznidazole
- 1 new drug registered for chronic Chagas disease

(1) PAHO, *Estimación cuantitativa de la enfermedad de Chagas en las Américas*, 2006 (2) PAHO 2010, <http://new.paho.org/blogs/cd50/?p=1527&lang=en>
(3) *Ibid.* (4) Parada H, Carrasco HA, Anez N, Fuenmayor C, Inglessis I. Cardiac involvement is a constant finding in acute Chagas disease: a clinical, parasitological and histopathological study. *Int J Cardiol.* 1997; 60: 49-54.

DEVELOPMENT HISTORY OF THE PAEDIATRIC DOSAGE FORM OF BENZNIDAZOLE

Over the past 20 years, successful vector control programmes for Chagas disease in the Southern Cone countries of Latin America (Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay) have reduced vector-borne transmission of the *Trypanosoma cruzi* parasite and changed the epidemiology of the disease. Although hard-to-reach foci of transmission remain, linked to poverty, lack of access to health care, and varying vector habitats, non-vector-borne infections such as oral, blood transfusion, and congenital (vertical; pregnant mother to newborn infant) transmission have received increased attention.

In areas of successful domiciliary and peri-domiciliary vector control, the majority of new cases are children born with Chagas from infected mothers. With reported regional seroprevalence rates in asymptomatic women of reproductive age of 5-40% and vertical transmission rates of up to 12%¹, congenital infection remains a public health issue not only in Chagas disease-endemic countries but worldwide, due to migration flows from Latin America.

Treatment of Chagas disease has always focused on paediatric patient populations. Initially, treatment was recommended only for acute and congenital cases (including newborns diagnosed at birth), with favourable parasitological response of 60-85% of patients in the acute phase² and more than 90% of congenitally infected infants treated in the first year of life.^{3,4,5}

More recently, treatment recommendations for Chagas disease have extended to children with the early chronic indeterminate form of disease up to 12-14 years old, based on evidence indicating efficacy of ~60%, as assessed by seroconversion 3 to 4 years post-treatment.^{6,7} In 2002, the second report of the

¹ Carlier Y, Torrico F. Congenital infection with *Trypanosoma cruzi*: from mechanisms of transmission to strategies for diagnosis and control. *Rev Soc Bras Med Trop.* 2003 Nov-Dec;36(6):767-71.

² Kirchoff LV. Changing Epidemiology and Approaches to Therapy for Chagas Disease. *Curr Infect Dis Rep.* 2003 Feb;5(1):59-65.

³ Schijman AG, Altcheh J, Burgos JM, Biancardi M, Bisio M, Levin MJ, Freilij H. Aetiological treatment of congenital Chagas' disease diagnosed and monitored by the polymerase chain reaction. *J Antimicrob Chemother.* (2003) 52, 441-449

⁴ Rodrigues Coura J, deCastro SL. A critical review on Chagas disease chemotherapy. *Mem Inst OswaldoCruz.* 2002;97(1):3-24

⁵ Altcheh J, Biancardi M, Lapena A, Ballering G, Freilij H. Congenital Chagas disease: experience in the Hospital de Niños, Ricardo Gutierrez, Buenos Aires, Argentina [in Spanish]. *Rev Soc Bras Med Trop.* 2005; 38(suppl 2):41-45.

⁶ Sosa-Estani S, Segura EL, Ruiz AM, Velazquez E, Porcel BM, Yampotis C 1998. Chemotherapy with benznidazole in children in undetermined phase of Chagas disease. *Am J Trop Med Hyg* 59: 526-529.

WHO Expert Committee on Etiological Treatment in the Chronic Phase recommended that all individuals with positive serology for Chagas disease be treated with specific drugs.

Despite these treatment recommendations for children, adequate available treatment options for them have been lacking. Benznidazole, developed over 30 years ago and the main drug of choice for treating Chagas, was only available in an adult tablet strength of 100 mg (Radanil®, Rochagan®, LAFEPE Benznidazol®). Most treatments for infants and young children were based on the use of tablet fractions, macerated tablets and other extemporaneous formulations, which introduce variation and imprecision in drug dosing.⁸

Policymakers and clinicians have long stressed the urgent need for a paediatric drug formulation in Chagas control. Several international meetings (most notably the 2005 Scientific Working Group for Chagas Disease of the Special Programme for Research and Training in Tropical Diseases (TDR) and the 2007 TDR Working Group on Chagas Disease) have highlighted the unmet medical need for new paediatric formulations for Chagas disease.

Therefore, in July 2008, DNDi and Brazil's Pernambuco State Pharmaceutical Laboratory (Laboratório Farmacêutico do Estado de Pernambuco; LAFEPE) joined efforts and signed an agreement to develop a paediatric dosage form of benznidazole for the treatment of children with Chagas disease.

⁷ de Andrade ALS, Zicker F, de Oliveira RM, Almeida Silva S, Luquetti A, Travassos LR, Almeida IC, de Andrade SS, de Andrade JG, Martelli CM 1996. Randomised trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection. *Lancet* 348: 1407-1413

⁸ van Santen E, Barends DM, Frijlink HW. Breaking of scored tablets: a review. *Eur J Pharm Biopharm.* 2002 Mar;53(2):139-45.

IMPLEMENTATION AND ACCESS

Production

The paediatric dosage form of benznidazole will be manufactured by LAFEPE.

LAFEPE will make paediatric benznidazole available at cost to all public health institutions.

Registration

The paediatric dosage form of benznidazole was officially granted registration in late 2011 by the National Health Surveillance Agency (ANVISA) of Brazil. DNDi is working with LAFEPE to register the drug in other Chagas disease-endemic countries, including Argentina, Bolivia, Colombia, and Paraguay.

Additional Tools to Facilitate Implementation and Access

- Demand Forecast: a guide to help national Chagas control programmes and others gauge demand for benznidazole.
- Procurement Guide: step-by-step instructions for countries to order the paediatric dosage form of benznidazole from LAFEPE.
- Tool Box: education, communication, and training materials to help in implementation of the paediatric dosage form of benznidazole in the field. The Tool Box contains key information for health professionals, patients, and mothers and caregivers to promote correct and safe administration of the drug, including treatment guidelines, leaflets, posters, photographs, a flip chart, and a dosing table.

DONORS AND PARTNERS

Donors

Funding support for the drug development project and for the implementation and access tools came from the Department for International Development (DFID), UK; the Dutch Ministry of Foreign Affairs (DGIS), The Netherlands; Médecins Sans Frontières/Doctors without Borders (International, Italy, Brazil); the Spanish Agency for International Development Cooperation (AECID), Spain; the Swiss Agency for Development and Cooperation (SDC), Switzerland; United States Agency for International Development, via the 4th Sector Health Project implemented by Abt Associates, Inc; and Swiss private foundations and individual donors.

Partners

LAFEPE: The industrial partner in this project is LAFEPE (Pernambuco State Pharmaceutical Laboratory; Laboratório Farmacêutico do Estado de Pernambuco) of Brazil. LAFEPE is the second largest public laboratory in Brazil and the only producer of benznidazole in the world, after a successful technological transfer of the production from the original producer, Roche. LAFEPE was created in 1966 to produce medicines at low cost for people with limited purchasing power. Based in Recife, the capital of the state of Pernambuco in northeastern Brazil, LAFEPE focuses on developing, producing, and marketing drugs to support the needs of public health policy.