



Application for addition of 50 mg form of isoniazid to the WHO model list of essential medicines

Geneva, 10 August 2006

Focal Point: Hugo Vrakking
Global Drug Facility (GDF)
StopTB (STB)
TB Partnership (TBP)

Isoniazid 50 mg Oral Formulation

1. Summary statement of the proposal for inclusion, change or deletion

Proposal for the inclusion of pediatric dosage form isoniazid 50 mg in the WHO Model list of essential medicines for chemoprophylaxis of tuberculosis in pediatric populations with concurrent HIV infection, HIV infection risk or others with increased risk of contracting the disease. Isoniazid is currently included in the WHO formulary, and in addition this application supports the inclusion of the dosage formulation of 50 mg strength.

2. Name of the focal point in WHO submitting or supporting the application

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

UNICEF Hanne Bak Pedersen

The International Union Against Tuberculosis and Lung Disease. Arnaud Trebucq, MD PhD

KNCV Tuberculosis Foundation Dr. Jerome van Gorkorn

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

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

Isoniazid 50 mg: scored oral tablet

6. International availability - sources, if possible manufacturers

Lupin Laboratories Ltd. Mumbai (Bombay), India

Svizera Labs Pvt Ltd. Mumbai, India

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

Isoniazid is already listed as an individual medicine on the list of Essential medicines.

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

From current assessments it is evident that tuberculosis continues to be a leading killer among adults and children worldwide. In 2004 there existed 14.6 million prevalent cases of TB. WHO estimated that in 2004 alone, 8.9 million new cases of TB arose and 1.7 million deaths were due to TB that year. Developing countries and populations with HIV infection suffer disproportionately. 250,000 deaths were due to TB/HIV coinfection. 13% of new incident cases of TB were attributable to HIV in 2004. There were 741,000 cases of TB/HIV coinfection, and TB is more lethal in these immunocompromised populations. Thus, 11% of adult AIDS deaths were due to TB in 2003. Many of the patients suffering from TB/HIV coinfection do not receive appropriate treatment for both diseases.

HIV is a cause for tuberculosis events to increase in pediatric populations worldwide. Children co-infected with TB and HIV respond negatively to tuberculin skin test, are less responsive to drug therapy, and have increased mortality compared to children infected with TB alone. Pediatric populations are immunocompromised, and therefore more likely to contract TB and HIV from adults in close contact through secondary infection.

Isoniazid therapy is recommended according to WHO treatment guidelines for use in TB prevention in at-risk populations including adults and children with HIV. Appropriate formulations of the drug for use in children are required for increased access and improved administration among these populations. Pediatric formulations of TB medications are essential in stemming disease prevalence and death rates in children.

8.2 Assessment of current use

Isoniazid is given preventatively for 6 to 12 months in at risk patients. Preventative medical treatment is administered in adults and children with positive tuberculin skin test, concurrent HIV infection, HIV infection risk, close contact with patient with infectious tuberculosis diagnosis or newly infected persons, and persons with increased risk of contracting the disease (immunocompromised, malnourished individuals). Children with negative skin test may still be administered preventative therapy if they are in close contact with infectious patients or HIV patients. Children and adults with

HIV infection or other immunosuppression should receive 12 months of preventative therapy. Patients under 35 years of age should be monitored monthly for adverse effects.

8.3 Target population

Pediatric tuberculosis patients

An estimate of total TB prevalence in children has not been properly elucidated, due to difficult diagnosis and lack of early detection in children. Incidence rates of TB in children range from 15% of all new cases of tuberculosis in developing countries to less than 6% in industrialized countries such as the US. An estimated 20-50 percent of children who live in households with active TB become secondarily infected.

HIV coinfection is a further challenge to paediatric populations, leading to weakened immune system, increased chance of contracting the disease, and increased susceptibility to infection. Malnutrition and other concomitant infections also decrease resistance to TB infection. Priority has been given in TB control efforts to treatment of adult cases. Pediatric tuberculosis is less contagious and poses less risk to the community, therefore childhood cases of TB remain underreported and under-diagnosed. However, children of all ages have great risk of contracting the disease from infectious adults and progressing to severe and lethal stages of the disease. Pediatric populations require adequate medical intervention and access to medication therapy.

