

## **The shortage of benznidazole leaves thousands of Chagas patients without treatment**

Médecins Sans Frontières (MSF) has been working on Chagas disease since 1999 in a number of Latin American countries, providing access to diagnosis and treatment to people infected by this neglected parasitic disease. From 1999 to the beginning of 2011, a total of eight projects were implemented in Honduras, Nicaragua, Bolivia, Guatemala, Colombia and Paraguay. During this period, MSF tested more than 80,000 people, diagnosing 6,185 and treating 4,160 with benznidazole (BZD) as a first-line option for treatment.

Until recently, treatment with benznidazole was thought to be safe and effective only for the acute phase of Chagas disease. But evidence began to converge on the benefits of treating during the chronic phase. At the same time, greater political prioritisation of Chagas treatment at the World Health Organization (WHO) and Pan-American Health Organization (PAHO) levels is encouraging countries to actively tackle the disease, with screening, diagnosis and etiological treatment for all children and offered to all adults.

Just as this promising turn of events unfolds, however, a major shortage of benznidazole threatens to stop this progress, and leave patients without access to the mainstay of treatment against Chagas disease. Already, MSF's programme in Paraguay has been forced to suspend diagnosis of new patients in a bid to mitigate the effects of the shortage, and in Bolivia stocks will run out early 2012. Any plans for new projects have been put on hold.

This crisis could have been prevented, but the major player involved, the Brazilian Ministry of Health, has shirked its responsibilities and seen to be unwilling to overcome the various challenges.

### **Step 1 – The right to produce benznidazole is transferred to the Brazilian government**

Benznidazole was initially developed by Swiss pharmaceutical company Roche over 40 years ago, but the company decided to transfer the manufacturing technology to another producer, with a view to ultimately ceasing its own production. In 2003, Roche transferred the licence and rights of the drug to Brazil's Pernambuco state. This was followed by an agreement between Roche and Pernambuco state to subcontract manufacturing and marketing to a public Brazilian agency – Laboratório Farmaceutico do Estado de Pernambuco (LAFEPE) - in July 2003.

In August 2004, LAFEPE received enough active pharmaceutical ingredient (API – the substance in a drug that is biologically active) from Roche to produce three batches of benznidazole – a total of 1.2 million tablets, enough to register the drug with Anvisa, the Brazilian Drug Regulatory Authority (Agência Nacional de Vigilância Sanitária). In March 2006, LAFEPE submitted the benznidazole dossier for a 100mg tablet to Anvisa and the drug was approved in November 2006.

On the same day, Roche withdrew the registration for its own medicine in Brazil. This left LAFEPE as the sole producer of benznidazole, although products previously produced by Roche continued to be available until their expiry date, with stocks available up to October 2010.

Even though LAFEPE has the capacity to produce benznidazole, it does not take the responsibility for logistical issues, nor is supported by the Ministry of Health to do so. This includes distribution of the drug to all the countries, and registration of the product in all other countries.

### **Step 2 – LAFEPE identifies a new source for the active pharmaceutical ingredient (API) necessary to make benznidazole**

As Roche began to cease production, a new source of active pharmaceutical ingredient (API) needed to be found.

The Brazilian private company Nortec Química was identified to produce the API necessary for the production of benznidazole once the Roche stock ran out. To bridge any potential shortfall, Roche provided further quantities of the API.

By 2010, Nortec Química was technically able to produce the API in their own facility, following documentation provided by Roche at the laboratory level.

Nortec is today the only producer of the API for benznidazole worldwide. Nevertheless, at this moment, full-scale production of the API has just started to be undertaken, as the initial orders for the product were only made at a late stage.

### **Step 3 – Clear signs show that the demand for benznidazole is set to increase**

Until recently, treatment of Chagas with benznidazole was thought to be safe and effective only for patients in the acute phase of disease. But evidence began to converge on the benefits of also providing treatment to those chronically infected and asymptomatic, up to the age of 60 years. There is already evidence that etiological treatment of those chronically infected with mild cardiovascular symptoms can delay the progression of the disease, and more quantitative results will be published next year from the BENEFIT multi-centric study.

It has also been confirmed that those treated with benznidazole within three months of infection have the best chance of cure (between 90 and 100%).

MSF programmes have shown that treatment was indeed possible – and safe – for both acute and chronic phases, provided regular medical checks were performed. A review in 2009 in the medical journal *PLoS Neglected Tropical Diseases* of the 10-year-long experience of MSF programmes showed that the etiological treatment of children and adolescents was indeed viable, and that treatment of adults is safe.

This evidence was a clear signal that demand for benznidazole was set to increase as it became clear the drug was a viable treatment option for many more patients. Because demand for benznidazole depends on active engagement by Chagas control programmes, MSF and the Drugs for Neglected Diseases Initiative (DNDi) launched campaigns to raise the awareness of Chagas disease and stimulate coordinated demand from countries in order to facilitate demand forecasting.

At the same time, greater prioritisation of Chagas treatment promises to put an end to the neglect of Chagas disease, and thereby also boost demand for benznidazole treatment. Resolutions adopted by the World Health Organization and the Pan American Health Organization have served to boost countries' response to the disease. In 2009, PAHO passed a landmark resolution entitled "Elimination of Neglected Diseases and Other Poverty-Related Infections". It recommended the provision of etiological treatment to all children with Chagas disease, the integration of Chagas diagnosis in the primary healthcare system, and the extension of care to adults where possible.

Several countries have implemented these guidelines. Bolivia, the country with the highest Chagas burden in the world, now recommends that all persons up to the age of 60 years diagnosed with the disease should be offered treatment. Groups of patients living with the disease, in both endemic and non-endemic countries, have also increased their mobilisation for access to etiological treatment.

