



Application for addition of 150 mg form of pyrazinamide to the WHO model list of essential medicines

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Pyrazinamide 150mg Oral Formulation

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

Proposal for inclusion of pediatric dosage form pyrazinamide in the WHO Model list of essential medicines for treatment of tuberculosis. Pyrazinamide is currently included in the WHO formulary, therefore this application supports the inclusion of the dosage formulation of the 150mg strength. Pyrazinamide 150mg should be made available in pediatric formulations for ease of use:

Formulations for pediatric use:
Dispersable tablet
Scored oral tablet

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

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

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

Pyrazinamide (INN, BAN, USAN, DCF)

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

Pediatric formulation pyrazinamide 150mg: dispersable tablet, oral tablet

6. International availability - sources, if possible manufacturers

Lupin Laboratories Ltd. Mumbai (Bombay), India

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

Pyrazinamide 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. With the rise of resistant tuberculosis strains, MDR-TB was found present in 102 of 109 settings surveyed¹.

Incidence rates of TB in children range from 15%² of all new cases of tuberculosis in developing countries to less than 6%³ in industrialized countries such as the US. An estimated 20-50 percent of children who live in households with active TB become secondarily infected⁴. 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 TB⁵.

Human immunodeficiency virus (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 infection⁶.

Medication therapies to treat and cure tuberculosis infection prove highly effective in children, with near 100% cure rates. Children with TB respond quickly to treatment, and are no longer infectious within 2 to 3 weeks⁶. Thus there is vital need for increased access and improved administration of TB medications through novel pediatric formulations, and appropriate dosage formulations, which are essential in stemming prevalence and death rates in children⁴.

8.2 Assessment of current use

Pyrazinamide is administered in combination with other antimycobacterial medications to treat tuberculosis infection. Pyrazinamide is only effective against mycobacterium. Combination therapy

may include isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol and thioacetazone, which attack mycobacteria by varying methods including sterilization, bacteriostatic, and bactericidal methods. Monotherapy is not used, to avoid development of resistant strains of TB. Short course, 6-month therapy consists of isoniazid, rifampicin, and pyrazinamide given for 2 months followed by isoniazid and rifampicin for 4 months. If compliance is enforced, DOTS short course therapy proves to be 98% effective⁷.

Pyrazinamide formulations currently included on the EML	
Pyrazinamide (Z)	Tablet, 400 mg
R+H+Z	Tablet, 60 mg + 30 mg + 150 mg; 150 mg + 75 mg + 400 mg; 150 mg + 150 mg + 500 mg
R+ H+Z+E	Tablet, 150 mg + 75 mg + 275 mg

Source: Operational guide for national tuberculosis control programmes⁸

The 3-FDC R60/H30/Z150 is the best option for use in children when this product is available. However, RHZ of proven acceptable quality is still very difficult to find in the market. By making it possible to procure single strength tablets of pyrazinamide 150 mg, country TB programmes can find treatment solutions when the 3-FDC is not available. Paediatric 2-FDC RH can be complimented with the Z150, rather than currently available adult Z400. Therefore, preparation of the pediatric dose via crushing and measuring can be avoided. Z150 could also be useful when treating a child who develops adverse reaction to either rifampicin or isoniazid, so that the treatment may continue with single strength R or H and the Z150.

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 US⁶. Pediatric tuberculosis is less contagious and poses less risk to the community, therefore children are not consistently identified or treated for TB. However, children of all ages have great risk of contracting the disease from infectious adults and progressing to severe and lethal stages of the disease⁹. Pediatric populations require adequate medical intervention and access to medication therapy⁴.

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. HIV coinfection is a further challenge to pediatric 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.

TB in children is unique in that it indicates recent transmission from directly within the infected community. An estimated 20-50 percent of children who live in households with active TB become secondarily infected. Priority has been given in TB control efforts to treatment of adult cases, however 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. Once TB infection is diagnosed, treatment should begin immediately to avoid development into life-threatening disease⁵.

Many cases of TB in children remain under-reported and undetected by diagnostic procedures, because signs and symptoms of the disease are non-specific⁹. Children suspected of TB infection include those in close contact with sputum positive patients, children with positive tuberculin skin test, and those with signs and symptoms⁷. Non-specific signs include 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 may be lethal⁵. Pulmonary TB, 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.