The risk of TB infection and disease progression is greatest in infancy and childhood. Risk decreases with age, but again resurges in late adolescence and adulthood. TB in children is unique in that it indicates recent transmission from directly within the infected community. Children are susceptible to infection from sputum positive family members and adults living in close quarters. Transmission from mother to child may occur during pregnancy, but it is rare in the case of pulmonary tuberculosis. In miliary tuberculosis or tuberculosis endometriosis, bacilli may enter the fetal circulation.

Children suspected of TB infection include those in close contact with sputum positive patient, children with positive tuberculin skin test, and those with signs and symptoms. Symptoms are often non-specific such as loss of appetite, weight loss, and fever. TB manifests in extra-pulmonary form in 40% of childhood cases such as lymphadenitis, meningitis, and miliary TB, which are more lethal. Pulmonary TB in children, often asymptomatic in children, is less common. Extra-pulmonary disease is more common, and thus medications must penetrate body fluids and tissues to be effective.

Once TB infection is diagnosed, treatment should begin immediately to avoid dissemination into life-threatening disease. Children with TB respond quickly to treatment, and are no longer infectious within 2 to 3 weeks. Compliance to full course of therapy is imperative. In children and other groups who cannot self-administer medication directly observed, short-course therapy (DOTS) is effective. In high incidence and HIV communities, BCG vaccine immunization is administered to infants before the first year of birth. However, the vaccine is only effective until 15 years of age. BCG vaccine may be administered in infants, however the vaccine in infants may be delayed and prevention of infection may be inadequate.

Treatment of pediatric patients has been further challenged by lack of appropriate dosage formulations. Currently adult fixed dose and single dose combinations are used for treatment in children. Anti-tuberculosis drugs are well-tolerated in pediatric populations, with little occurrence of adverse effects. Increased metabolism in children requires higher dose per kilogram body weight. Studies of stability, bioavailability, and tolerance of this urgently needed formulation have been conducted in support of this formulation. Modification of the inconvenient large size and dosage of oral tablets is required for administration. Currently, isoniazid dosage adjustment in infants is made by breaking and fractioning the tablets. Accuracy of the dosage after fractioning the tablet cannot be ensured, which may make the short-course medication therapy ineffective.

Isoniazid is given preventatively for 6 to 12 months in at risk patients. Preventative medical treatment is administered in adults and children with positive tuberculin skin test, and concurrent HIV infection, HIV infection risk, close contact with patient with infectious tuberculosis diagnosis or newly infected persons, and persons with increased risk of contracting the disease (immunocompromised, malnourished individuals). Children with negative skin test may still be administered preventative therapy if they are in close contact with infectious patients or HIV patients. Children and adults with HIV infection or other immunosuppression should receive 12 months of preventative therapy.

The risk of TB infection and progression to active disease is greatest in early infancy and childhood, and resurges in late adolescence and early adulthood. Primary TB infection in children may progress to severe TB disease in extrapulmonary forms such as tuberculosis meningitis and miliary TB. These manifestations of TB are more lethal in children than adult forms of TB.

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

Isoniazid is administered in combination with other antituberculosis drugs in the treatment of tuberculosis. It is also given for TB prophylaxis. A bacteriostatic drug which works against many actively dividing bacteria including mycobacterium, the mechanism of action may be linked to inhibition of mycolic acid synthesis and disruption of the cell wall. Oral administration is absorbed rapidly, although it undergoes first pass metabolism and is substantially effected when taken with food. It is widely distributed to all fluids and tissues including CSF, sputum, saliva, lungs and muscle. Isoniazid crosses the placenta and is distributed into breast milk. It is weakly protein bound. It is metabolized in the liver by acetylation. The rate of acetylation in humans is widely variable, depending on genetic determination of slow acetylators and fast acetylators. Half-life in fast acetylators is 0.5 to 1.6 hours, children 2.3 to 4.9 hours, and neonates 7.8 to 19.8 hours due to undeveloped metabolism (acetylators). Isoniazid reaches peak serum concentration in 1 to 2 hours. In 24 hours 75-95% of isoniazid is renally eliminated in the form of inactive metabolites.

