PROPOSAL FOR THE INCLUSION OF BENZNIDAZOL PEDIATRIC DOSAGE FORM AS TREATMENT FOR CHAGAS DISEASE IN CHILDREN YOUNGER THAN 2 YEARS OLD IN THE WORLD HEALTH ORGANIZATION MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN

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Glossary:

**ANVISA**: Brazilian Drug Regulatory Authority (*Agência Nacional de Vigilância Sanitária*, in Portuguese)
**API**: Active Pharmaceutical Ingredient
**BPCRS**: British Pharmacopoeia Chemical Reference Substances
**Bz**: Benznidazole
**CDC**: Centers for Disease Control and Prevention
**CFT**: Complement Fixation Test
**DNA**: Deoxyribonucleic acid
**DNDi**: Drugs for Neglected Diseases initiative
**EIA**: Enzyme Immuno Assay
**ELISA**: Enzyme-Linked ImmunoSorbent Assay
**Hc**: Hemoculture
**HIV/AIDS**: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
**ICRS**: International Chemical Reference Substances
**IgG**: Immunoglobulin G
**IgM**: Immunoglobulin M
**IHA**: Indirect Hemagglutination Assay
**IIF**: Indirect Immunofluorescence
**INN**: International Nonproprietary Name
**IRD**: Institut de Recherche pour le Développement
**LAFEPE**: Brazilian Pharmaceutical Laboratory of the State of Pernambuco (*Laboratório Farmacêutico do Estado de Pernambuco*, in Portuguese)
**MH**: Microhematocrit
**MSF**: Doctors Without Borders (Médecins Sans Frontières, in French)
**Nx**: Nifurtimox
**PAHO**: Pan American Health Organization
**PCR**: Polymerase Chain Reaction
**RENAME**: Brazilian Essential Medicines List (Relação Nacional de Medicamentos Essenciais, in Portuguese)
**SAE**: Serious Adverse Event
**T. cruzi**: Trypanosoma cruzi
**TDR**: Tropical Disease Research
**TPP**: Target Product Profile
**UNICEF**: United Nations International Children's Emergency Fund
**USA**: United States of America
**USP**: United States Pharmacopeia
**WHA**: World Health Assembly
**WHO**: World Health Organization
**WS**: Work Standard
**Executive Summary**

Benznidazol (Bz) pediatric dosage form (tablet 12.5mg) is proposed for inclusion in the World Health Organization (WHO) Model List of Essential Medicines for Children, section 6.5.5.2, as new dosage form indicated for children below 2 years old with Chagas disease.

A recent report published by WHO on Neglected Tropical Diseases in 2010\(^1\) estimates that 10 million people worldwide are infected by *T. cruzi*, mostly in the endemic areas of 21 Latin American countries, but also including non-endemic countries, as a consequence of population mobility. An estimate published by Pan American Health Organization (PAHO) in 2006, indicates a prevalence of approximately 8 million infected individuals and an incidence of 55,185 new cases each year, among which 14,385 are congenital infections. Despite advances over recent years in the control of vector and transfusions related Chagas disease, there is agreement that congenital transmission is likely to remain of importance in the decades to come.

The treatment of Chagas disease is recommended for all cases of acute, congenital and reactive infections among all children, and for patients up to 18 years old in the indeterminate chronic phase (PAHO, 1998; WHO, 2002, 2011). Most infections occur during childhood, involving children, including new-borns who are diagnosed at birth.

Notwithstanding existing recommendations for treatment of children, until recently the only registered dosage form was an adult tablet of 100 mg. For years, the inadequacies of the current form of administration and need for alternative formulations have been a consensus of among experts.

This submission for inclusion of the new dosage form of benznidazole is thus presented in the context of an unmet medical need where it is held that the benefit of using this new 12.5 mg benznidazole strength minimizes the risk of continued use of extemporaneous formulations of the present 100 mg tablet for the pediatric population, and notably the very young.

Benznidazole is highly efficacious for the treatment of congenital infections. Seroconversion rates vary from 87% (Schijman et al., 2003) at 36 months (100% in the 0 to 3 months old group) to 100% (Russomando et al., 1998) at 24 months in children up to two years old. For the treatment of acute infections, these rates vary from 76% (Cançado et al., 2002) at 13 years in children under 10 years old to 100% (Ferreira, 1988) at 15 years in children between 2 and 18 years old.

Safety data summarized in this submission indicates a better tolerability for benznidazole among children than adults, with treatment discontinuation due to adverse events being rare among new-borns, and no greater than 10% in children in the indeterminate phase, while these rates may rise to 40% among adults, usually hovering at around 20%.

The assessment of risk-benefit ratio of the use of the new strength of 12.5 mg versus the continued use of the 100 mg tablet in the pediatric population points to the benefit of prescribing a known concentration of the product, with easier management in the conditions use, by parents and health professionals. The new strength of benznidazole in the form of rapidly disintegrating tablet, would allow an easy and reliable administration, especially in long-term home care.
pediatric
1. Summary statement of the proposal for inclusion, change or deletion

Benznidazol (Bz) pediatric dosage form (tablet 12.5mg) is proposed for inclusion in the World Health Organization (WHO) Model List of Essential Medicines for Children, section 6.5.5.2, as new dosage form indicated for children by 2 years old with Chagas disease.

2. Name of the focal point in WHO for this application

Pedro Albajar Viñas - WHO / HTM / NTD / IDM / Chagas disease
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HIV/AIDS, Tuberculosis, Malaria and Neglected Diseases
Control of Neglected Tropical Diseases
Innovative & Intensified Disease Management
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Tel.: +41 (0)22 7911261; fax: +41 (0)22 7914777
http://www.who.int/neglected_diseases
albajarvinasp@who.int

3. Name of the organization(s) consulted and/or supporting the application

Brazilian Ministry of Health – Appendix 1
Honduras Ministry of Health – Appendix 2
Argentinean Ministry of Health – Appendix 3
Médecins Sans Frontières – Appendix 4
Bolivian Ministry of Health – Appendix 9

4. International Nonproprietary Name (INN, generic name) of the medicine

Benznidazolum
Benznidazole
N-benzyl-2-nitroimidazole-1-acetamide
C₁₂H₁₂N₄O₃
Source: International Nonproprietary Names for Pharmaceutical Substances, 1974²

5. Formulation proposed for inclusion; including adult and pediatric (if appropriate)

The formulation of pediatric benznidazole (12.5mg) has the same qualitative composition and manufacturing process of the adult (100mg) registered by LAFEPE manufacturer⁽¹⁾, with an adjustment on the proportion of diluents (starch and lactose). This adjustment was needed due to the quantity of benznidazole contained in each dosage (8 times difference) and the appropriate size of tablets, as shown in table 1.
Table 1: Formulation of adult (100mg) and pediatric (12.5mg) benznidazole

<table>
<thead>
<tr>
<th>FORMULATION</th>
<th>PEDIATRIC (%)</th>
<th>ADULT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.5 mg Bz</td>
<td>100 mg Bz</td>
</tr>
<tr>
<td>Benznidazole</td>
<td>10.00</td>
<td>40.00</td>
</tr>
<tr>
<td>Starch</td>
<td>51.20</td>
<td>31.20</td>
</tr>
<tr>
<td>Lactose 200</td>
<td>36.80</td>
<td>26.80</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>Talcum</td>
<td>1.60</td>
<td>1.60</td>
</tr>
<tr>
<td><strong>Average weight of tablets (mg)</strong></td>
<td><strong>125.00</strong></td>
<td><strong>250.00</strong></td>
</tr>
</tbody>
</table>

Note\(^{(1)}\): Between 2004 and 2006, Roche manufacturer transferred to LAFEPE manufacturer in Brazil the process technology and ownership of benznidazole 100 mg product, cancelling at this time its product registration in Brazil.

6. **International availability - sources, if possible manufacturers and trade names**

**Availability of Pediatric Benznidazole 12.5mg**

Pediatric benznidazole (tablet 12.5mg) is produced by Brazilian Pharmaceutical Laboratory of the State of Pernambuco (LAFEPE, in Portuguese).

One box contains 24 blisters and each blister contains 10 scored tablets. Thus, the box contains 240 tablets, the equivalent for a treatment.

There is no brand name for the product and it is supplied with a package “LAFEPE Benznidazol – 12.5mg”.

The product was issued marketing authorization by the Brazilian Drug Regulatory Authority (ANVISA) in December 2011 (ANVISA registration number: 1018301450062 – see Appendix 5). The product’s registration was granted in Brazil with a shelf life of 24 months.

There are package inserts for both patient and health professionals (Appendix 6 and 7, respectively) and secondary package are available in Portuguese and Spanish (Figure 1).

**Characteristics**: tablets containing 12.5mg of Benznidazole
Storage conditions: The product should be stored at room temperature of 15 to 30° C, sheltered from light and humidity.

Figure 1– Secondary package of Lafepe benznidazole 12.5mg (Spanish and Portuguese)

Any interested country – international organizations, control programs, non-governmental organizations or private sector – can purchase from LAFEPE.

As a contribution to facilitate a sustainable access and international availability, a Procurement guide in English, Spanish and Portuguese was elaborated with the step-by-step process to be taken, available LAFEPE’s website: http://www.lafepe.pe.gov.br/LAFEPE/noticias/noticiario/guiabenznidazol.htm

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

It is requested that Benznidazole 12.5mg be listed in the WHO Model List of Essential Medicines for Children, for the treatment of infection due to Trypanozoma cruzi (Chagas Disease) as an additional dosage form.

Benznidazole tablets 100mg is already listed in section 6.5.5.2 (in both, adult and Children WHO Model List) as an essential medicine for American trypanosomiasis (Chagas disease).

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1 Epidemiological information on disease burden

Chagas disease is caused by the Trypanosoma cruzi (T. cruzi) kinetoplastid parasite and is endemic in 21 countries of Central and South America, with an estimated 100 million people at risk of being infected by the parasite\(^3\). The main mode of transmission (>80%) is through triatomine vector, insects known as ‘kissing bugs’ (barbeiro in Brazil, vinchuca in Spanish,
etc). Other forms of transmission are blood transfusions and organ transplants (~15%), congenital/vertical transmission (4%), oral transmission (<1%) and accidental transmission (<1%)⁴.

This disease appears in two clinical phases: an acute phase, usually asymptomatic or characterized by non-specific symptoms that, if left untreated, might progress to a chronic phase, where 20% to 30% of infected patients develop severe forms of cardiopathy or digestive megaformations (megacolon or megaesophagus). According to estimates published by the World Health Organization (WHO) in 2000, there were 18 million people infected in the Americas, of who some 5.4 million progress to severe cardiopathies and 900,000 to digestive megaformations⁵. More recent estimates issued by the Pan American Health Organization (PAHO) indicate that 7.7 million people were infected in 21 countries in Central and South America in 2005.³

A recent report published by WHO on Neglected Tropical Diseases in 2010⁶ estimates that 10 million people worldwide are infected by T. cruzi, mostly in the endemic areas of 21 Latin American countries, but also including non-endemic countries such as in the Region of the Americas (Canada and the United States of America), the Western Pacific Region (mainly Australia and Japan) and the European Region (mainly in Belgium, France, Italy, Spain, Switzerland and the United Kingdom, but also in Austria, Croatia, Denmark, Germany, Luxembourg, the Netherlands, Norway, Portugal, Romania and Sweden) as a consequence of population mobility (see Figure 2).

The morbidity resulting from the chronic phase generates serious social and economic impacts, causing unemployment and a reduction in productive capability. In Brazil alone, it is estimated that more than US$ 1.3 billion in wages and industrial productivity were lost through workers with Chagas disease.⁷
A recent publication estimates the number of immigrants infected by *T. cruzi* at around 39,000 in 2003, and estimated the European countries. In Spain of some 400,000 immigrants living there in 2003 some 12,000 were infected *T. cruzi*. Up to 2007, the number of immigrants from Latin American reached 1,600,000 and, if the prevalence of infection remains similar, some 40,000 of these immigrants will be infected by *T. cruzi* in Spain alone, as shown in Table 2.
Table 2: Estimated number of infected immigrants in Spain, based on immigrant population by country of origin and seroprevalence estimates issued by the Pan American Health Organization (2006).

Based on published seroprevalence estimates, a paper by Bern & Montgomery\textsuperscript{12} calculates that, among 300,167 immigrants infected with \textit{T. cruzi} living in the USA, there are 30,000 to 45,000 cases of cardiomyopathies and between 63 and 315 cases of congenital infections a year, as shown in Table 3.

Table 3. Calculated prevalence of infection with \textit{T. cruzi} among people from Latin American living in the USA in 2005.
<table>
<thead>
<tr>
<th>Country of origin</th>
<th>Immigrant population living in the USA</th>
<th>Prevalence of <em>T. cruzi</em> in countries of origin, %</th>
<th>Estimated Nº of immigrants infected with <em>T. cruzi</em> in the USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>22,843,939</td>
<td>1.31</td>
<td>300,167</td>
</tr>
</tbody>
</table>

In Latin America, successful vector control and transfusion transmission reduction programs run by governments in endemic countries have reshaped the epidemiology of the disease, resulting in a significant drop in the appearance of new cases, as shown in Table 4, as well as halting vector transmission in some of the Latin America countries (vector and transfusion transmission in Uruguay in 1997; vector transmission in Chile in 1999; vector transmission by through the main domestic vector, *Triatoma infestans*, in Brazil in 2006; vector transmission in four provinces in Argentina in 2001 and in one department in Paraguay in 2002).