In addition to underdiagnosis, 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 to avoid under-dosing⁷. Studies of stability, bioavailability, and tolerance of this urgently needed formulation have been conducted in support of pyrazinamide 150 mg. Modification of the inconvenient large size and dosage of oral tablets is required prior to administration. Currently, pyrazinamide dosage adjustment is made by breaking and fractioning the tablets. Accuracy of the dosage after fractioning the tablet cannot be ensured, with the potential to cause the short-course medication therapy to be ineffective.

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

Pyrazinamide is effective only in combination with other TB drugs, greatly reducing length of treatment required. Although weakly bactericidal, it has potent sterilizing activity in acidic, inflammatory environment during the first few months of therapy. The mechanism of action is as yet unknown. Through bactericidal and primarily bacteriostatic effects, pyrazinamide limits resistance of bacteria when used in combination with rifampicin and isoniazid antibacterial medications.

Pyrazinamide is a prodrug which is converted to active metabolite, pyrazinoic acid by hepatic hydrolysis in acid environment of less than pH 5.6. Pyrazinamide is ingested in inactive form, which is converted to active pyrazinoic acid by the enzyme pyrazinamidase produced from *M. tuberculosis* in acid environment. Fatty acid synthetase I is blocked by pyrazinoic acid, which prevents bacterial growth¹⁰.

Pyrazinamide undergoes rapid absorption from the gastro-intestinal tract, penetration into cerebrospinal fluid, and wide dissemination to liver, lungs, kidneys, and bile. Active and inactive forms of the drug are weakly protein bound (10 to 30 percent). Half-life is approximately 1.6 hours. Pyrazinamide reaches peak serum concentration within 1 to 2 hours, and active metabolite, pyrazinoic acid reaches peak in 4 to 5 hours. 3% of the drug is eliminated unchanged renally as pyrazinamide, 33% as pyrazanoic acid, and 36% as other metabolites.

Precautions should be taken in patients who are hypersensitive to pyrazinamide or related medications, or in patients with severe liver impairment, which impairs metabolism. Side effects are rare such as arthralgia, gouty arthritis, and hepatotoxicity. Resistance may develop if pyrazinamide is not administered with concurrent anti-tuberculosis medications.

9.1 Dosage regimen of tuberculosis treatment with pyrazinamide

Pyrazinamide exerts greatest activity against *M. tuberculosis* during the initial phase of active TB. Adult dosing for pyrazinamide is strictly based on lean body weight to minimize side effects, with a maximum dose between 2,000 and 4,000 mg, depending on the frequency given during a seven-day period. Studies have not established proper age-dose relationships in the pediatric population. Currently, children are administered treatment according to adult guidelines with minimal adverse effects. Pyrazinamide is well tolerated by infants and children¹⁰.

Pyrazinamide is administered in adults and children in combination with other anti-tuberculosis medications, orally 15-30 mg/kg once daily, or 50-70 mg/kg two to three times a week. Maximum daily dose in adults and children is 2000 mg when taken daily, or 3000 mg when taken three times a week. Currently, doses are generally available in 400 mg and 500 mg strengths, and within combination tablets in 150 mg, 400 mg, or 500 mg strengths. Pediatric patients are to take single dose 200-800 mg pyrazinamide daily for 2 months, based on weight in kilograms, as part of initial phase therapy. Addition of single dose 150 mg to the WHO model list is required for use in pediatric patients.

Children's Daily Dosing for Pyrazinamide 150 mg						
	Weight (kg)					
Weightband	Up to 7	8-9	10-14	15-19	20-24	25-29
Tablets	1	1 ½	2	3	4	5
Milligrams	175	200	250	375	500	625

Source: WHO Treatment Guidelines⁷

9.2 WHO treatment guidelines

Pyrazinamide is a component of all 6- and 8-month TB treatment regimens currently recommended by the WHO: 25 mg/kg daily for 3 months and 35 mg/kg three times a week for 3 months⁷.

Compliance to the long-term, combination therapy has been increased through Directly Observed Treatment, Short-course therapy (DOTS) implementation. Medication 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. The supervisor of the medicine ingestion may be a health professional, or a trained person within the community.

9.3 Diagnostic tests for tuberculosis in children

The diagnosis of childhood tuberculosis presents a major challenge. 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 sample and smear results may be negative, because children often do not suffer from cavitory 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 members. 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. Also, respiratory symptoms persistent for more than 2-3 weeks, which are unresponsive to antibiotics, weight loss, and skin test, chest x-ray may be indicative. 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 TB¹¹.

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.