9.1 Dosage regimen of tuberculosis treatment with isoniazid

9.2 WHO treatment guidelines

According to WHO treatment guidelines, isoniazid monotherapy can be used to prevent transmission to close contacts at high risk of disease, progression of infection in recently infected individuals, and to prevent development of active TB in immunodeficient individuals.

Children: 5 mg/kg daily (maximum daily dose 300 mg) for at least 6 months.

Combination therapy is given under direct observation for a minimum six months, during the initial and continuation phases of treatment. The initial phase involves the use of at least three drugs for 2 months to reduce bacterial growth and resistance rapidly. The second continuation phase (4-6 months) in order to prevent recurrence, involves fewer drugs. Isoniazid is a component of all 6- and 8-month TB treatment regimens currently recommended by the WHO:

Adults and children: 5 mg/kg daily or 10 mg/kg three times weekly.

9.3 Diagnostic tests for tuberculosis in children

All pulmonary TB suspects based upon clinical signs and symptoms will be referred to give a sputum sample. If the smears are not indicative of infection then the culture is repeated, or a chest x-ray is conducted for conclusive results. The most common type of TB in children is extra-pulmonary TB

(EPTB) such as meningitis, spinal TB, or pleural effusions. EPTB diagnosis is straightforward, through characteristic clinical signs such as spinal deformity, and fluid cultures. PTB diagnosis is through indirect measures because smear cultures are inadequate. Young children cannot produce the sputum and smear results may be negative, because children often do not suffer from cavitary PTB, but rather primary TB, or they have difficulty producing adequate sputum samples for microscopy. Positive samples can be obtained from school-aged children and in adolescence with adult-like presentation of PTB (cavitation). Instead the most important indicator for PTB in children is contact with infected patients such as close family. Also, respiratory symptoms persistent for more than 2-3 weeks which are unresponsive to antibiotics, weight loss, and skin test, chest x-ray. Positive TB skin test may be suppressed under immunosuppression (HIV) or malnutrition, and therefore obtain a false negative result. Positive skin test only indicates infection, not necessarily TB.

If the mother of a newborn infant is infected, preventative therapy may be required, and contact with the infant should be minimized. Infants less than 12 months of age with tuberculosis infection are asymptomatic. Unexplained pneumonia, cervical adenitis, bone or joint infections, or asymptomatic meningitis should have a Mantoux tuberculin skin test and household investigation for infected family members.

10. Summary of comparative effectiveness in a variety of clinical settings

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

The following databases were searched in October 2006 to identify published studies: CDSR and CENTRAL (The Cochrane Library, Issue 4, 2006), DARE (via CRD website), MEDLINE (via PubMed), and EMBASE (Ovid 1988 to 2006). The searches were conducted iteratively using a combination of MeSH/EMTREE terms and text words. Reference lists in retrieved articles were checked to identify additional studies, citation searching on relevant articles was conducted in EMBASE and related articles were checked in MEDLINE.

In the absence of studies comparing the effectiveness of different isoniazid doses or dose formulations in children, randomized trials, observational studies and pharmacokinetic data provide some evidence of effective doses that need to be achieved in children⁵⁻⁹. The primary studies are summarized in the Evidence Table.

10.2 Summary of available data (appraisal of quality, outcome measures, summary of results)

A Cochrane review showed isoniazid to be effective in preventing the development of active tuberculosis in approximately 60% of non-HIV infected individuals in various at-risk groups⁵. The included trials were conducted in mixed populations, largely household contacts of known cases and villagers in endemic areas. Children were included in six placebo controlled trials published between 1962 and 1965, in which a 5 to 15 mg/kg or 300mg daily dose of isoniazid was used⁵. Prophylaxis with isoniazid in combination with other drugs had good effect in a prospective cohort study of children less than five years old who were contacts of adult cases of MDR pulmonary tuberculosis⁶. Prophylaxis was tailored to the susceptibility of the index case and most of the children treated received isoniazid, 15 to 20 mg/kg/d⁶. A recent randomized controlled trial in children with HIV in South Africa showed a significant reduction in mortality and tuberculosis with daily or intermittent isoniazid prophylaxis using 100mg tablets to administer a dose of 10mg/kg: the dose range achieved was 8 to 12mg/kg depending on whether ½ or ¼ tablets were used⁷.