**Table 4: Evolution of some epidemiological parameters for Chagas disease between 1990 and 2000**

<table>
<thead>
<tr>
<th>Epidemiological Parameters</th>
<th>1990</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº deaths x year</td>
<td>&gt; 45,000</td>
<td>21,000</td>
</tr>
<tr>
<td>Nº cases of human infection</td>
<td>16-18 million</td>
<td>18 million</td>
</tr>
<tr>
<td>Nº new cases x year</td>
<td>700,000</td>
<td>200,000</td>
</tr>
</tbody>
</table>

*Source: WHO, 2000*

In 2001, the estimates for the number of people infected were revised to 9.8 million, with the WHO estimating a reduction in the number of deaths caused by thus disease to 13,000.
An estimate published by Pan American Health Organization (PAHO) in 2006, indicates a prevalence of approximately eight million infected individuals and an incidence of 55,185 new cases each year, among which 14,385 are congenital infections\(^7\) (tables 5 and 6).

Table 5: Estimated prevalence and incidence of Chagas disease in Latin America, 2005

<table>
<thead>
<tr>
<th>Countries</th>
<th>Nº of people infected (Million)</th>
<th>New cases x year</th>
<th>Total Population (Million)</th>
<th>Exposed Population (Million)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vector</td>
<td>Congenital</td>
</tr>
<tr>
<td>21</td>
<td>7.5</td>
<td>40,800</td>
<td>14,385</td>
<td>55,185</td>
</tr>
<tr>
<td></td>
<td></td>
<td>526,95</td>
<td>95,595</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Countries affected by Chagas disease

<table>
<thead>
<tr>
<th>Countries</th>
<th>Nº of people infected (Million)</th>
<th>New cases x year</th>
<th>Total Population (Million)</th>
<th>Exposed Population (Million)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vector</td>
<td>Congenital</td>
</tr>
<tr>
<td>8. Argentina</td>
<td>1.6</td>
<td>1,300</td>
<td>1,800</td>
<td>39</td>
</tr>
<tr>
<td>9. Bolivia</td>
<td>0.620</td>
<td>10,300</td>
<td>1,500</td>
<td>9.1</td>
</tr>
<tr>
<td>10. Brazil</td>
<td>1.9</td>
<td>0</td>
<td>5,000</td>
<td>186.8</td>
</tr>
<tr>
<td>11. Chile</td>
<td>0.1602</td>
<td>0</td>
<td>445</td>
<td>16.4</td>
</tr>
<tr>
<td>12. Paraguay</td>
<td>0.150</td>
<td>900</td>
<td>600</td>
<td>6.3</td>
</tr>
<tr>
<td>13. Uruguay</td>
<td>0.0217</td>
<td>0</td>
<td>20</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>Southern Cone Initiative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Colombia</td>
<td>0.436</td>
<td>5,250</td>
<td>1,000</td>
<td>46.8</td>
</tr>
<tr>
<td>15. Ecuador</td>
<td>0.230</td>
<td>2,350</td>
<td>800</td>
<td>13.3</td>
</tr>
<tr>
<td>16. Peru</td>
<td>0.192</td>
<td>3,100</td>
<td>200</td>
<td>28.4</td>
</tr>
<tr>
<td>17. Venezuela</td>
<td>0.310</td>
<td>1,400</td>
<td>600</td>
<td>27</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4.4519</strong></td>
<td><strong>12,500</strong></td>
<td><strong>9,365</strong></td>
<td><strong>260.9</strong></td>
</tr>
<tr>
<td>18. Belize</td>
<td>0.002</td>
<td>20</td>
<td>10</td>
<td>0.3</td>
</tr>
<tr>
<td>19. Costa Rica</td>
<td>0.023</td>
<td>30</td>
<td>60</td>
<td>4.3</td>
</tr>
<tr>
<td>20. Salvador</td>
<td>0.232</td>
<td>2,500</td>
<td>230</td>
<td>7</td>
</tr>
<tr>
<td>21. Guatemala</td>
<td>0.250</td>
<td>2,200</td>
<td>400</td>
<td>13</td>
</tr>
<tr>
<td>22. Honduras</td>
<td>0.220</td>
<td>2,800</td>
<td>450</td>
<td>7.4</td>
</tr>
<tr>
<td>23. Nicaragua</td>
<td>0.0586</td>
<td>750</td>
<td>100</td>
<td>5.6</td>
</tr>
<tr>
<td>24. Panama</td>
<td>0.021</td>
<td>200</td>
<td>50</td>
<td>3.3</td>
</tr>
<tr>
<td>25. F. Guiana</td>
<td>0.018</td>
<td>400</td>
<td>20</td>
<td>0.15</td>
</tr>
<tr>
<td>26. Suriname</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Countries

<table>
<thead>
<tr>
<th>Countries</th>
<th>Nº of people infected (Million)</th>
<th>New cases x year</th>
<th>Total Population (Million)</th>
<th>Exposed Population (Million)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vector</td>
<td>Congenital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. Guiana</td>
<td>0.8246</td>
<td>8,500</td>
<td>1,320</td>
<td>42.25</td>
</tr>
<tr>
<td>Other countries</td>
<td>1.1</td>
<td>7,700</td>
<td>1,100</td>
<td>108.3</td>
</tr>
</tbody>
</table>

Source: PAHO, 2006

Regardless of the success attained through vector control programs, vertical transmission remains an important form of transmission. With an estimated prevalence of *T. cruzi* infection among pregnant women varying from 5% to 40%, depending on the geographical area, this may reach 81% in some rural areas. With a vertical transmission rate estimated at around 5%, varying from 1% to 12%, congenital Chagas disease will constitute a major public health problem for many years to come, not only in the endemic countries but also in countries absorbing significant population flows, until efficacious new treatment options can prevent the progression of the disease or its vertical transmission.

A retrospective study of mother-to-child transmission of Chagas infections among 278 patients in the chronic phase, born in different Brazilian States to 145 mothers testing seropositive for *T. cruzi*, Rassi et al. (2004) estimated the vertical transmission rate at 0.7% (2/278 children or 2/289 births), consequently not distinguishing between congenital transmission and that acquired through breast milk.

Recent data obtained through a serological screening study conducted among children less than five years old in Brazil, Luquetti et al. (2005) recorded anti-*T. cruzi* antibodies in nineteen of 9,556 of them (preliminary data for Minas Gerais State). These data indicate a lower prevalence of congenital infections in Brazil, compared to other countries in Latin America.

### 8.2 Assessment of current use

Benznidazole (Bz) and Nifurtimox (Nx) are the only two medicines currently available for the etiological treatment of Chagas disease, and both of them have been used for years. Benznidazole constitutes the drug of first choice in most of the Latin American countries due to its greater tolerability and easier accessibility. Nx is usually recommended as an alternative for cases of intolerance to benznidazole, as its availability has varied over the years, in addition somewhat less data with regards to its safety and tolerability profile.

The treatment of Chagas disease is recommended for all cases of acute, congenital and reactive infections among all children, and for patients up to 18 years old in the indeterminate chronic phase (PAHO, 1998; WHO, 2002). As most infections occur during childhood, most cases involve children, including newborns diagnosed at birth.
Recommendations arise from clinical experiences and studies with patients in the acute phase and with congenital disease, who have seen that the treatment that reduces the severity of the treatment, while slowing clinical progression and shortening the duration of detectable parasitemia.\textsuperscript{26,27,28,29,30}

During the 1970s, several treatment experiments were published with Benznidazole in children with acute and congenital infections (Barclay et al.\textsuperscript{31}, 1978; Russomando et al.,\textsuperscript{32,33} 1998, 2005; Cançado et al.,\textsuperscript{34} 2002; Torrico et al.,\textsuperscript{35} 2004; Salas et al.\textsuperscript{36}, 2007; Chippaux et al.,\textsuperscript{37} Instituto de Recherche pour le Développement [IRD], 2008-2009) and in the indeterminate chronic phase (de Andrade et al.\textsuperscript{38}, 1996; Sosa Estani et al.\textsuperscript{39,40}, 1998, 2002; Flores-Chavez et al.\textsuperscript{41}, 2006, Duffy et al.\textsuperscript{42},2009), or comparing the efficacy and tolerability of benznidazole and nifurtimox in the same age brackets (Blanco et al.\textsuperscript{43}, 2000; Silveira et al.\textsuperscript{44}, 2000), in different age bracket groups (Ferreira,\textsuperscript{12,13} 1988, 1990; Streiger et al.\textsuperscript{45}, 2004) as well as for different age groups and stages of the disease (Schijman et al.\textsuperscript{4}, 2003). Parasitological responses occur in 60% to 85% of patients during the acute phase, and in more than 90% of children with congenital infections treated during the first year of life.\textsuperscript{46,47} Further information and detail about the clinical evidence will be discussed in Section 10 (identification of clinical evidence).

In Brazil, the Health Surveillance Bureau under the Ministry of Health recommends “treatment for children and young adults in the chronic indeterminate form and the mild cardiac and digestive forms.”\textsuperscript{48}

In 2010, during the World Health Assembly it was approved a Resolution “Chagas disease: control and elimination (WHA 63.20)” which urges WHO Members States “to promote the development of public health measures in disease-endemic and non-endemic countries, with special focus on endemic areas, for the prevention of transmission through blood transfusion and organ transplantation, early diagnosis of congenital transmission and management of cases” (paragraph 8).

In 2011, a summary of the recommendations from the Technical Group IVa “Prevention and Control of Congenital Transmission and Case Management of Congenital Infections” of the WHO’s Programme on Control of Chagas disease was made public.\textsuperscript{50}

With regards to the treatment of neonates and infants, both benznidazole and nifurtimox are recommended for the treatment of congenital cases. Doses for benznidazole are respectively from 5-7mg/kg/day and up to 10mg/kg/day for infants and infants/neonates by 1 year old, divided in 2-3 doses per day, during 60 days and not less than 30 days. The WHO recommendation (2011) supports the need of a dosage form of 12.5mg of benznidazol to facilitate the preparation of pediatric suspension.

Recent case reports of congenital Chagas disease in non-endemic countries, such as Switzerland and United States of America, have been published\textsuperscript{51,52}, as well as proposal of screening programme for congenital transmission, such as in Spain.\textsuperscript{53}

In Switzerland, Jackson \textit{et al.} (2009) reported two congenital cases, in 2001 and 2006, of women from Bolivia who delivered their babies in the Geneva University Hospital.
Congenital cases were confirmed by positive blood microscope examination and PCR for the infants and positive serologic and PCR for the mothers. Newborns were treated with nifurtimox (10mg/kg/day) during 60 days, without notable adverse effects. Parasitemia became undetectable at the end of treatment and at subsequent serologic tests.

The authors also developed a retrospective serologic survey for *T. cruzi* infection with serum samples stored in the Hospital from 72 pregnant women from Latin America countries who received care in the Hospital and 9.7% were positive for *T. cruzi*.

In 2008, the Geneva University Hospitals set up a systematic Chagas disease screening of pregnant women at risk (those from Mexico, Central and South America) and newborns. For positive diagnosis, all women (after completion of breastfeeding), newborns and siblings are offered treatment.

More recently, the first case report of congenital Chagas in United States of America (USA) was published by CDC in July 2012. In August 2010 a boy was born to a mother who moved to US from Bolivia. Physicians learned from the mother that at her previous pregnancy she had been told to have Chagas disease. The child was diagnosed positive by identification of *T. cruzi* trypomastigotes in the blood smear, and both serologic tests for anti-*T. cruzi* antibodies and PCR were positive. The baby was treated with benznidazole during a 60 days. Follow-up tests at age of 10 months showed the baby was cured based negative results of *T. cruzi* PCR and serologic tests.

Basile *et al.* (2011) described the screening programme for congenital transmission of Chagas disease, implemented from January 2010, in Catalonia (Spain) developed with the WHO Department of Neglected Tropical Disease. The diagnosis for Chagas was offered in the 1st semester of pregnancy following PAHO recommendations of two serological tests. For serological positive mothers, newborns are diagnostic screened and in case of positive parasitological test at birth or a positive serological result at nine months, it is adopted the treatment, having benznidazole more widely used. Siblings, if needed, are also treated.

Despite widely accepted consensus on the efficacy of treatment for children and its greater tolerability compared to administration in adults (described in next topics) and the treatment recommendations for the pediatric population, pediatric formulations of these drugs used were until recently not available.


Produced as 100 mg tablets, benznidazole is administered twice a day, at doses of 5-7 mg/Kg for adults during 30-60 days and 5-10 mg/Kg for children during 60 days (Appendix 6 and 7).
Consequently, for treatment of most children, the tablet must be cut into two, four or more fractions, which are administered directly or crushed and diluted in liquid, presenting a risk of possible overdose and increased toxicity, particularly for smaller or undernourished children, or else under-dosing with a possible loss of efficacy. Figure 3 illustrates the most frequent ways of administering benznidazole to children.

There are no studies on the stability of these different extemporaneous forms of administration. Extemporaneous preparations undertaken by healthcare workers or mothers have been shown to be imprecise, as shown in Graph 1. The weight of a split tablet may vary between 50% and 150% of the real weight of half a tablet.⁵⁴
Graph 1 – Assessment of extemporaneous formulations of benznidazole

CV = 23.82%

CV = 28.82%

CV = 30.37%

CV = 13.83%

CV = 27.27%

CV = 7.70%

CV = 3.75%
8.2.1 Target population

The target population for the benznidazole 12.5 mg pediatric dosage form is children up to two years old, mostly congenital cases. The rational to establish the dose and the age range are described in the next paragraphs.

Legislators and physicians have long emphasized the pressing need for a pediatric dosage form for the treatment of Chagas disease, particularly the TDR/WHO Scientific Working Group for Chagas Disease (2005) and the TDR/WHO Working Group on Chagas Disease (2007), which highlighted the unmet need for a pediatric dosage form for the treatment of Chagas disease.

Thus, in July 2008, DNDi and the Pernambuco State Pharmaceutical Laboratory (Laboratorio Farmacêutico do Estado de Pernambuco - LAEPE) established a partnership designed to bridge this gap, implementing a project developing a pediatric dosage form of benznidazole.

The characteristics of the pediatric dosage form were established through a review of the current treatment recommendations; a compilation of the databases on children treated in Latin America, and a comparison of the current doses prescribed, in order to determine the target population for the pediatric dosage form and the therapeutic margins (upper and lower limits), in addition to a definition of the pharmaceutical form and composition established by a specialist panel.