A randomized trial provides evidence that short-course intermittent therapy containing pyrazinamide provides good long term results in children with respiratory tuberculosis¹². Pharmacokinetic studies in children demonstrate delayed absorption and lower serum concentrations following administration of adult dosage form pyrazinamide¹⁴⁻¹⁶. These studies are summarized in the Evidence Table together with additional studies reporting adverse effects.

10. 2 Summary of available data (appraisal of quality, outcome measures, summary of results)

Long term follow-up of 134 children with respiratory tuberculosis treated in a randomized trial in India with intermittent 2RHZ/4RH or daily 9RH showed both regimens to be highly effective in terms of response and relapse^{12,13}. The dose of pyrazinamide was 45mg/kg (maximum daily dose 1g). At

five years follow-up fewer residual radiographic lesions were found among children treated with the pyrazinamide containing regimen.

Pyrazinamide pharmacokinetic parameters generated from a prospective, multiple-dose, population study conducted in the USA differed significantly between children and adults with tuberculosis¹⁴. The participants, 67 adults and 23 children, received oral pyrazinamide in the form of 200 or 500mg tablets in combination with other drugs in daily or intermittent regimens prescribed according to clinical judgment or institutional standard practice. Most of the children received daily treatment. In children with daily dosing the median C_{max} was 21.1µg/ml compared to 41.1µg/ml in adults. The estimated absorption rate was 32% slower in children compared with adults, the median volume of distribution normalized for body weight was 32% higher and the median elimination rate was 1.7 times higher, resulting in a median half-life 43% shorter in children (3.47 hours) than in adults (6.04 hours). Patient variables other than body weight had minimal effect on the pharmacokinetics of pyrazinamide¹⁴. An earlier pharmacokinetic study of pyrazinamide in Indian children with pulmonary tuberculosis also reported slow absorption compared with adults, on average 2.9 hours (range 1 to 6) to reach maximum serum concentration following a single oral dose of 35mg/kg¹⁵. Values for C_{max} and V/F in children were comparable between the two studies. Findings from the two studies were inconsistent with regard to the half-life being longer and clearance slower¹⁵ or vice versa¹⁴ in paediatric relative to adult populations. A pharmacokinetic study of 27 Malawian children with tuberculosis found low serum concentrations using intermittent pyrazinamide at recommended doses administered in tablet form apportioned according to body weight range¹⁶. Children younger than five years of age reached significantly lower serum concentrations than older children. In this study pyrazinamide levels were not significantly lower in HIV-infected or malnourished children¹⁶.

Summary of pharmacokinetic parameters in children		
Parameter	Lok Nayak Hospital 1998	U.S. hospitals 2002
Kel (hr-1)	0.08	0.20
Ka (hr-1)		1.02
V/F (L)	16.1	10.9
Vs/F (L/kg)	0.86	0.75
Cl/F (L/hr)	20.2ml/min	1.95
Cl/F (L/hr/kg)	0.13	0.13
Half-life (Kel;hrs)	10.9	3.47

10. 3 Summary of available estimates of comparative effectiveness

Published data on pyrazinamide pharmacokinetics in adults and children provide support for a paediatric dosage form with the potential to reduce dosing inaccuracies and the risk of treatment failure in children¹⁴⁻¹⁶. A literature search failed to identify published estimates of effectiveness comparing different pyrazinamide doses or dose formulations in children.

Evidence Table

Study	Aim	Methods	Population	Intervention	Outcome measures	Results
Swaminathan 2004 ^{12,13} India	Assess long term outcomes of two SCT regimens	RCT, method of allocation not reported; follow-up 5 years; X-ray readers were blinded; last available radiographs were evaluated for 8% lost to final follow-up; trial conducted 1992 to 1997	137 children with respiratory TB; age 1 to 12 years, 77 were <5 years old Exclusion criteria: EPTB, evidence of renal or hepatic disease	Group 1: 9RH daily Rifampicin 12mg/kg (max 300mg), isoniazid 6mg/kg (max 150mg) Group 2: 2RHZ ₃ /4RH ₂ Rifampicin 12mg/kg (max 300mg), isoniazid 15mg/kg (max 300mg), pyrazinamide 45mg/kg (max 1g); DOT	Residual radiographic lesions at final follow-up; relapse Adverse effects during treatment are in the original trial report ¹³	At 5 years follow up: Normal radiographs 115/134 Residual lesions 11/134 (10 in Group 1, 1 in Group 2) Calcification 7/134 (2 in Group 1, 5 in Group 2) 3 died during treatment, 1 in Group 1 and 2 in Group 2; 1 relapse in Group 1; 3 developed jaundice, 1 in Group 2, 2 in Group 1 (1 developed Hepatitis B)
Zhu 2002 ¹⁴ USA	Determine pyrazinamide pharmacokinetic parameters in adults and children with TB	Prospective, multicentre, multiple-dose, population pharmacokinetic study; blood sampling over 12h after dosing (most	90 patients with active TB including 23 children; all children were HIV negative Exclusion criteria: severe anaemia (Haematocrit <27%)	Pyrazinamide daily (most children), twice-weekly or thrice-weekly, with other antituberculosis drugs Administration: oral, 250 or 500mg tablets, under 'usual' practice	Population pharmacokinetic parameter estimates including: absorption rate (K_a), volume of distribution normalised by body weight (V_s/F), elimination rate (K_{el}),	Children, median (range) K_{el} 0.20 (0.02, 0.47) K_a 1.02 (0.11, 6.98) V_s/F 0.75L/kg (0.15, 1.62) $t_{1/2}$ 3.47h (1.47, 34.65) Adults, median (range) K_{el} 0.12 (0.03, 0.33) K_a 1.49 (0.40, 8.87)

