19th Expert Committee on the Selection and Use of Essential Medicines
April 8-12 2013

Expert peer review on application to add benznidazole pediatric dosage 12.5mg.

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Benznidazole is highly effective for the treatment of Chagas disease in all its forms (acute, congenital, reactive or chronic indeterminate infections) in both adults and children and particularly so in children below 2 years. In congenital infections cure rates vary from 87% at 36 months (Schijman et al 2003) to 100% at 24 months in children up to 2 years (Russomando et al 1998). In acute infections the rates are between 76% at 13 years for children below 10 years (Cancado et al 2002) and 100% at 15 years for children in the 2 to 18 years age bracket (Ferreira et al). In the chronic indeterminate phase serology remains positive for many years after treatment and so cure can be difficult to define but in most studies seroconversion after six years remains in the upper eighty per cent.

   c. Please provide any additional relevant information with reference

   Both Nifurtimox and Benznidazole, the two drugs approved for the treatment of Chagas disease show comparable efficacy, but the former has more adverse effects.

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   There is little data on safety of Benznidazole in children particularly for the treatment of acute and congenital infections; it is not recommended in pregnancy (as it is teratogenic in animal models) and in women of child bearing age not on contraception except in severe emergency. Adverse events during treatment are higher and more severe in adults than in children, particularly low for children below 1 year and may be completely absent in the newborns (Chippaux et al 2010, Russomando et al 1998). Generally side effects occur in 25 to 30% of cases on treatment with Benznidazole (Brazilian consensus on Chagas disease) and these include allergic dermopathies, dose-dependent peripheral neuropathy, GIT disorders, CNS disturbances notably headache and dizziness, neuromuscular and joint pains and hematological disorders (leucopenia, neutropenia, agranulocytosis, thrombocytopenia and medullar hypoplasia), increased hepatic enzymes and constitutional symptoms of asthenia and fatigue. Toxic effects may be severe, moderate or mild with severe and moderate events occasioning discontinuance or temporary interruption of treatment accordingly.
c. Please provide any additional relevant information with reference

There is also some concern about genotoxicity as occurs in animal models with noted chromosome aberrations in human cells in vitro (Gorla et al 1988) but this has not be correlated in human clinical settings.

3. Assessment of cost and availability
a. Have all relevant data on cost been provided?
   Yes
b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Benznidazole is produced by one pharmaceutical company, LAPEFE and the cost per treatment of a child comes to about US$ 7 minus transport. Scuri et al 2011, by developing an economic evaluating scheme, showed that it was more cost effective to screen both mothers and newborns (and hence treat) of Latin American immigrants to Spain. The alternative drug, Nifurtimox is provided to patients free from the WHO which obtains it as a donation from Bayer, but this scheme may not be sustainable in the long run.

c. Please provide any additional relevant information with reference

It could even be cost effective in screening and treating all newborns in endemic areas with faster possibility of eradication of the disease since vector control is feasible.

d. Is the product available in several low and middle income countries?
   Yes

4. Assessment of public health need
a. Please provide the public health need for this product (1-2 sentences)

Trypanosoma cruzi is endemic in 21 countries of Central and South America with about 100 million people at risk. The WHO in 2010 estimated that there were 10 million people infected, and though the vast majority of these cases are in this endemic area countries, modern population movements have given a much wider spread of the disease. Without a conscious effort at eradication Chagas disease will remain a serious health problem as mother-to-child transmission is an important means of acquiring the disease.

Morbidity is a serious social and economic problem for endemic countries with Brazil estimating a loss of more than 1.3 billion dollars in wages and industrial production annually

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable
   Yes

The WHO guidelines already recommend the product in the adult tablet form and the paediatric formulation has the same qualitative composition. Both the WHO technical group on Chagas disease in 2011 and the WHO drug information in 2012 already support this formulation.

The Brazilian Drug Regulatory Authority (ANVISA) has guidelines for this dosage.

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

   No

6. Is the proposed product registered by a stringent regulatory authority?
   Yes   o

7. Any other comments

8. What is your recommendation to the committee (please provide the rationale)

I recommend that Benznidazole pediatric dosage of 12.5mg be included in the WHO Model List of Essential Medicines for children for the treatment of children under 2 years.

The efficacy of the drug is not in doubt, the most targeted group for treatment are neonates and the very young. The 12.5mg dosage tablet is 1/8 the adult tablet but is qualitatively the same providing a practical means of ensuring more accurate dosing of the drug and an easier management in the very young children even by none trained persons in home settings. This is of particular importance since the treatment is long and will normally be continued or done out of hospital.