Table 7 summarizes the recommended dosages identified through a systematic review of the WHO Guides, National Control Programs and medical literature.

Table 7 - Recommended dosage of Benznidazole for Chagas disease infections

<table>
<thead>
<tr>
<th>Source</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO – Consensus - Specialist Group Chagas Disease Control Experts</td>
<td>Congenital infections: 5-10 mg/kg/day</td>
</tr>
<tr>
<td>WHO – Prescription model</td>
<td>Children &gt;= 12 y.o.:5-7 mg/kg/day, Children &lt;12 y.o.:10 mg/kg/day (interval not stated)</td>
</tr>
<tr>
<td>Package Insert - Hoffman-La Roche</td>
<td>Children &gt;= 12 y.o.:5-7 mg/kg/day, Children &lt;12 y.o.:10 mg/kg/day (interval not stated)</td>
</tr>
<tr>
<td>Package Insert - Roche. Radanil®</td>
<td>5-8 mg/kg/day 2x/day for 60 days</td>
</tr>
<tr>
<td>Package Insert - Roche. Rochagan®</td>
<td>5-7 mg/kg/day 2x/day by mouth for 30-60 days</td>
</tr>
<tr>
<td></td>
<td>Children &lt; 12 y.o., especially with acute infections: up to 10 mg/kg/day for the first 10-20 days of treatment</td>
</tr>
<tr>
<td>Ministry of Health, Health Surveillance Bureau.</td>
<td>Adults: 5 mg/kg/day, Children: 5-10 mg/kg/day two or 3x/day by mouth for 60 days</td>
</tr>
<tr>
<td>Source</td>
<td>Age Range</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Brazilian Ministry of Health, Health</td>
<td>Acute phase, congenital infections, immunocompromised and transplant patients: 8 mg/kg/day 2x/day by mouth for 60 days</td>
</tr>
<tr>
<td>Surveillance Bureau.</td>
<td></td>
</tr>
<tr>
<td>Mazza Chagas Disease Council,</td>
<td>5 mg/kg/day for 30-60 days</td>
</tr>
<tr>
<td>Argentine Cardiology Society</td>
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</tbody>
</table>

The recommended benznidazole dosages indicate variations in milligrams by kilogram of weight in the recommended dose-category. In general, the doses recommended for children are higher than those for adults. The main variations appear between the recommended dosage of 5-10 mg/kg, where 10 mg/kg is a maximum acceptable dose, with recommendations of 10 mg/kg as the target dose, with no mention of any acceptable margin or error for this dosage. No recommendation offers guidance on the practical aspects and challenges of administering accurate doses to children, with the 100 mg formulation currently available.

In order to confirm the therapeutic margins based on clinical experience and identify the pediatric population for which the administration of the correct dose constitutes the greatest problem, and which would benefit the most from a pediatric dosage form, treatment data were compiled for patients with Chagas disease in Latin America, with various specialists in treating pediatric T. cruzi infections being contacted.

Secondary analyses of anonymous treatment data were also conducted on the basis of 2,769 records drawn from ten sources, supplied by the contacted congenital Chagas experts in different countries. Figures 4 and 5 present the age distribution of the compiled patient population.
Although not aiming to constitute a representative sample of patients with Chagas disease in Latin America, these compiled data offer an overview of children population treated by age range for which dosing data was available, indicating the existence of three specific groups of pediatric patients: congenital infections confirmed by microscopy, for which treatment is initiated at birth, congenital infections diagnosed through serology during the second half of
childhood; and early indeterminate infection among schoolchildren, detected more systematically through Chagas disease screening programs run in schools.

Considering the therapeutic margins currently in place and the weight-age distribution in this data compilation (Figure 6a and 6b), it is clear the significant variation of dosing the adult tablet of 100 mg.

**Figure 6a and 6b – weight-age distribution**

When analyzing the dose prescribed in mg/kg in this data compilation, it is apparent that the daily dose is maintained for a therapeutic interval of 5-10 mg/kg/day for most of the children (Figures 7a and 7b), except for infants under one year old. In this group, the doses vary from 5 mg/kg to 15 mg/kg, while for new-borns, a significant proportion children receive doses exceeding 10 mg/kg, reflecting the difficulties associated with fragmenting the 100 mg tablet. Consequently, the group that would benefit most with a pediatric dosage form consists of infants up to a year old with congenital infections.

**Figure 7a - Dose by age bracket. All age brackets (n=2,424)**

**Figure 7b - Dose by age bracket. Dose administered at <1 year (n=317)**
After an analysis of the current benznidazole dose recommendations and the doses prescribed in clinical practice, a panel of specialists\(^1\) defined a therapeutic interval for the pediatric dosage form of 5-10 mg/kg, twice a day for 60 days for children under 12 years of age, consistent with the recommendations issued by the Chagas Disease Control Technical Specialists Group with the WHO (2002).\(^55\) This panel of experts indicated that, despite the lack of pharmacokinetic data available for support in this therapeutic range, such as the ideal range for children, benznidazole seems to be tolerated better by small children than by adults\(^31\), for whom toxicity is a significant problem. Furthermore, the treatment is more efficacious among small children, reaching parasitological clearance rates of more than 90% for congenital infections treated during the first year of life, as mentioned and explained in further detail in the section on clinical efficacy overview.

The recommended interval of administration at twice a day is based on the benznidazole terminal half-life, which varies from 10.5 to 13.6 hours, with an average of 12 hours\(^56,57\).

With regard to the definition of the pharmaceutical form, after considering the current forms of administration for benznidazole (see Figure 3) and the recommendations in the international guidelines, particularly the Treatment Guidelines for Scaling up Antiretroviral Therapy in Resource-limited Settings\(^58\) issued by the WHO which “strongly encourages the development of formulations appropriate for pediatric use, particularly solid forms that may be taken by pediatric patients (for example, dissolvable tablets or capsules that can be opened), as the conservation times for liquid formulations may be shorter than those of the solid formulations, in addition to being more expensive and harder to store, and possibly requiring the use of syringes for correct administration”. Consequently, the panel of experts agreed on the decision to develop a solid pediatric presentation of benznidazole in the form of a rapidly disintegrating tablet, as this would allow the use of a minimal quantity of non-toxic excipients, as well as being easy to produce, more stable and cheaper than the liquid form, for easy, reliable administration, particularly for long-duration home treatment.

For definition of tablet strength, an acceptable therapeutic interval of 5 to 10 mg/kg was agreed, with the ideal administration consisting of 1-2 tablets orally, with a maximum of single fractionation.

The adult tablet of 100 mg is designed for patients weighing more than 20 kg (see Figure 8), which constitutes the group of children at school age, greater than eight years old and with early indeterminate infection, while half the adult tablet (or 50 mg tablet) could encompass the weight range between 10 and 20kg.

\(^1\) Chagas disease Expert Panel Dr. Jaime Altcheh, Hospital de Niños Ricardo Gutierrez, Buenos Aires, Argentina; Dr. Laurent Brutus, Institut de Recherche pour le Développement, La Paz, Bolivia; Dr. Sérgio Sosa Estani, Centro Nacional de Diagnóstico e Investigación de Endemo-epidemias (CeNDIE) ANLIS Dr. Carlos G. Malbrán, Ministry of Heath, Argentina
The strength of 12.5 mg was selected for the pediatric tablet, equivalent to 1:8 of the adult tablet of 100 mg, in order to reduce the need for splitting the tablet for administration to new-borns. The 12.5 mg pediatric tablet thus encompasses a broad range of age and weight for small children, as shown in Figure 9.
As benznidazole is a medication whose use is established for adults as well as the pediatric population, and has already been registered under international standards (Radanil®, Rochagan®) and in Brazil (LAFEPE Benznidazole®) for the treatment of Chagas disease, the development plan focused on the registration requirements for the inclusion of a new pediatric presentation and indication. The development strategy complied with the latest Brazilian domestic and international guidelines, especially Executive Board Resolution RDC No. 48/09 - on Post-Registration of Medication.

The main elements taken into consideration in this process included the following points:

- The well-established therapeutic indication of benznidazole as the first line treatment for Chagas disease in Brazil, and in most of the endemic countries;

- The inclusion of benznidazole in the list of essential medications drawn up by the WHO and in Brazil’s Essential Medications Listing (Rename), as well as its inclusion in the list of strategic products established by Edict Nº 978 promulgated on May 16, 2008, replaced by Edict Nº 1,284 on May 26, 2010.

- The existence of a therapeutic consensus (WHO, PAHO and assorted national Chagas disease control programs) regarding the recommendation for treatment of all acute and congenital infections, and reactivation for all children;

- The balance of evidence confirming the efficacy of benznidazole treatment for children;

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**Figure 9: Range of the pediatric table (12.5 mg)**

Assumed tablet strength = 12.5mg, therapeutic dose range = 5 to 10 mg/kg

Assumes 1) equal split of the daily doses AM + PM: 1 tab = 1tab AM + 1tab PM
2) use of half tab only in those < 5kg, rest full tablets only, 3) PK linear across all age groups.
• The availability of safety and tolerability data, indicating that benznidazole is better tolerated among the pediatric population than by adults;
• The composition of the pediatric presentation with the same qualitative composition as the adult formulation and comparative dissolution profile data for both presentations; and
• The maintenance of the dosage schedule recommended by the Brazilian Ministry of Health and WHO (5 – 10 mg/kg/day administered twice a day for 60 days).

As a result of the established use of benznidazole for the pediatric population, it was not considered necessary to conduct in vivo clinical trials in order to support the pediatric dosage form registration dossier. Following registration, a population pharmacokinetics study in children aged 0 to 12 years of age has been recently concluded and provides additional data in support to the efficacy and safety of the benznidazole 12.5 mg and 100 mg tablets in the treatment of Chagas disease.

In Brazil, benznidazole pediatric dosage form (tablet 12.5mg) is already included in the Brazilian Essential Medicines List (RENAME) 2012\textsuperscript{62}.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

9.1 Dosage regimen, duration
Benznidazole 12.5mg (oral tablets): 5-10mg/kg/day, twice a day, during 60 days.

Table 8 – Summary of the categories of weight per dose for tablets Benznidazole 12.5mg

<table>
<thead>
<tr>
<th>Weight (Kg)</th>
<th>Recommended Dose (5 – 10 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,5 a &lt; 5 kg</td>
<td>1 tablet in twice a day during 60 days (total dose of 25 mg per day)</td>
</tr>
<tr>
<td>5 a &lt; 10 kg</td>
<td>2 tablets (25 mg) in twice a day during 60 days (total dose of 50 mg per day)</td>
</tr>
<tr>
<td>10 a &lt; 15 kg</td>
<td>3 tablets (37,5 mg) in twice a day during 60 days (total dose of 75 mg per day)</td>
</tr>
</tbody>
</table>

Source: Lafepe benznidazole package insert – Appendix 6.

9.2 Reference to existing WHO and other clinical guidelines
According to the Second Report of the WHO Expert Committee (2002)\textsuperscript{63}, nifurtimox (a nitrofuran derivative) and benznidazole (a nitroimidazole) are the only medicines used for the treatment of the acute phase of Chagas disease and for congenital infection.

In congenital cases, recommended treatment of full-term neonates is with a daily dose of 10mg/kg of benznidazole. In this report, suggested treatment must start with a dose of 5mg/kg daily and if, after 3 days of treatment, there is neither leukopenia nor thrombocytopenia, the dose should be increased to 10mg/kg daily.

As discussed in section 8.2 (Assessment of Current Use), in 2011 WHO updated its recommendation for the diagnosis, treatment and control of newborns, siblings and pregnant women related to congenital Chagas disease\textsuperscript{48}. A summary of the recommendations from the Technical Group IVa “Prevention and Control of Congenital Transmission and Case Management of Congenital Infections” of the WHO’s Programme on Control of Chagas disease was made public. With regards to the treatment of neonates and infants, both benznidazole and nifurtimox are recommended for the treatment of congenital cases. Doses for benznidazole are respectively from 5-7mg/kg/day and up to 10mg/kg/day for infants and infants/neonates by 1 year old, divided in 2-3 doses per day, during 60 days and not less than 30 days. In the WHO recommendation (2011) there is a clear support to the need of a dosage form of 12.5mg of benznidazole to facilitate the preparation of pediatric suspension.

In 2012, the WHO Drug Information also published a reference with regards to the benznidazole pediatric 12.5mg\textsuperscript{64}.

\textbf{9.3 Need for special diagnostic or treatment facilities and skills}

In most endemic countries, Chagas disease diagnosis and treatment is organized through vertical programs that ensure the necessary specific training and equipment required. In comparison with current practice, no additional special diagnostic or treatment facilities are needed.

\textbf{10. Summary of comparative effectiveness in a variety of clinical settings:}

There are no comparative studies on the effectiveness in a variety of clinical settings. The following sub-sections will provide an overview of the clinical evidence on the efficacy of benznidazole in children.

The rationale behind the development of the benznidazole dosage form 12.5mg considered the fact that the target pediatric population is very small, thus clinical studies to provide information on comparative effectiveness would take several years to achieve the appropriate sample size. In the risk benefit assessment, this would mean additional years in
which children would be treated with benznidazole adult formulation with a significant variation in the dose administrated, as discussed previously.

In addition to the existing clinical evidence in support to the efficacy and safety of benznidazole in children, DNDi in collaboration with partners also implemented a population pharmacokinetic study for evaluation of the pediatric dosage form 12.5mg (section 11.7).

10.1 Identification of clinical evidence and summary of available data

10.1.1 Studies of Benznidazole efficacy in congenital infections

A number of studies have been conducted in children with congenital infections, treated with benznidazole.