A pharmacokinetic study of isoniazid in children with respiratory tuberculosis concluded that children less than five years of age should receive a dose of at least 10mg/kg to ensure that fast acetylators are exposed to adequate serum concentrations⁸. In the study 64 children received a 10mg/kg single oral dose of isoniazid measured accurately using a pharmaceutical grade powder. The mean isoniazid serum concentration two hours after administration was 8.599mg/L (SD 1.974) in homozygous slow acetylators (n=25, median age 2.8 years), 5.131mg/L (SD 1.864) in heterozygous fast acetylators (n=24, median age 3.9 years), and 3.938mg/L (SD 1.754) in homozygous fast acetylators (n=15, median age 4.1 years). Median regression showed a significant decline in the isoniazid elimination rate with increasing age within each genotype group. Statistical analysis did not detect any significant association of pharmacokinetic parameters with body weight⁸.

10. 3 Summary of available estimates of comparative effectiveness

On the basis of the dose range used in children in clinical trials demonstrating the efficacy of preventive therapy^{5,7}, and observed to have good effect in preventing tuberculosis in childhood contacts⁶, a 50mg dose formulation would help reduce paediatric dose inaccuracies and enable dose to be matched more accurately with elimination rate for particular groups⁸.

Evidence Table

Study	Aim	Methods	Population	Intervention	Outcome measures	Results
Schaaf 2002 ⁶ South Africa	Determine prevalence of TB in children in household contact with MDR-TB and assess effectiveness of prophylaxis	Prospective cohort study; 1994 to 2000; follow-up 30 months	125 children, household contacts of adult index cases; of 105 children without disease 41 received prophylaxis: median age 19 months (range 1, 60); 20 male, 21 female; 28 infected (asymptomatic with initial Mantoux test $\geq 15\text{mm}$)	Prophylaxis for 6 months with isoniazid 15 to 20mg/kg/d, pyrazinamide 25 to 35mg/kg/d, ethionamide 10 to 15mg/kg/d and/or ethambutol 15 to 20mg/kg/d and/or ofloxacin 15mg/kg/d; formulations not reported; DOT	TB disease confirmed or probable	2/41 children who received prophylaxis developed TB disease (probable); it is unclear if these were among the 37 children who received regimens containing isoniazid
Zar 2006 ⁷ South Africa	Investigate impact of isoniazid prophylaxis on mortality and TB in children with HIV	RCT, concealed allocation, double blind; median follow-up 5.7 months (interquartile range	263 children with HIV; median age 24.7 months (range 9.4, 51.6); 146 male; TST positive 22/257; most were	Group 1: Co-trimoxazole plus isoniazid daily (n=64) or thrice weekly (n=68), 10mg/kg/d (range 8 to 12mg/kg	Mortality, incidence of TB, toxicity graded 1 to 4 according to NIH DAIDS	Mortality: isoniazid 11/132, placebo 21/131, HR 0.46 (95% CI 0.22, 0.95) TB: isoniazid 5/132, placebo 13/131, HR 0.28 (95% CI 0.10, 0.78)

		2.0, 9.7); trial conducted 2003 to 2004	malnourished; 81 receiving HAART	depending on whether ½ or ¼ tablets used); 100mg tablets (Be-Tabs Pharma, S. Africa) Group 2: Co-trimoxazole plus placebo, daily or thrice weekly Multivitamins		Toxicity, grade 3 or 4: isoniazid 5/132 (haematological events), placebo 8/131 (elevated ALT and haematological events) No cutaneous or neurological toxicity
Schaaf 2005 ⁸ South Africa	Define isoniazid pharmacokinetics in children with TB in relation to N-acetyltransferase (NAT2) genotype	Pharmacokinetic study; HPLC analysis of isoniazid in blood sampled at 2, 3, 4, 5h; NAT2 genotyping; regression analysis	64 children with respiratory TB; median age 3.8 years (interquartile range 1.8, 7.8): 0 to 2 yrs n=18, >2 to 5 yrs n=24, >5 to 13 yrs n=22; sex not reported; 13 had HIV infection Exclusion criteria: severely ill children	Isoniazid, powder obtained from Fluka Chemie AG (Switzerland), 10mg/kg oral single dose in water	AUC, elimination rate (<i>k</i>), NAT2 genotype defined as homozygous slow (SS) or fast (FF), or heterozygous fast (FS)	SS n=25, FS n=24, FF n=15 Mean <i>k</i> , AUC, and isoniazid concentration at 2, 3, 4, 5h differed significantly between genotypes Median regression showed significant decline in <i>k</i> with increasing age within each genotype