Yet just as signs in a future surge in demand for Chagas treatment began to appear, the production of benznidazole became fragile.

#### **Step 4 - Finalisation of the new API source draws to a standstill, even as the clock is ticking before Roche's API and drugs expire**

Once a new source of API had been identified and the new producer develops the capacity to produce the API, numerous regulatory hurdles still needed to be overcome before the generalised production of benznidazole could be switched to the new source. Stability studies needed to be conducted, both for the API itself and the finished product made with the new API, and the regulatory agency needs time to approve the dossier. All of this could take at best a number of months – estimates vary from 10 to 12 months. This is the entirely legitimate minimum required time by most regulatory authorities for the validation of a change in the source of API for a product.

Had the planning process been undertaken by all actors with coordination from the Brazilian Ministry of Health, there would have been a new API approved and available without an interruption to the production of benznidazole.

Yet despite the urgency of finalising Nortec as the new source for the API before Roche's products – whether the finalised benznidazole tablets or the Roche API – expire, little progress was realised on this front. There was no effective direction from the Brazilian Ministry of Health to ensure timely resolution of challenges, and insufficient demand forecasting from PAHO and other countries' Ministries of Health.

#### **Step 5 - All purchasers of benznidazole turn to LAFEPE as Roche's remaining stocks expire**

In October 2010, the last batches of benznidazole produced by Roche expired. From now on, the only source of benznidazole was LAFEPE's own production using Roche's active pharmaceutical ingredient. But because this had also expired, the threat of a global shortage of benznidazole immediately began to surface.

LAFEPE at first informed MSF that a batch of new tablets using the expired Roche API, subsequently re-processed by Nortec, would be available as temporary solution by October 2010. The production of the new batch was postponed several times, and was eventually delayed until early 2011, due to the miscalculation of the time this process would take by Nortec.

The scramble for other stopgap solutions began. When for example the Brazilian Ministry of Health returned over half a million unused tablets, MSF was offered to purchase them. But given the time it took to authorise the purchase and organise shipment to MSF projects, customs authorities refused to allow the treatments to enter the country as the expiry date was too near.

### **Step 6 – Orders for benznidazole are unmet and contingency measures need to be put in place**

This summer, LAFEPE informed MSF that it will not be able to meet the orders for 460,000 tablets for MSF projects in Bolivia and 360,000 tablets for MSF projects in Paraguay. The last batch of 78,000 benznidazole tablets arrived in Bolivia and 35,000 tablets in Colombia for MSF projects, enough to last until December 2011.

In MSF programmes, contingency measures have now been put in place to deal with the crisis. MSF's programme in Paraguay has been forced to suspend diagnosis of new patients in a bid to mitigate the effects of the shortage, and in Bolivia stocks will run out early 2012. Any plans for new projects have been put on hold.

### **Conclusions and recommendations**

In the last years and months, numerous signals have made it clear that a shortage of benznidazole was a crisis waiting to happen. Indeed a working group including the Ministry of Health, LAFEPE, Nortec, PAHO and the DNDi was created before the crisis, in order to ensure smooth production and coordination between all actors for the benznidazole paediatric formulation. Unfortunately, this group did not remain functional.

Before it happened MSF on several occasions has reached out to the Brazilian Ministry of Health to warn of the looming shortage, and to demand action be taken once it became clear a shortage was inevitable – most recently last month.

Resolution of this crisis will only be possible if the different parties involved stop blaming each other. In successive communications with MSF, LAFEPE has blamed Nortec for failing to deliver the API. Nortec has blamed LAFEPE for failing to make precise orders. Both companies have blamed the Ministry of Health for not unblocking the funds in a timely fashion. In its latest communication with MSF, the Ministry of Health again shifted the blame onto LAFEPE.

MSF firmly places the onus on the Brazilian Ministry of Health. LAFEPE, as a public producer, is under the Ministry's responsibility. At a PAHO-organised Chagas Initiative meeting in Bogotá earlier this year, endemic countries "express[ed] concerns on the possible difficulty in the supply of benznidazole, and for this reason suggest that the Brazilian Ministry

of Health, currently the only single producer for the world, pursue mechanisms to optimize the production and exportation of the drug by the manufacturer, in order to be able to appropriately address people's need for the medicine.”

The Ministry of Health has taken the responsibility of being the sole producer of benznidazole. It must now show strong leadership in solving the benznidazole shortage.

The **Brazilian Ministry of Health** should:

- Publicly clarify the extent of the supply shortage.
- Notify all treatment providers and groups of patients living with the disease.
- Lead a contingency plan for rational use of benznidazole at the regional level, in partnership with PAHO, to manage the remaining stocks. Such a plan should include prioritising the most vulnerable groups in most prevalent endemic countries.
- Immediately commit to accelerating the current process for the production of benznidazole, and assume coordination role between all actors.
- Guarantee long-term and sustainable production of benznidazole.
- Guarantee price of product, regardless of cost of API
- To communicate a transparent production schedule of the current and future process of production.
- Expedite the validation of the active ingredient produced by Nortec via ANVISA (the Brazilian regulatory agency).
- Explore, in the medium-term, the possibility of additional producers to mitigate the dependence on a single supplier of API or a unique production facility.

**PAHO** should:

- Support the creation of a working group or 'emergency mechanism' to assist countries within PAHO region to form contingency plan for rational use of benznidazole so as to coordinate available stock.
- Continue to facilitate demand forecast and use of Rotation Fund for the buys of benznidazole and its delivery.
- Facilitate at a country level the importation of benznidazole.
- Facilitate that benznidazole becomes part of the Essential Drug List in endemic countries.