A randomized clinical study was conducted by the IRD (2008-2009) on T. cruzi transmission, comparing the reduction in anti T. cruzi antibodies titers among non-infected new-borns, with those of new-borns with congenital infections treated with two therapeutic benznidazole schemes, in order to determine the serological cure criteria. The other available studies were conducted in situations of pre-natal screening, upon detection of congenital infections among newborns of mothers infected by T. cruzi, and following determination of the prevalence of a congenital transmission (Blanco et al., 2000; Russomando et al., 1998; Salas et al., 2007; Torrico et al., 2004) or evaluating the PCR assay as a tool for diagnosing and assessing parasitological response to treatment (Schijman et al., 2003).

Although main purpose of these studies was not to assess the efficacy of benznidazole, these studies provide evidence of the efficacy of treating congenital infections, as described below and summarized in Table 9.

In a randomized controlled study conducted by IRD (2008-2009) in Bolivia of 111 new-borns with congenital infections diagnosed at birth through direct microscopic observation (microhematocrit [MH]), 58 children were treated from the first day of life with benznidazole 2.5 mg/kg/day administered twice a day for 60 days, and 52 children with benznidazole 7.5 mg/kg/day administered once a day for 30 days. In order to compare the reduction in anti T. cruzi antibody titers, two other study arms included 68 new-borns with seropositive mothers who did not present parasitemia at birth, and 78 new-borns with seronegative mothers. Blood samples were taken at 30 and 60 days and 10 ± 2 months and, with seropositive ELISA testing after ten months, every two months until seroconversion. All parasitology tests (MH) showed negative results before the ninth month. After ten months of follow-up, ELISA was negative for 90.7% of the children treated (98/108) with all the seropositive tests becoming negative after 16 months, indicating a response to treatment. No significant difference was noted in the proportion of children presenting seroconversion after ten months between the groups treated with different therapeutic schemes (p=1.0), nor among the average figures for the antibody titers.
In the study conducted by Blanco et al. (2000) in Argentina, 32 children born to infected mothers and diagnosed as positive up to six months old through parasitology (MH) and serology tests (IHA, ELISA [IgG and IgM antihuman] and IIF in case of IgG serology findings) were treated orally with Nx at 10 mg/kg per day, two or three times a day for 60 days (29 children) or with benznidazole, 5 mg/kg per day, two or three times a day for three days (3 children presenting adverse reactions to Nx). The 32 children treated presented negative parasitology (MH) tests when examined between 6 and 24 months after the end of treatment, and 30 of the 32 children presented seronegative tests, indicating response to treatment of congenital infections, regardless of the medication administered.

In the study conducted by Russomando et al. (1998) in Paraguay, six children born from infected mothers and diagnosed as positive through direct microscopic observation (MH) and/or hemoculture (Hc), IIF, ELISA and the PCR technique, were treated with benznidazole, 7 mg/kg per day, taken twice a day for 60 days. Treatment began at different times: two babies were treated at birth, and four others began treatment at between 3 months to 22 months after birth. After 24 months of follow-up, all babies presented negative results in the parasitology tests (Hc, MH, PCR) with negative seroconversion by IIF and ELISA. Seroconversion occurred at between two months and eight months after the end of the treatment, suggesting better outcomes for early treatment.

In the prospective study conducted by Schijman et al. (2003) in Argentina, 40 of the 152 children born to mothers sero-reactive for T. cruzi, diagnosed by MH and PCR (50 children between 0 and six months old) and through serology (IHA, ELISA) and PCR (102 children between seven months and 17 years old), were treated with Nx, 10-15 mg/kg/day or benznidazole, 5-8 mg/kg/day in two doses per day for 60 days. The efficacy of the treatment was assessed by age group, and the treated children were monitored for 36 months after the end of the treatment. No differences were observed in clinical and serological results, nor on the PCR testing between the two treatment groups. 100% of children between 0 to 3 months old age (10 children), and 66.7% of children between seven months to two years old (6 children) were considered cured based on the serology test (negative for IgG anti T. cruzi antibodies), while for the age group more than 3 years old (24 children), cures were documented in only 12.5% of the cases during the study observation period ($P = 0.023$). It was also noted that seroconversion occurred faster in children who began treatment during the first few months of life, indicating the possibility of greater efficacy for early treatment, despite difficulties in determining cures for patients in the indeterminate phase, as conventional serology remains positive for many years after treatment.

Table 9 summarizes the data on the efficacy of the main clinical studies in children with congenital infections.
Table 9 – Overview of data on the efficacy of the main clinical studies in children with congenital infections

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th></th>
<th>Benznidazole</th>
<th></th>
<th>Nifurtimox</th>
<th></th>
<th>Design*</th>
<th></th>
<th>Follow-up (months)</th>
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<th>Efficacy Measurements †</th>
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<tr>
<td></td>
<td></td>
<td>n</td>
<td>Dose (mg/kg/d)</td>
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<td>Russomando 1998</td>
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<tr>
<td>Schijman 2003</td>
<td>Congenital</td>
<td>16</td>
<td>5-8</td>
<td>60</td>
<td>-</td>
<td>10-15</td>
<td>60</td>
<td></td>
<td>C, nR, nB</td>
<td>36m</td>
<td>(EIA, IHA)</td>
<td></td>
<td>(MH, PCR)</td>
</tr>
<tr>
<td></td>
<td>&lt;2</td>
<td></td>
<td></td>
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<tr>
<td>Chippaux (IRD)</td>
<td>Congenital</td>
<td>68</td>
<td>NT</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>C, R, B</td>
<td>10m</td>
<td>(EIA, IC)</td>
<td></td>
<td>(MH a 2m)</td>
</tr>
<tr>
<td>2008 -2009</td>
<td>&lt;1</td>
<td>59</td>
<td>5</td>
<td>60</td>
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<td></td>
<td>52</td>
<td>7.5</td>
<td>30</td>
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<td></td>
<td>(Control=not infected)</td>
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</tbody>
</table>

Key
- Design: C (controlled: control or comparison group), nC (not controlled); R (randomized), nR (not randomized); B (blind), nB (not blind)
- † Efficacy Measurements: IHA (Indirect Hemagglutination), IIF (Indirect Immunofluorescence), EIA (Enzyme Immunoassay), IC (Immunochromatography), MH (Microhematocrit), HC (hemoculture), PCR (Polymerase Chain Reaction molecular assay).

Source: IRD 2009
10.1.2 Studies of the efficacy of benznidazole in children with acute infection

Table 10 presents an overview of the treatment efficacy data for patients in the acute phase of benznidazole, in three non-randomized, open-label, controlled studies.

Barclay et al. (1978) followed 139 cases of acute infection during 18 months, mostly children, diagnosed through xenodiagnosis and the Strout technique. 107 patients were treated with progressive doses of benznidazole, starting at 3 mg/kg/day until reaching a dose of 7.5 – 10 mg/kg/day after 12 days, which was then maintained through to the end of treatment at 30 days; 32 patients received a dose of 5 mg/kg/day during 30 days. The efficacy of the treatment was assessed in 86 patients through parasitology (xenodiagnosis) and serology tests (Complement Fixation Test (CFT), IIF and IHA), conducted systematically during a period of 18 months. At the end of the treatment, the Strout test proved negative for 86% of the children. At 18 months, the accumulated percentage of negative xenodiagnoses was 88%, with a negative CFT for 87% of children examined (27/31) and the IIF presenting negative findings or low titers in 91% of children without parasitemia examined (41/45; p <0.001).

In the cohort study conducted by Ferreira (1988), a total of 38 children with acute infections were monitored, with 17 children between 2 and 18 years old treated with oral benznidazole 5 mg/kg/day for 60 days and monitored for 9 years, and 21 children between 6 and 13 years-old treated with Nx 15 mg/kg/day for 90 days monitored for 15 years. At the end of the follow-up period, 100% of the patients in both groups presented negative serology tests (IHA, IIF, CFT) and no patient in either group presented positive parasitology tests (xenodiagnosis).

Cançado et al. (2002) monitored a group of 21 patients with acute infections between 7 months and 60 years old, for a period of 13 to 21 years, treated with benznidazole between 1974 and 1982, with therapeutic schemes varying from 5 to 10 mg/kg/day, taken two or three times a day, for periods varying between 30 and 60 days. During follow-up period of 13 years, 16 (76%) of the patients presented negative serology tests (IHA, IIF and ELISA) and were defined as cured. The other five patients presented persistently positive tests, indicating treatment failure.
Table 10 – Overview of efficacy data for the main clinical studies in children with acute infections

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th>Benznidazole</th>
<th>Nifurtimox</th>
<th>Design*</th>
<th>Follow-up (months)</th>
<th>Lost in FU (%)</th>
<th>Efficacy Measurements†</th>
<th>Parasitology Test (% pos)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Dose (mg/kg/d)</td>
<td>Time (days)</td>
<td>n</td>
<td>Dose (mg/kg/d)</td>
<td>Time (days)</td>
<td>Serological Test (% neg)</td>
<td></td>
</tr>
<tr>
<td>Barclay 1978</td>
<td>Children ?</td>
<td>107</td>
<td>32</td>
<td>7.5-10</td>
<td>5</td>
<td>30</td>
<td>10</td>
<td>87% (CFT)</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>32</td>
<td>7.5-10</td>
<td>5</td>
<td>30</td>
<td>10</td>
<td>87% (CFT)</td>
<td>12% (xeno)</td>
</tr>
<tr>
<td>Ferreira 1988</td>
<td>6-13</td>
<td>-</td>
<td>-</td>
<td>21</td>
<td>15</td>
<td>90</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>5</td>
<td>60</td>
<td>15</td>
<td>90</td>
<td></td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Cançado 2002</td>
<td>&lt;10</td>
<td>6</td>
<td>40-60</td>
<td>10-20</td>
<td>30-60</td>
<td></td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>30-60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key

- **Design**: C (controlled: control or comparison group), nC (not controlled); R (randomized), nR (not randomized); B (blind), nB (not blind)
- **† Efficacy Measurements**: IHA (Indirect Hemagglutination), IIF (indirect immunofluorescence), EIA (Enzyme Immuno Assay), Xeno (Xenodiagnosis), Strout (Strout Technique)

Source: IRD 2009
10.1.3 Efficacy studies of benznidazole in children in the indeterminate chronic phase

There are many trials providing evidence of the efficacy of treatment during the indeterminate chronic phase in children and adolescents, whose findings are presented briefly in Table 11.

This section highlights two randomized controlled double-blind clinical trials, in which patients were monitored for lengthy periods of time: the study by de Andrade et al. (1996), conducted between 1991 and 1995 in Goiás State, with follow-up for six years, and the study of Sosa Estani et al. (1998), conducted in Argentina during the same period, with follow-up of nine years.

In the study conducted by Andrade et al. (1996), 129 children from 7 to 12 years old with three positive serology findings for Chagas (IHA, IIF and ELISA) who were asymptomatic, were randomised into two groups. The experimental group (64 children) received treatment with benznidazole at 7.5 mg/kg/day for 60 days and the control group (65 children) received a placebo. 88.7% of children (58 treated and 54 of the control group) were monitored for a total period of six years.

The primary efficacy measurement consisted of negative seroconversion of ELISA test (disappearance of the antibodies directed to a purified trypomastigote glycoconjugate) after three years of follow-up. Seroconversion occurred in 37 of the 58 children (58%) who completed treatment with benznidazole, and for three of the 65 children in the control group (5%). The treatment efficacy was estimated at 55.8% (95% CI, 40.8-67.0) for intention to treat and 64% by protocol. At the end of three years of follow-up, the children who received benznidazole still presented mean IF antibody titers that were 5 times lower than children in the control group (196 [147–256] vs 1068 [809–1408] p<0·00001).

The treatment efficacy after three years was also assessed by Galvão et al. (2003) through PCR assays of 111 children (58 of the experimental group and 53 of the control group) who participated in the clinical trial conducted by de Andrade et al. At the end of the follow-up period, the PCR assay was positive for 39% of patients treated with benznidazole and for 64.2 % of patients receiving a placebo (P= 0.01).

After six years of follow-up, 33 of the 37 children treated with benznidazole and presenting negative seroconversion after three years remained seronegative, while 14 of the 21 children in this group refuted a positive serology in this group, resulting in 47 children with negative seroconversion and six seropositives (cure rate of 88.7%). In the control group of 52 children who were seropositive after three years of follow-up, 32 remained seropositive after six years, while 11 presented seronegativisation (26.1% of negative seroconversion). Consequently, the benznidazole efficacy estimated by the per-protocol analysis and by intention-to-treat was respectively 84.7% (confidence interval [CI] of 95% – 66.8-92.9) and 64.7% (confidence interval [CI] of 95% – 50.2-78.7), indicating the efficacy of benznidazole for children in the early chronic phase.

In the study conducted by Sosa Estani et al. (1998), 55 children between 6 and 12 years old were treated with benznidazole 5 mg/kg/day for 60 days and 51 children in the same age range received placebos. The children were monitored for 48 months and different serology tests (ELISA, IHA, IIF) were conducted before and at 3, 6,12, 24 and 48 months after the start of treatment. The efficacy of
the treatment was assessed through ELISA testing using a *T. cruzi* flagellate protein (F29). In the experimental group, the negative seroconversion rate through the ELISA F29 rose from 35.7% to 62.1% after six and 48 months respectively, while seroconversion did not occur in any of the children in the control group.

Through conventional serology, negative seroconversion occurred in 11.3% (5 out of 44) of the children in the experimental group (P = 0.05) and in 4.5% (2 out of 44) of the children in the control group (P= 0.05) after 48 months. Children treated with benznidazole also presented a significant reduction in the geometric mean IHA and IIF antibody titers, while no significant changes were noted in the control group. Xenodiagnosis conducted after 48 months of follow-up proved positive in 4.7% of children treated with benznidazole compared to 51.2% of children of the control group (P = 0.05). After 9 years (108 months) follow-up, 77% of the treated children presented negative conventional serology (ELISA, IIF), of whom 88.2% were in the 5-9 age bracket and 69% in the age bracket between 10 and 14 years old age.