Marais 2006 ⁹ South Africa	Document adherence to preventive therapy with isoniazid	Prospective, community-based study in two suburban locations; 2003 to 2005; adult (>15 years) index cases identified from treatment registers	236 children in household contact with an adult PTB index case and eligible for preventive therapy; age <5 years; 178 male, 96 female; TST positive 122/243 tested; 38 diagnosed with TB, 236	Unsupervised isoniazid monotherapy for 6 months, dose not reported	Adherence defined by monthly tablet collection as very poor (≤ 2 months), poor (3 to 4 months), reasonable (≥ 5 months), or not treated TB diagnosed within 6 to 12 months Side effects	Adherence: very poor 130/236, poor 14/236, reasonable 36/236, not treated 56/236 TB: 4/130 with very poor adherence and 2/56 not treated developed TB Side effects : no cases of peripheral neuropathy or liver damage
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11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to date

Isoniazid became available in ____, and has been used commonly in standard tuberculosis treatment.

11.2 Description of adverse effects/reactions

Side Effect Table	
Main Effects	Rare Effects
Peripheral neuropathy	Convulsions, optic neuritis and atrophy, toxic encephalopathy, toxic psychosis, hyperreflexia, difficulty with micturition
Elevated serum ALT, AST and bilirubin	Hepatitis
	Nausea, vomiting, epigastric distress, dry mouth
	Hypersensitivity reactions, including rash, fever, lymphadenopathy, vasculitis
	Agranulocytosis, haemolytic, sideroblastic or aplastic anaemia, thrombocytopenia, eosinophilia
	Pyridoxine deficiency, pellagra, hyperglycaemia, metabolic acidosis, gynaecomastia

Adverse effects mostly involve the nervous system. Higher doses, slow acetylator status, HIV infection and malnutrition are factors associated with increased risk of adverse effects. Pyridoxine administration can counteract peripheral neuropathy complicating isoniazid use^{10,11}.

A recent prospective community-based study conducted in South Africa observed no peripheral neuropathy or liver damage with the use of isoniazid monotherapy among 236 children less than 5 years of age⁹. However, treatment was unsupervised and adherence was generally poor.

A recent randomized controlled trial in South Africa recorded low incidence of grade 3 or 4 toxicity among children with HIV receiving isoniazid prophylaxis for tuberculosis⁷. These were haematological events including neutropenia, thrombocytopenia or anaemia, experienced by 5/132 children receiving isoniazid. Isoniazid was given daily or intermittently in the form of 100mg tablets using ½ or ¼ tablets where necessary to achieve a dose of 8 to 12mg/kg. In the placebo group two out of 131 children had increased ALT and six had haematological events classified as grade 3 or 4 toxicity. Cutaneous or neurological toxicity was not observed and permanent discontinuation of treatment was not required in either group. Multivitamin supplements were given according to standard protocol in this trial and none of the grade 3 or 4 adverse event occurred among children receiving HAART⁷.

Three children in two early randomized trials reviewed by Smeija *et al* died of accidental isoniazid overdose⁵.

Side Effect Table

11.3 Identification of variation in safety due to health systems and patient factors

11.4 Summary of comparative safety against comparators

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

12.1 Range of costs of the proposed medicines

Drug	Highest Cost US\$	Lowest Cost (US\$)	Median Cost (US\$)
Isoniazid 50 mg blister package	0.00532/Tab-cap	0.00532/Tab-cap	0.00532/Tab-cap

International Drug Price Indicator Guide as of 01/07/06

12.2 Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented)

Drug	Maximum Daily	Cost per tablet	Total cost per	Total cost
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Child Dose		(US\$)	day treatment (US\$)	per180 day treatment (short-course) US\$
Isoniazid 50 mg	300 mg	0.00532/Tab-cap	0.0319	5.75

Lupin Pharmaceuticals, Inc. as of 21/07/06

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

N/A

14. Availability of pharmacopoeial standards (BP, IP, USP)

N/A

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

To be provided.

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