Sosa Estani *et al.* (2002) also accompanied the serological findings by age among two groups of children between 1 and 14 years treated with benznidazole 5 mg/kg/day during 30 days through the Argentine Public Health System. In the first group of 147 children treated in 1994, the follow-up at 20 months proved negative for conventional serology (IHA, ELISA) in respectively 49.3%, 32.7% and 0% of children in the 0 to 4 years, 5 to 9 years old and 10 to 14 years old age range. In the second group of 40 children treated in 1995, the 5 years follow-up showed negative conventional serology in respectively 91.7%, 69.2% and 54.5% of children in the 0 to 4 years, 5 to 9 years and 10 to 14 years age groups.

These findings corroborate the efficacy of treatment with benznidazole of the early indeterminate form of disease in this age range, suggesting better outcomes for treatment among younger children.
Table 11 – Overview of the main clinical trials examining efficacy in children early chronic infection

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th>Benznidazole</th>
<th>Nifurtimox</th>
<th>Design*</th>
<th>Follow-up (months)</th>
<th>Efficacy Measurements†</th>
<th>Parasitology Test (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferreira 1990</td>
<td>&lt;18</td>
<td>50</td>
<td>60</td>
<td>50</td>
<td>24m</td>
<td>(CFT,IHA,IIF)</td>
<td>(xeno)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-8</td>
<td>-</td>
<td>-</td>
<td></td>
<td>10%</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>-</td>
<td>-</td>
<td></td>
<td>6%</td>
<td>50%</td>
</tr>
<tr>
<td>de Andrade 1996; 2004 Galvão 2003</td>
<td>7-12</td>
<td>65</td>
<td>P</td>
<td>60</td>
<td>36m</td>
<td>(atEIA)</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.5</td>
<td>60</td>
<td>-</td>
<td></td>
<td>36m</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>17%</td>
<td>29%</td>
<td>20%</td>
<td></td>
<td>6%</td>
<td>40%</td>
</tr>
<tr>
<td>Sosa Estani 1998; 2002</td>
<td>6-12</td>
<td>51</td>
<td>P</td>
<td>60</td>
<td>48m</td>
<td>(EIA,IHA)</td>
<td>(xeno)</td>
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<tr>
<td></td>
<td></td>
<td>5</td>
<td>60</td>
<td>-</td>
<td></td>
<td>0%</td>
<td>51%</td>
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<td></td>
<td></td>
<td>14%</td>
<td>20%</td>
<td>20%</td>
<td></td>
<td>4%</td>
<td>5%</td>
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<tr>
<td>Silveira 2000</td>
<td>7-12</td>
<td>7-12</td>
<td>60</td>
<td>2</td>
<td>8 a 20y</td>
<td>(CFT,IHA,IIF)</td>
<td>(PCR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-7</td>
<td>60</td>
<td>7-8</td>
<td></td>
<td>10%</td>
<td>10%</td>
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<td></td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>20%</td>
<td>0/2</td>
</tr>
<tr>
<td>Sosa Estani 2002</td>
<td>1-4</td>
<td>83</td>
<td>5</td>
<td>30</td>
<td>20m / 60m</td>
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<tr>
<td></td>
<td></td>
<td>42%</td>
<td>0%</td>
<td>0%</td>
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<td></td>
<td></td>
<td>92%</td>
<td>33%</td>
<td>92%</td>
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<td></td>
<td></td>
<td>69%</td>
<td>0%</td>
<td>69%</td>
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<tr>
<td>Schijman 2003</td>
<td>3-17</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>36m</td>
<td>(EIA,IHA)</td>
<td>(PCR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-8</td>
<td>-</td>
<td>-</td>
<td></td>
<td>12%</td>
<td>12%</td>
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<tr>
<td>Streiger 2004</td>
<td>1-14</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td></td>
<td>(IHA,IIF,TAD)</td>
<td>(xeno)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NT¶</td>
<td>-</td>
<td>-</td>
<td></td>
<td>4-24y</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Age (years)</td>
<td>Benznidazole</td>
<td>Nifurtimox</td>
<td>Design*</td>
<td>Follow-up (months)</td>
<td>Efficacy Measurements†</td>
<td>Parasitology Test (% pos)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>n Dose</td>
<td>n Dose</td>
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<td>Lost in FU (%)</td>
<td>Serology Test (%) neg</td>
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<td></td>
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<td>(mg/kg/d)</td>
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<tr>
<td>Flores Chavez</td>
<td>5-10</td>
<td>64</td>
<td>5</td>
<td>30</td>
<td>7</td>
<td>nB</td>
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<tr>
<td>2006</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12-15</td>
<td>45-60</td>
<td>31%</td>
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<td></td>
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<td>62%</td>
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<td>7-8a:58%</td>
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<td></td>
<td>9-14a:43%</td>
</tr>
<tr>
<td>Duffy 2009</td>
<td>18d-18a</td>
<td>35</td>
<td>8</td>
<td>69</td>
<td>-</td>
<td>nC</td>
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<td>Source: IRD 2009</td>
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</tr>
</tbody>
</table>
Further to the data presented so far, there are data presented on children and adolescents treated in the indeterminate chronic phase in field conditions in projects from the Doctors Without Borders / Médecins Sans Frontières (MSF) reported by Yun et al.\textsuperscript{68} (2009). For 10 years, MSF implemented Chagas disease control programs for Chagas disease at Yoro, Honduras (1999-2002), Olapa, Guatemala (2003-2006), Entre Ríos, Bolivia (2002 – 2006) and Sucre, Bolivia (2005-2008), focused on the diagnosis and treatment of patients up to 18 years old.

Diagnoses were confirmed by positive results in two different serology tests (conventional ELISA and recombinant IHA, and IIF for indeterminate or discordant findings). Patients testing positive for \textit{T. cruzi} were treated with benznidazole 7.5 mg/kg/day administered two or three times a day for 60 days. The efficacy of the treatment was assessed between 18 and 36 months post-treatment through convention ELISA serology, confirming the negative findings through recombinant ELISA. According to the WHO protocol, patients presenting two non-reactive serology tests (conventional and recombinant ELISA) on the same sample and on the same day were rated as cured.

Table 12 summarizes some characteristics and findings obtained in each Program.

\textbf{Table 12- Characteristics and findings obtained by the Chagas Disease Control Programs implemented by the MSF between 1999 and 2008.}

<table>
<thead>
<tr>
<th>Program Duration</th>
<th>Yoro, Honduras</th>
<th>Olapa, Guatemala</th>
<th>Entre Rios, Bolivia</th>
<th>Sucre, Bolivia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated</td>
<td>&lt;12 years</td>
<td>&lt; 15 years</td>
<td>&lt; 15 years</td>
<td>&lt; 18 years</td>
</tr>
<tr>
<td>Patients with confirmed diagnoses</td>
<td>232</td>
<td>124</td>
<td>1,475</td>
<td>1,145</td>
</tr>
<tr>
<td>Patients treated</td>
<td>232*</td>
<td>124</td>
<td>1,409</td>
<td>1,040</td>
</tr>
<tr>
<td>Negative seroconversion rate</td>
<td>87.1</td>
<td>58.1</td>
<td>5.4</td>
<td>0</td>
</tr>
</tbody>
</table>

\textit{* one patient with acute Chagas disease
Source: Yun et al. (2009)}

There was a marked difference in results among the various programs. At Yoro, the seroconversion rate was 87.1% (202/232) after 18 months of follow-up and 92.7% (215/232) after 36 months, indicating that the treatment was extremely efficacious. In a more detailed analysis of the Program at Yoro, Honduras, Escriba et al.\textsuperscript{69} (2009) showed an overall seroconversion rate at 18 months of 88.2% (95% CI, 84-92.4%), rising to 93.9% (95% CI, 90.8-97%) at three years. However, this increase was not statistically significantly. Of the 229 patients who were monitored for more than 18 months, 85.2% (95% CI, 80.5-89.8%) presented a reaction in the antibody titrations (recombinant ELISA by optical density) of ≥
75% in relation to the initial values, and 93.4% (95% CI, 90.2-96.7%) after three years. This difference is statistically significant. No material differences were noted by gender or age range in the seroconversion rate and anti *T. cruzi* antibody titers.

At Olopa, the seroconversion rate after 18 months was 58.1% of patients for whom data were available (25.5% of the cohort patients or 18/31), also suggesting that the treatment was efficacious.

The seroconversion rates were lower at the two centers in Bolivia. In Entre Ríos, preliminary findings indicated a seroconversion rate of 5.4% (59/1,101) post-treatment up to 60 months post-treatment, with 950 patients monitored for a period of more than 18 months. The seroconversion rates during the follow-up at 18 to 60 months were higher in the lower age group (24.2% [16/66] among children < 5 years, 4.6% [14/305] in the age group of 5 to 9 years old and 1.9% [12/638] in the 10 to 14 years old age range). At Sucre, none of the 276 patients monitored for a period of 9 to 27 months post-treatment, presented seroconversion.

According to Yun *et al.*, these differences in the seroconversion rates may be explained by i) the delay in negativisation by conventional serology, which may take between 5 to 10 years in Latin America; ii) different susceptibility to treatment of the various parasite lineages (predominance of type I *T. cruzi* in Central America type II in South America); iii) potential differences in treatment efficacy as a function of the proximity of the acute phase; and iv) constraints of data analyses due to in age groups and post-treatment follow-up times.

**10.1.4 Population Pharmacokinetics Study in Children 0-12 years**

There is an absolute lack of information on Benznidazole PK data for pediatric population and its relationship with treatment safety and efficacy. In order to respond to this need, DNDi and partners joined efforts in the design and implementation of this clinical trial “Population Pharmacokinetics Study of Benznidazole in Children with Chagas’ Disease” (clinicaltrial.gov registry # NCT01549236; Appendix 8 – clinical study protocol).

The Principal Investigator of the study is Dr. Jaime Altcheh, a well-recognized specialist in pediatric Chagas disease. Five participating sites took part in this clinical trial (Hospital de Niños Ricardo Gutiérrez, Instituto Nacional de Parasitología in Buenos Aires, and sites in Jujuy, Salta and Santiago del Estero).

The target study population of 80 patients was reached on 14-Jun-12 (LPI) and last patient last visit was performed on 10-Aug-12. This is the first pharmacokinetics study with benznidazole carried out in peadiatric population younger than 2 years old.

The trial is designed as open, uncontrolled, single group assignment clinical trial, stratified by age groups of population pharmacokinetics study in children 1 day to 12 years old adopting treatments with Bz 12.5mg or 100mg Bz tablet (LAFEPE), 7.5 mg/Kg/day per oral in two daily doses, for 60 days.
Newborns-2 years-old children have been included as they represent the population of congenital cases. Children 2-12 years-old have also been included as the target population, to represent those who may have been infected via congenital or vector-borne transmission, and usually present with the early chronic indeterminate form of the disease.

Population pharmacokinetics has been chosen as the study design as it would minimise the number of samples in the pediatric population. The dearth of PK in adults and lack of information on the variability in the target population does not allow for power calculations and the use of optimal sampling design for definition of the timing of samples. Experts reviewed the available information and recommended sparse sampling, with 4 PK samples distributed over the absorption phase (1 sample), steady-state (2 samples) and elimination phase (1 sample), and 2 additional micro-samples collected in filter-paper at steady-state. With a total of 6 PK measurements per patient and a total of 80 patients stratified by age, it is expected that PK curves and variability can be drawn with an adequate level of precision.

Diagnosis of T. cruzi infection was confirmed at entry by direct microscopic examination or at least two positive conventional serologies (ELISA, IIF or HAI). Subject enrolment was stratified by age GROUPS: 41 patients in the group of newborns to 2 years (minimum of 8 newborns) and 40 patients in the group of > 2-12 years.

For the pharmacokinetics (PK) sampling five blood samples per patient, representing a total of approximately 100µL of blood, were collected in filter-paper at randomly pre-assigned time-points as follows:
- Day 0 (absorption phase one sample at randomly selected time-point 2-5hs after first dose),
- Steady State phase (two samples to be collected: one sample at Day 7, and another at day 30; both at randomly selected time-points from pre-dose to 8 hours post-dose)
- End of treatment AT DAY 60 (two samples at randomly selected time-points 12 – 24 hours after last dose).

Benznidazole in plasma was measured by HPLC-MS-MS and POP-PK modeling was performed with NONMEM software (nonlinear mixed effects analysis).

Clinical study report is currently in preparation. A total of 83 patients were screened for the study, of which 2 patients resulted in screening failures and a total of 81 subjects enrolled. Seventy six (76) patients completed the study treatment and 5 subjects discontinued. PCR analysis showed no treatment failures, with 100% negativisation at end of treatment.

10.1.5 Conclusions on efficacy

Despite the heterogeneity of the studies presented in terms of objectives, geographic location, age ranges, numbers of children included in these studies, therapeutic schemes used, duration of post-treatment monitoring and the cure control tests deployed, there is clear evidence of the efficacy of benznidazole for treatment of children infected by T. cruzi,
particularly those less than a year old, targeted by the pediatric formulation, and suggesting greater efficacy for early treatment.

For the treatment of congenital infections, the serum-negative rates vary from 87% (Schijman et al., 2003) at 36 months (100% in the 0 to 3 months old group) to 100% (Russomando et al., 1998) at 24 months in children up to two years old.

For the treatment of acute infections, these rates vary from 76% (Cançado et al., 2002) at 13 years in children under 10 years old to 100% (Ferreira, 1988) at 15 years in children between 2 and 18 years old.

For early chronic phase treatment, the studies show significant variability, with a serological cure rate than may be less than 10% (Yun et al., 2009; Ferreira, 1990; Flores-Chavez et al., 2006) but possibly over 60%. At this phase of the disease, it is difficult to determine serological response, as conventional serology may remain positive for a period of 5 to 10 years after treatment. Two placebo-controlled randomized clinical trials conducted with children between 6 and 12 years old, with follow-up periods lasting several years, presented very positive outcomes, with seroconversion rates of around 60% (Sosa Estani et al., 1998; follow-up at 48 months; de Andrade et Al, 1996; follow-up at 36 months), reaching 89% at 6 years old (de Andrade et al, 2004) and 77% at 9 years old (Sosa Estani et al., 2002).

Finally, as it is described in section 11.7 (Update information about safety preliminary results of Population-Pharmacokinetics study in Argentina) the study just concluded in Argentina which brings evidence in relation to efficacy of benznidazole 12.5mg in children younger than 2 years old (including newborns) showing 100% cure rates measured by PCR after treatment.

11. Summary of comparative evidence on safety*:

11.1 Safety Overview

11.1.1 Introduction and Overview

The literature review presented in this section was presented as part of the dossier for submission for marketing authorization (registration) by the Brazilian Drug Regulatory Authority (ANVISA) in March 2011. Additional information and recent publications were incorporated in this summary.

Considering that benznidazole is a medication with well-established use for the treatment of Chagas disease, with well documented efficacy, safety and tolerability in the literature, and with the adult tablet already registered by the Brazil's Drug Regulatory Authority (ANVISA). In addition, as the pediatric formulation consists of the same qualitative composition as the adult 100 mg tablet, and as its dosage follows the recommendations followed by the Brazilian Ministry of Health and the WHO (5 – 10 mg/kg/day administered twice a day for 60
days), *in vivo* clinical trials were not deemed necessary to support the registration of the new pediatric dosage form.

The dossier confirming the clinical safety of the new pediatric tablet consists of a review of published benznidazole safety data in general, with a comparison of the individual data resulting from clinical trials resulting from clinical trials conducted with the adult population and the pediatric population that is the target, indicating better tolerability for this medication in the pediatric population.

However, as mentioned previously, the pediatric formulation development plan includes conducting *in vivo* clinical pharmacology trials, during which aspects related to clinical tolerance and safety were observed and analyzed, in order to contribute to the evidence already available in the literature on the pediatric population, monitoring the frequency and intensity of adverse reactions in children and / or notifying new adverse events. A safety and tolerability assessment plan under usage conditions will also be implemented, as part of the risk management plan presented to ANVISA.

### 11.2 Safety and Tolerability of Benznidazole

The tolerability of benznidazole is considered as generally better in children and for patients in the acute phase, regardless of age range, than for adults in the chronic phase. There is limited evidence regarding the safety of benznidazole for children, particularly with congenital and acute infections. However, the reported data indicates excellent tolerability in children under one year old, with no significant of adverse reactions.

Most of the existing data relates to tolerance and safety in children during the indeterminate chronic phase and for adults in the chronic phase. For children in the indeterminate phase, good tolerability has been demonstrated, with treatment interruption rates due to adverse events varying from 0% (Steiger *et al.*, 2004; Sosa Estani *et al.*, 2002) to 10% (Sosa Estani *et al.*, 1998), while for adults in the chronic phase, the treatment drop-out rate due to the appearance of adverse reactions is generally higher, although varying by author: 0% (Sanchez *et al.*, 2008; Viotti *et al.*, 1994), 9.5% (Pinazo *et al.*, 2010), 11.5 % (Coura *et al.*, 1997), 13% (Viotti *et al.*, 2006), 18% (Gallerano *et al.*, 2000; Fabbro *et al.*, 2007; Sosa Estani *et al.*, 2004), 25% (de Pontes *et al.*, 2010) and 41 % (Levi *et al.*, 1996), indicating greater intolerance for benznidazole.

### 11.3 Adverse effects during treatment with Benznidazole

Adverse reactions are frequent, generally occurring in 25% to 30% of patients. Due to toxicity, treatment is not recommended during pregnancy, and for women of child-bearing
age not taking contraceptives, except for severe acute cases. Indications for patients with severe disease must be carefully assessed.

The most frequent adverse reactions are d**ermopathies due to hypersensitivity** that are not dose-dependent, generally appearing on the ninth day of treatment, and expressed in the form of pruriginous, non-blisterring polymorphous erythema, followed by scaling and peeling. In < 20% of patients, the dermopathies are mild, not requiring the interruption of the treatment. In < 5%, they may be moderate, accompanies by fever and purpura, with the recommended temporary interruption of treatment, to be reintroduced as indicated by clinical tolerance after treatment with antihistamines or corticosteroids. In < 1% of patients, dermopathies may be severe, requiring the suspension of the treatment.

Another frequent adverse reaction is dose-dependent **peripheral polyneuropathy**, generally appearing after the fifth week of treatment. This occurs in less than 1% of cases, appearing in the form of paresthesia or peripheral polyneuritis symptoms, particularly after prolonged treatment. It is advisable to interrupt the treatment until the symptoms improve.

**Gastrointestinal disorders**, such as nausea, vomiting, diarrhea and intestinal cramps, may occur during the initial stage of treatment in around 10% of cases, and must receive symptomatic clinical treatment, with no need to interrupt the treatment or lower the dose.

Other side effects are rare, such as ageusia, which may occur in less than 0.5% of cases, generally towards the end of treatment, and medullar hypoplasia, which occurs in <1% of cases, generally between the 20th and 30th day of treatment. In case of ageusia or leukopenia, granulocytopenia, neutropenia, agranulocytosis and thrombocytopenia, the treatment must be interrupted.

Some authors also noted other adverse reactions such as headache, dizziness, fatigue, arthralgias, generalized edema or in the extremities, anorexia, and an increase in hepatic enzymes. Table 13 summarizes the adverse events identified in the literature.

**Table 13- Main adverse events observed during treatment with benznidazole**

<table>
<thead>
<tr>
<th>Systems and Organs</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Dermatological</td>
<td>• Maculo-papular cutaneous eruptions</td>
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<tr>
<td></td>
<td>• Erythematous Plaques</td>
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<td></td>
<td>• Rash</td>
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<td></td>
<td>• Itching</td>
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<td></td>
<td>• Blistering eruptions</td>
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<td></td>
<td>• Peeling skin</td>
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<tr>
<td>Neurological (central and peripheral nervous system)</td>
<td>• Paresthesia</td>
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<td></td>
<td>• Hypoesthesia</td>
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<td></td>
<td>• Tremors</td>
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<td></td>
<td>• Dizziness</td>
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<td></td>
<td>• Headaches</td>
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<td></td>
<td>• Psychiatric manifestations</td>
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<tr>
<td>Gastro-intestinal</td>
<td>• Nausea</td>
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</tbody>
</table>
* based on classification defined by the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE version 3.0).

One author also reported a case of jaundice with alterations to the bilirubin dosing in the serum after preventive treatment with benznidazole of a laboratory accident.82

Another author reported a case of disabling pain syndrome in a Bolivian woman (31 years old) in the course of treatment with benznidazole.83

The teratogenetic potential of benznidazole has been reported in some in vivo trials with animal models, confirming that treatment is counter-indicated for pregnant women and women of child-bearing age not taking some type of contraceptive.84,85,86

The toxicity of benznidazole in several organs has also been described in vivo with animal models.87,88,89,90

With regard to the potential genotoxicity of do benznidazole, some authors report the induction of chromosome aberrations during in vivo trials with animal models85,91,92,93 and in human cells in vitro,87,94,95 at doses close to the plasma concentration limits of treated patients.97 Gorla et al. (1988) noted a slight but significant increase in micronucleus formation and the appearance of chromosome aberrations in lymphocyte cultures for two groups of children with Chagas disease, before and after treatment with benznidazole.87,98

At the same time, Gorla & Castro (1985) did not report any significant increase in the formation of micronuclei in the bone marrow or spleen lymphocytes of rats treated with benznidazole,87,96 while Souza et al. (1991) did not report any significant increase in the

<table>
<thead>
<tr>
<th>Symptom Category</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Vomiting</td>
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<td>Diarrhea</td>
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<td>Abdominal pain</td>
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<td>Epigastric pain</td>
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<td>Anorexia</td>
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<td>Dry mouth</td>
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<td>Ageusia</td>
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<td>Arthralgia</td>
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<td>Myalgia</td>
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<td>Fever</td>
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<td>Asthenia</td>
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<td>Increased appetite</td>
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<td>Generalized edema</td>
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<td>Edema in the extremities</td>
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<tr>
<td>Lymphadenopathy</td>
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<td>Leukopenia</td>
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<td>Thrombocytopenia</td>
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<td>Granulocytopenia,</td>
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<td>Neutropenia,</td>
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<tr>
<td>Agranulocytosis</td>
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<tr>
<td>Alteration to the hepatic enzymes</td>
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frequency of chromosome aberrations in bone marrow cells of the appearance of micronuclei in the peripheral blood cells of rodents receiving different dosages and with different exposure times to benznidazole. Similarly, the clastogenic and mutagenic effects were reversible, and were not accompanied by any clinical manifestations in the study conducted by Moyá & Trombotto (1988) of children treated with benznidazole and nifurtimox.

Other authors also identified an increased risk of developing lymphomas in animal models in vivo. However, no increase in the rate of human lymphomas was reported among the large number of patients treated, despite a higher rate of neoplasias reported in the few patients infected by T. cruzi with heart transplants. The toxicity of benznidazole is closely linked to its trypanocide mechanism, deployed through a covalent binding of free radicals produced by the nitro-reduction of macromolecules and their interaction with the host DNA.

11.4 Adverse events in adults

Adverse events occur frequently among adults taking benznidazole. However, among adults treated with benznidazole, the frequency and type of adverse events most frequently notified varied among authors.

In the study conducted by Gallerano et al. (2000) of 130 patients between 10 and 79 years old (average age 33, 4 ± 14.2) treated with benznidazole at 4 to 8 mg/kg/day, for 45 to 60 days, adverse events were observed in 32% of patients treated with benznidazole, mainly gastric intolerance, cutaneous eruptions and peripheral neuropathy, also observed in the study by Coura et al. (1997), including 26 patients receiving benznidazole at doses of 5m/kg/day for 30 days. However, in this latter study, the authors identified the appearance of mild adverse events in 29.1% patients treated with placebo (aerophagia, post-prandial fullness, anorexia, headache, drowsiness and lassitude), with two patients (8.3%) abandoning treatment.

Fabbro et al. (2007) reported adverse events in 27% of 33 patients treated with benznidazole at a dose of 5m/kg/day for 30 days, consisting of maculo-papular erythema (18% or 6/33), edema (9% or 3/33), nausea (3% or 1/33), headache (3% or 1/33), itching (3% or 1/33) and a slight increase in the hepatic transaminases (3% or 1/33).

The main adverse effects noted by Viotti et al. (2006) in 283 patients between 30 and 50 years old completing treatment with benznidazole at 5m/kg/day for 30 days (55/246 or 22%) were allergic dermatopathy; mild (36 patients or 14.6%), and moderate (2 patients or 0.8%), gastrointestinal disorders (11 patients or 4.5%); headache (3 patients or 1.2%); itching (2 patients or 0.8%) and fever (1 patient or 0.4%). Also in this study, 33 of the 37 patients who interrupted the treatment, dropped out due to the appearance of severe allergic dermatopathy, while the other 4 were prompted by gastrointestinal disorders.
In another study by Viotti et al. (1994) of 131 patients, with an average age of 46 years, treated with benznidazole (5 mg/kg/day) during 30 days, adverse reactions were noted in 20% of those patients, with the most frequent being moderate allergic dermatitis (77%), gastrointestinal intolerance (16%), widespread allergic dermatitis (7%). Other less significant effects were headache, itching and edema of the lower extremities.

The frequency of the adverse reactions noted in these studies matches the estimated frequency in the Brazilian Consensus on Chagas Disease, hovering between 20% and 30%. However, three studies identified higher rates of adverse reactions in adults.

In the study conducted by Pinazo et al. (2010) of 105 patients between 16 and 58 years old (average age 38.7 years) treated with benznidazole at 5 mg/kg/day for 60 days, 57.1% (60/105) presented adverse reactions, with 47% of them (27/60) presenting more than one adverse reaction. The most frequent adverse reactions were headache (56.2% or 59/105 patients), dermatopathies (50.5% or 53/105 patients), notably urticaria, rash and itching, anorexia (40% or 42/105 patients), joint disorders (36.2% or 38/105 patients), asthenia (30% or 32/105 patients), paresthesias (27.6% or 29/105 patients) and gastrointestinal disorders (15% or 16/105 patients), mainly epigastralgia. Ten patients halted the treatment due to the appearance of adverse reactions, eight of whom presented severe urticaria and fever, with two dropping out due to digestive intolerance.

In a study of 18 patients between 19 and 41 years old (average age 25 years) treated with benznidazole at 5mg/kg/day for 60 days, Sanchez et al. (2008) noted adverse events in 67% of these patients, consisting of dermatopathy due to hypersensitivity (39%), headache (33%), gastrointestinal disorders (22%), arthralgia and peripheral neuropathy (11%), with a slight increase in the hepatic enzymes (11%) and asthenia (6%).

In a study conducted by Pontes et al. (2010) with evaluation of adverse reactions in 32 adults patients treated with benznidazole at 5 mg/kg/day, for 60 days, adverse events were observed in 87.5% of these patients. This study identified 20 different types of adverse reactions, with the most frequent being itching (50%), paresthesia (43.8%), asthenia (37.5%), headache (34.4%) cutaneous rash (31.3%) and peeling skin (25%). The dermatological system was the most severely affected, with 35% of the symptoms, followed by the central and peripheral nervous systems with 22% of the reported symptoms.

Differences in the frequency in the adverse reactions rates among these studies may be due to the prolonged durations of the treatment in the last three of those trials mentioned above (60 days versus 30 days).

**11.5 Adverse events in children**

As mentioned previously, the data available in the literature indicated better tolerability for benznidazole among children, with fewer adverse effects appearing, compared to adults. The evidence is detailed below taken from studies conducted with children with congenital infections, during the acute and early chronic phases of the disease.
11.5.1 Children with congenital infections

In the study conducted in Bolivia by the IRD of 111 new-born infants diagnosed with congenital infections at birth and treated with benznidazole (59 with a therapeutic scheme of 2.5 mg/ kg twice a day for 60 days and 52 with therapeutic scheme of 7.5 mg/ kg once a day for 30 days), no reports were found of any adverse reactions (Chippaux, et al., 2010). A similar finding was reported in the study by Russomando et al. (1998) that did not identify any adverse reaction or toxicity when monitoring six children treated with benznidazole (7 mg/kg and per day, taken twice a day for 60 days).

Other studies of children with congenital infections addressed in the efficacy analysis section did not provide sufficient information on the safety and tolerability aspects of benznidazole. Despite the limited amount of information, these studies indicate the excellent tolerability and safety of benznidazole in new-born infants with congenital infections.

The authors suggest that the nitro-reduction metabolism capacity of new-borns, which is responsible for toxicity, is low, while susceptibility to T.cruzi remains unaltered. This would explain the excellent tolerability of benznidazole among babies, despite the excessive high doses to which they are exposed, due to inaccurate splitting of the 100 mg tablet.

11.5.2 Children with acute infections

In the study conducted by Barclay et al. (1978) of 139 children (ages not stated) with acute infections treated with two therapeutic schemes (benznidazole, progressive doses of up to 7.5 mg-10 mg/ kg/day for 30 days and benznidazole at a uniform dose of 5 mg/kg/ day for 30 days), adverse events were noted in 18% of these children, with 23 of them presenting dermatological manifestations (morbilliform exanthema), none of them severe, and vanishing with the temporary suspension of the treatment for a few days; and two children with complaints of arthralgia, although with no signs of inflammation.

Other studies in children with acute infections addressed in the efficacy analysis section did not mention the safety and tolerability aspects of benznidazole related directly to the study.

11.5.3 Children with indeterminate chronic infections

The literature provides more information on adverse reactions occurring in children at the early indeterminate phase. We highlight and detail six studies below.

In a double-blind randomized, control clinical trial conducted by Andrade et al. (1996) of 129 children between 7 and 12 years old, 64 were treated with benznidazole at 7.5 mg/kg/day for 60 days, and 65 with placebo. The treatment was well tolerated, interrupted for only one patient (1.6%) due to the appearance of maculo-papular cutaneous eruptions and severe itching. Dermatological reactions occurred more frequently in the experimental
Minor adverse events such as nausea, anorexia, headache, epigastric pain and arthralgia occurred in less than 5% of these patients, with no significant differences between the two groups. No signs of toxicity were identified. The anemia rate (Hb < 110g/L) proved similar in both groups, and no patient developed leukopenia or neutropenia. Hepatic and renal function tests remained within the normal limits throughout the entire study.

During the double-blind randomized control-case clinical trial conducted by Sosa Estani et al. (1998) of 106 children between 6 and 12 years old, with 55 of them treated with benznidazole at 5 mg/kg/day for 60 days and 51 children with placebo, the treatment was well tolerated, although it had to be interrupted due to moderate adverse events for six patients in the experimental group (10%). The symptoms regressed after suspending the treatment. Less than 20% of these patients reported adverse events that included intestinal cramps, maculo-papular cutaneous eruption, headache, anorexia, vomiting, nausea, diarrhea, dizziness, paresthesia and mild hand tremors. However, a significant difference between the two groups was identified only with regard to intestinal cramps and cutaneous eruptions (p=0.05) which appeared respectively at around the 11th and 19th days of treatment. No severe adverse events were notified for any patient. Additionally, no signs of toxicity were observed, with the laboratory examinations remaining within the normal limits for both groups.

In a supplementary follow-up study of the serological progress of 252 Argentine children treated with benznidazole, including 46 of the children participating in the clinical trial mentioned above, Sosa Estani et al. (2002) did not identify any long-term adverse events that could be attributed to benznidazole in this group. In a group of N 147 children between 1 and 14 years old, treated for 30 days in 1994, 4.8% of the children presented some adverse reaction during treatment, and in the group of 40 children between 1 and 14 years old treated for 30 days in 1995, no adverse events were notified. In both these groups, treatment was not interrupted due to adverse reactions.

In a cohort study conducted with 95 children between 1 and 14 years old, with 64 of them treated with benznidazole at 5 mg/kg/day, split into two daily dos for 30 days, Streiger et al. (2004) noted good tolerability for the treatment which had to be interrupted for two children (2/53 or 3.8% of children who had at least one post-treatment control) due to benznidazole intolerance. In the group treated with benznidazole, the authors identified adverse events such as vomiting, widespread erythema with edema and itching without specifying the level of severity nor the frequency of occurrence.

In the course of the Chagas Disease Control Program implemented by the MSF at Yoro, Honduras, Olapa, Guatemala, Entre Rios and Sucre, Bolivia, focused on the diagnosis and treatment of patients up to 18 years, adverse reactions to benznidazole were recorded by type and severity. Table 14 presents a detailed listing of the number of patients with adverse events by program and severity level.
A higher rate of adverse reactions was noted in the programs conducted in Central America, compared with the Bolivian programs. However, most of the adverse events were mild, with a higher proportion of severe events (10.8%) noted in Sucre. The proportion of patients interrupting treatment due to adverse events is low (<6%), indicating good tolerability for benznidazole.

Severe reactions reported at Yoro were neurological (neuromuscular disorders of the lower limbs appearing after six weeks of treatment in three patients); neuromuscular (2/63) and dermatological (1/63) in Olopa. In Entre Rios and Sucre severe adverse reactions occurred in 6 and 41 patients respectively, particularly a case of Lyell’s syndrome in a 13-year old girl, which occurred in the 34th day of treatment, and 1 case of Stevens Johnson syndrome.

At Yoro, the most frequent adverse reactions were 26 gastrointestinal disorders (.8%), mainly epigastralgia and abdominal pain, and to a lesser extent nausea and / or vomiting and anorexia, followed by cutaneous reactions (13%, mainly itching and maculo-papular exanthema less frequently), as well as neurological (10.4%). At Olopa, the most frequent adverse reactions were dermatological (26%), gastrointestinal (25%), neuromuscular (23%) and assorted (26%). At Entre Rios, the main adverse reactions were dermatological (56%), gastrointestinal (25%), neuromuscular (18%), of which 11% were mixed. At Sucre the adverse events were predominantly dermatological (68.5%).

The authors also identified a significant difference in the proportion of adverse reactions by age brackets (chi-square test) in the two Bolivian centers. This difference was not noted at Yoro and Olapa.

In the Bolivian programs, the risk of developing adverse reactions to the treatment rose with age (12% of adverse reactions in children under five years old, compared to 25% in the age
range between 10 and 14 years at Entre Rios; 13.4% in children under five years old, compared to 50% in the age bracket between 15 and 18 years old at Sucre). And also at Sucre, a higher treatment interruption rate was noted, due to adverse effects among older children (0% in children under five years old, compared to 8.6% in the age range between 15 and 18 years old) (Yun et al., 2009).

These evidences corroborate the greater tolerability and safety of benznidazole among small children, noted by several authors.

Another prospective cohort study published recently, conducted between 2003 and 2007 at the Ricardo Gutierrez Pediatric Hospital in Buenos Aires (Argentina) by Altcheh et al. 2011 described adverse events in 107 children between 10 days and 19 years old (average of age 6.9 years), diagnosed with asymptomatic infections of T. cruzi, treated with benznidazole at 5 to 8 mg/kg/day, administered two or three times a day for 60 days, and monitored for a period of three years. Among them, 62 adverse events were noted, related to treatment in 44 children (41.1% of patients), mostly mild (80.6%) and moderate (16%). Only two adverse events (3.2%) were rated as severe (widespread rash). In this cohort, seven patients (6.5%) abandoned the treatment due to the adverse events (6 dermatological and one gastrointestinal), while six of them were more than seven years old. The adverse events resulted in the temporary suspension of treatment for seven children (4 due to the appearance of rash, 2 for gastrointestinal discomfort and 1 for headache), although all of them later returned and completed the treatment with no other interruptions. Among them, 71% of the adverse events noted were clinical, being dermatological for 21% of the cases (22/107 children), mainly rash and eczema; gastrointestinal in 8.5% of these children (9/107); neurological (central nervous system) in 9% of these children (10/107), mainly headaches; and neuromuscular for 2.8% of these children (3/107). Alterations in the laboratory examinations accounted for 29% of the adverse events recorded, with the most frequent being hematological (12 occurrences), mainly eosinophilia and leukopenia, and metabolic (6 occurrences), mainly an increase in hepatic enzymes.

The average duration of the adverse events was 8.2 days (95% CI: 4.1–12) and in 73% of the patients, they occurred during the first ten days of treatment, with some differences in the average appearance time due to the type of event. Neurological adverse events appeared during the first two days, on average, followed by gastrointestinal events (average of five days) and dermatological events (average of nine days, with a statistically significant difference compared to the neurological events).

The statistical analysis also showed that the occurrence of adverse events varied by age, being more frequent among older children. The average age of the children presenting adverse reactions was 9.9 years (95% CI: 8.2–12), significantly higher than the average age of the children with no adverse events (4.8 years [95% CI: 3.7– 6.0]; p<.001, t test). Moreover, 77.3% of the adverse events occurred in children more than seven years old, while only 18% of children less than two years old (7/38) presented adverse events, at rates significantly lower than those noted for older children (18% vs 53%; P <.001, test X2).103
This evidence matches the observation in the studies presented previously, in terms of the better tolerability of benznidazole in children, with the occurrence of a higher proportion of mild adverse events, and the increased risk of their appearance with rising age, with the risk being lower in young children, who are the target public of the pediatric formulations.

Table 15 summarized the benznidazole safety and tolerability data for children in the studies presented above.
Table 15 – Overview of the benznidazole safety and tolerability data for children

<table>
<thead>
<tr>
<th>Reference</th>
<th>Phase Age (in years)</th>
<th>Sample</th>
<th>Dose (mg/kg/d)</th>
<th>Time (days)</th>
<th>Administration/day</th>
<th>Adherence (%)</th>
<th>Number (%) of e patients abandoning treatment due to AE</th>
<th>Main adverse events and number (%) of patients</th>
<th>Number of severe adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chippaux (IRD) 2008 -2009</td>
<td>Congenital (&lt; one month)</td>
<td>59</td>
<td>5 7.5</td>
<td>60 30</td>
<td>2 1</td>
<td>80 (≥55d) 76 (≥25d)</td>
<td>?</td>
<td>- -</td>
<td>0 0</td>
</tr>
<tr>
<td>Russomando 1998</td>
<td>Congenital (&lt;2 y)</td>
<td>6</td>
<td>7-10</td>
<td>60</td>
<td>2</td>
<td>?</td>
<td>0</td>
<td>- -</td>
<td>0 0</td>
</tr>
<tr>
<td>Barclay 1978</td>
<td>Acute Children (?)</td>
<td>107</td>
<td>3-10† 5 30</td>
<td>? ?</td>
<td>- -</td>
<td>?</td>
<td>} dermatological 23/137 (17%)</td>
<td>- -</td>
<td>- -</td>
</tr>
<tr>
<td>de Andrade 1996</td>
<td>Chronic indeterminate (7-12)</td>
<td>64</td>
<td>7.5</td>
<td>60</td>
<td>2</td>
<td>98</td>
<td>1/64 (1.6%)</td>
<td>Dermatological 8/64 (12.5%) Digestive and assorted (5%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Sosa Estani 1998</td>
<td>Chronic indeterminate (6-12)</td>
<td>55</td>
<td>5</td>
<td>60</td>
<td>?</td>
<td>90</td>
<td>6/55 (10%)</td>
<td>Dermatological Digestive (20%?)</td>
<td>0</td>
</tr>
<tr>
<td>Sosa Estani 2002</td>
<td>Chronic indeterminate (1-14)</td>
<td>137</td>
<td>5 5</td>
<td>30 30</td>
<td>?</td>
<td>?</td>
<td>0 0</td>
<td>4.8% -</td>
<td>0 0</td>
</tr>
<tr>
<td>Reference</td>
<td>Phase Age (in years)</td>
<td>Sample</td>
<td>Dose (mg/kg/d)</td>
<td>Time (days)</td>
<td>Administration/day</td>
<td>Adherence (%)</td>
<td>Number (%) of e patients abandoning treatment due to AE</td>
<td>Main adverse events and number (%) of patients</td>
<td>Number of severe adverse events (%)</td>
</tr>
<tr>
<td>-----------</td>
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<td>-------------------------------------------------</td>
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<td>-------------------------------------</td>
</tr>
<tr>
<td>Streiger 2004</td>
<td>Chronic indeterminate (1-14)</td>
<td>53</td>
<td>5</td>
<td>30</td>
<td>2</td>
<td>87</td>
<td>2/53 (3.8%)</td>
<td>Dermatological Digestive</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td>Yun 2009 (MSF)</td>
<td>Chronic (Yoro &lt;12 y)</td>
<td>231</td>
<td></td>
<td></td>
<td></td>
<td>98.7</td>
<td>3/231 (1.3%)</td>
<td>116/231 (50.2%) Digestive (26.8%) Dermatological (13%) Neuromuscular (10.4%)</td>
<td>3 (1.3%) (2.6%)* neuromuscular</td>
</tr>
<tr>
<td></td>
<td>Chronic (Olopa &lt;15 y)</td>
<td>123</td>
<td></td>
<td></td>
<td></td>
<td>95</td>
<td>?</td>
<td>63/123 (50.8%) Dermatological (26%) Digestive (25%) Neuromuscular (23%) Assorted (26%)</td>
<td>3 (2.3%) (4.8%)* neuromuscular (2) dermatological (1)</td>
</tr>
<tr>
<td></td>
<td>Chronic (E. Rios &lt;15y)</td>
<td>1,409</td>
<td></td>
<td></td>
<td></td>
<td>90.5</td>
<td>28/1409 (2%)</td>
<td>361/1.409 (25.6%) &lt;5a:12% 10-14y:25% Dermatological (56%) Digestive (25%), Neuromuscular</td>
<td>6 (0.4%) (1.7%)*</td>
</tr>
<tr>
<td>Reference</td>
<td>Phase Age (in years)</td>
<td>Sample</td>
<td>Dose (mg/kg/d)</td>
<td>Time (days)</td>
<td>Administration/day</td>
<td>Adherence (%)</td>
<td>Number (% of patients abandoning treatment due to AE)</td>
<td>Main adverse events and number (%) of patients</td>
<td>Number of severe adverse events (%)</td>
</tr>
<tr>
<td>-----------</td>
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<td>------------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Altcheh, 2011</td>
<td>Chronic (Sucre &lt;18y)</td>
<td>1,040</td>
<td>5-8</td>
<td>60</td>
<td>2-3</td>
<td>87.7</td>
<td>61/1040 (5.8%) &lt;5a: 0% 15-18a: 8.6%</td>
<td>394/1.040 (37.9%) 5a: 13.4% 105-18y: 50% Dermatological (68.5%)</td>
<td>41 (3.9%) (10.4%)*</td>
</tr>
<tr>
<td>Altcheh, 2011</td>
<td>Asymptomatic (10 d – 19 y)</td>
<td>107</td>
<td>5-8</td>
<td>60</td>
<td>2-3</td>
<td>85.0</td>
<td>7/107 (6.5%) &lt; 7 a: 1 (0.9%) &gt;7a: 6 (5.6%)</td>
<td>44/107 (41.1%) &lt; 2a: 18% &gt;2ª: 53% Dermatological (21%) Digestive (8.5%) Neurological (CNS) (9%) Neuromuscular (2.8%) Laboratory (29% of AE)</td>
<td>2 (3.2%) dermatological</td>
</tr>
</tbody>
</table>

**Key**

Adherence = Percentage of treatments completed
† daily dose increased from 3 -to 7.5-10 mg/kg/day during the first 12 days and maintained at 7.5-10 mg/kg/day for a further 18 days
* Percentage x total adverse events
11.6 Conclusions on Safety and Tolerability

Despite the countless adverse reactions reported in the literature prompted by treatment with benznidazole, this is one of the only two treatment options available for Chagas disease, and is generally better tolerated than nifurtimox.

The data presented in this section shows better tolerability for benznidazole among children than for adults, with treatment abandonment rates due to adverse events being rare among new-borns, and no more than a maximum of 10% in children at the indeterminate phase, while these rates may rise to 40% among adults, usually hovering at around 20%.

Similarly, differences are noted in the frequency with which adverse reactions appear, comparing children and adults. While for the latter adverse reactions occur on average in between 20% and 30% of the patients, and may reach >60% with long-duration therapeutic schemes, the studies did not note any adverse reactions in new-borns. Among children of the indeterminate phase, the frequency with which adverse reactions appear varies between 5% and 50%, depending on the study, remaining within the standards noted in adults, although the scope of the age brackets encompassed by the studies is heterogeneous. However, the authors analyzing the occurrence of adverse reactions by age bracket (Yun et al., 2009; Altcheh et al., manuscript accepted for publication), noted significant differences, with lower occurrence rates among young children, indicating high risks of adverse reactions at older ages.

Furthermore, fewer neurological events were noted among children, who presented mainly dermatological and gastrointestinal adverse events, in contrast to adults.

It is thus believes that the pediatric formulation of benznidazole will offer good tolerability and safety, as its target public is less likely to present adverse events, while also allowing more accurate dosing within the established therapeutic margins of 5-10 mg/kg/day, in addition to reducing the risk of dose-dependent adverse events.

11.7 Update information about safety – preliminary results of POP-PK study in Argentina

As presented in Section 10.1.4, the “Population Pharmacokinetics Study of Benznidazole in Children with Chagas’Disease” started in April 2011 in Argentina as part of the follow-up strategy for the development of the pediatric formulation benznidazole 12,5mg. Details of study design were described earlier.
Preliminary results were presented in September 2012 at the International Congress of Tropical Medicine and Malaria. A total of 83 patients were screened for the study, of which 2 patients resulted in screening failures and a total of 81 subjects enrolled. Seventy six (76) patients completed the study treatment and 5 subjects discontinued.

Serious Adverse Event (SAE)'s occurred in 3 children (01 bronchitis, 01 gastroenteritis, 01 maculopapular exanthema) and the only the latter event was considered possibly related to the study drug. This subject was withdrawn from the study and the rash discontinued with treatment interruption. Adverse drug reactions were identified in 30 cases (14 rash, 11 gastroenteritis, 4 lab abnormalities and 1 maculopapular exanthema) and all recovered well. The age distribution of adverse events parallels previously published studies with lower occurrence rates among the very young, indicating high risks of adverse reactions at the older age group (2-12 years of age).

From those 76 patients who completed treatment, 45 children received Bz 12,5mg and 386 samples were collected for PK analysis. Close out visits have already taken place for all five participating sites and final study report is in preparation.

12. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group:

As presented in previous questions of this questionnaire, the two medicines indicated for the etiological treatment of Chagas disease are benznidazole and nifurtimox. According to the recent published WHO recommendations (October, 2011) for congenital Chagas disease, both medicines are indicated for the treatment of those cases.

Nifurtimox is provided by Bayer to WHO through a donation agreement[^iv]. WHO provides the medicines to countries free of charge.

Benznidazol tablet 12.5mg is a single-source medicine produced by Lafep. The development of this dosage form was a result of a partnership with DNDi established in 2008, leading to:

- The product available as package with 24 blisters of 10 tablets per blister, with a total of 240 tablets per package. This amount can be considered as one treatment for a child.
- A cost of US$ 7 per package of 240 tablets, excluding transportation cost.

The reference price available for the adult dosage form produced by Lafep was made public (July, 2012) at Brazilian Reais (R$) of 0,338 per tablet, which roughly means US$ 16,69[^v]/100 tablets (the adult package is 10 blisters of 10 tablets/blister).

[^iv]: Considering in 2012 currency rate US$1=R$2.
In relation to cost-effectiveness evidence, two publications were identified in the literature. They do not focus to the comparison of the two existing medicines (benznidazole and nifurtimox) for congenital Chagas disease cases, but rather on adoption of screening programs for congenital Chagas disease\(^{cv,cv}\).

Billot et al. (2005) studied the cost effectiveness of a control program of congenital Chagas disease in Bolivia. It was demonstrated that US$ 21 million per year for 2,718 infected new-borns reflected the direct and indirect costs estimated from the disease complications and death, from birth to adulthood. If a control program would detect and treat all cases, this would mean an investment of US$ 123 per new-born with the infection or US$ 1.2 per new-born.

Sicuri et al. (2011) developed an economic evaluation of to compare the adoption or not of an Active Detection of the Infection (ADI) of all pregnant women, as well as new-borns, from Latin America countries who are living in Spain. Several variables were adopted for this comparison and results were measured considering also QALYs (Quality-Adjusted Life Year) gained. Benznidazole was the medicine used for the cases of treatment. Comparison was made in relation to “test” or “not test” the mothers and also in relation to the newborn. Results have shown that it is more cost-effective to screen both mothers and newborns. For the first comparison – test or not test the mothers - the cost effectiveness ratio was 96 D /QALYs gained in the case of screening and 1675 D /QALYs gained in the case of no screening. For the second comparison, cost effectiveness was 22 D /QALYs gained in the case of screening the newborns and 125 D /QALYs gained in the case of no screening.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Benznidazole 12.5mg was registered for the treatment of infections due to \textit{Trypanosoma cruzi}. The product was approved as a new dosage form 12.5mg of the Benznidazole 100mg and also the new indication for children (Appendix 1).

The Brazilian National Regulatory Authority (ANVISA) granted this approval on December 12, 2011. Brazil is the only country worldwide where Benznidazole 12.5mg is registered.

The registration number is 25351.111801/2006-44 - 11/2011, and the official publication in the Brazilian Bulletin can be found at [http://www.in.gov.br/autenticidade.html](http://www.in.gov.br/autenticidade.html) under the code 10102011121200003

Benznidazole 12.5mg was approved for pediatric use, following years of off label use of the 100 mg tablet strength for the treatment of children.

Results from consultations in online search data bases (last update on 26/10/12) are the following:

- International Pharmacopoeia / WHO International Chemical Reference Substances (ICRS): Not available
- British Pharmacopoeia / British Pharmacopoeia Chemical Reference Substances (BPCRS): Not available
- United States Pharmacopeia / USP Reference Standards: Not available

As this standard was never officially available - it includes the Brazilian Pharmacopoeia 5 (2010) which has the monograph of the active principle ingredient (1), the manufacturer of the drug product used as reference the Benznidazole Work Standard (WS) assigned by the API manufacturer.

Work is planned in 2013 with US Pharmacopeia to develop USP and WHO reference standards.

15. Proposed (new/adapted) text for the WHO Model Formulary

The adaptation proposed as follows is in the WHO Model Formulary for Children 2010, in the section American trypanosomiasis (6.5.5.2) for the inclusion of the benznidazole 12.5mg as an additional dosage form. Proposed language *in italics* was obtained from the Lafepo package insert for benznidazole 12.5mg and 100mg (Appendix 6 and 7).

There is also a proposal of deletion (in WORD track-changes) in the neonate dose recommendation on the basis of the new WHO recommendation (2011).

**Benznidazole**

**ATC code:** P01CA02

**Tablet:** 100 mg

**Tablet:** 12.5 mg

**Indications:** Treatment of Chagas disease (American trypanosomiasis).

**Contraindications:** Pregnancy.

*This medicine should not be used in case of hypersensitivity to benznidazole or any other component is in the tablet composition. No health condition is considered an absolute contraindication to treatment. Benznidazole should only be administered to pregnant women in cases of an absolute medical indication.*

**Precautions:** Hepatic impairment; renal impairment; haematological conditions; history of neurological clinical manifestations; allergic condition to imidazoles; monitor
blood count, especially leukocytes, throughout treatment. *Benznidazole treatment in these conditions should be done under medical supervision.*

**Dose:**
Treatment of congenital, acute phase or early chronic phase of Chagas disease (American trypanosomiasis).

**Full-term neonate.** Dose must be given in 2–3 divided doses for 60 days.
Treatment of acute phase or early chronic phase of Chagas disease (American trypanosomiasis).

*Oral:*

**Infant or Child under 40 kg** 7.5 mg/kg daily in 2–3 divided doses for 60 days; 40 kg and over 5 mg/kg daily in 2–3 divided doses for 60 days.

*NOTE* Acute meningoencephalitis may require a dose of up to 25 mg/kg daily.

Treatment of chronic phase of Chagas disease (American trypanosomiasis).

*Oral:*

**Infant or Child** 5 mg/kg daily in 2–3 divided doses for 60 days.

*NOTE* The treating physician should determine the age limits and clinical suitability of this specific therapy.

*In children under twelve years old, especially those in the acute phase of the disease, it is recommended that doses of 5-10 mg / kg body weight be divided into two daily doses, for 60 days without interruption.*

**Summary of the weight categories per dose for tablets Benznidazole 12.5mg**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Recommended Doses (5-10 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between 2,5kg and &lt;5kg</td>
<td>1 tablet of 12.5mg twice a day for 60 days (total dose of 25mg/day)</td>
</tr>
<tr>
<td>Between 5kg and &lt;10kg</td>
<td>2 tablets of 12.5mg (25 mg) twice a day for 60 days (total dose of 50mg/day)</td>
</tr>
<tr>
<td>Between 10kg and &lt;15kg</td>
<td>3 tablets of 12.5 mg (37.5 mg) twice a day for 60 days (total dose of 75mg/day)</td>
</tr>
</tbody>
</table>

**Renal impairment:** Avoid use in renal failure (limited data available).

**Hepatic impairment:** Avoid use in hepatic failure (limited data available).

**Adverse effects:**

*Common* Rashes (discontinue treatment if severe and accompanied by fever and purpura), nausea, vomiting and abdominal pain, peripheral neuropathy.

*Uncommon* Paraesthesia, peripheral neuritis, leukopenia, arthralgia, myalgia.

*Rare* Agranulocytosis, bone marrow depression, headache, dizziness, fatigue.

**Interactions with other medicines (\* indicates severe):**
There are no known interactions where it is recommended to avoid concomitant use.

*Patients should avoid use of alcohol while using benznidazole.*

*Concomitant use of benznidazole and aspirin may increase the risk of bleeding.*

*The effect of anticoagulants such as warfarin may be increased when used together with benznidazole, due to the inhibition of enzymatic metabolism.*

*The patient should inform the physician if he/she are taking any other medications.*

**References:**

**List of Appendices**
Appendix 1 - Supporting letter from Brazilian government
Appendix 2 - Supporting letter from Honduras government
Appendix 3 - Supporting letter from Argentinean government
Appendix 4 - Supporting letter from Médecins Sans Frontières
Appendix 5 - ANVISA registration number: 1018301450062
Appendix 6 - Package insert for patient and health professionals
Appendix 7 – Package insert for health professionals
Appendix 8 – Clinical Trial Protocol - Population Pharmacokinetics Study in Children
References


10 http://www.ine.es/prodyser/pubweb/eni07/eni07_anexo.pdf


Russomando G, Almirón M, Candia N, Franco L, Sánchez Z, de Guillen I. Implementation and evaluation of a locally sustainable system of prenatal diagnosis to detect cases of congenital Chagas disease.


49 World Health Assembly, 2010. WHA 63.20 - Chagas disease: control and elimination.


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75 Viotti, R; Vigliano, C; Lococo, B; Bertocchi, G; Petti, M; Alvarez, MG; Postan, M; and Armenti, A. Long-Term Cardiac Outcomes of Treating Chronic Chagas Disease with Benznidazole versus No Treatment - A Nonrandomized Trial. Ann Intern Med. 2006;144:724-734.