		children had 2 to 5 samples over 10h); gas chromatography; analysis Nonparametric Expectation Maximization modelling		at each centre	elimination half-life ($t_{1/2}$) Response; adverse drug reactions (ADR)	V_s/F 0.57L/kg (0.13, 1.04) $t_{1/2}$ 6.04h (2.10, 23.1) All children responded to treatment during the study; 8 adults and 1 child experienced an ADR, not attributed to a specific drug
Roy 1998 ¹⁵ India	Evaluate pharmacokinetics of pyrazinamide in children with PTB	Pharmacokinetic study; spectrophotometry analysis of pyrazinamide in blood sampled at 0, 1, 2, 4, 6, 12, 24h	10 children with a Kenneth Jones score ≥ 7 ; mean age 7.9 years (SD 1.8); 5 male, 5 female; mean weight 20.9 kg (SD 5.1) Exclusion criteria: severe PTB, concomitant disease	Pyrazinamide 35mg/kg single oral dose after overnight fasting; formulation unclear, either tablets or powder (Cadila Chemicals Pvt Ltd, India)	C_{max} , T_{max} , $AUC_{0-\infty}$, $t_{1/2}$, elimination rate (k_{el}), volume of distribution (V), clearance (CL)	Mean (SD) C_{max} 41.2 μ g/ml (11.8) T_{max} 2.9h (1.7) $t_{1/2}$ 10.9h (4.5) k_{el} 0.08 (0.05) V 16.1L (10.9); CL 20.2mL/min (16.3)
Graham 2006 ¹⁶ Malawi	Characterise pyrazinamide pharmacokinetics in children with	Pharmacokinetic study; 2000 to 2001; HPLC analysis of pyrazinamide in	27 children with smear-negative PTB (23) or TB adenitis (4); mean age 5.7	Pyrazinamide, thrice weekly regimen, first oral dose after overnight fasting,	C_{max} , T_{max} , AUC_{0-24}	Mean (SD) C_{max} 36.6mg/L (19.7) T_{max} 3.4h (1.5) AUC_{0-24} 376mg/L/h (328)

	TB and the impact of age, nutritional status and HIV infection	blood sampled at 0, 2, 3, 4, 7, 24, 48h after administration of the first dose of anti-TB treatment; Mann-Whitney tests	years (range 0.9, 14); mean weight 14.3kg (range 6, 30); 18 were HIV infected	400mg tablets (Pharmamed, Amsterdam) ½ to 3 tablets according to body weight; mean dose 33mg/kg (range 25, 48); other drugs rifampin, isoniazid		C _{max} <25mg/L in 10 children, <20mg/L in 9 children; statistically significantly lower in children <5 years old; no significant difference for HIV or malnutrition
Sanchez-Albisua 1997 ¹⁷ Spain	Evaluate tolerance to pyrazinamide in SCT for PTB in children	Prospective series; 1985 to 1995; up to 5 months follow-up after treatment	114 children; age 6 months to 15 years (mean 4.5 +/- 3.4); 59 male, 55 female; Exclusion criteria: hepatic enzyme elevation, Hepatitis A, B, C, Epstein-Barr virus, cytomegalovirus	2RHZ/4RH daily Rifampicin 15mg/kg (max 600mg), Isoniazid 10mg/kg (max 300mg), Pyrazinamide 20 to 25mg/kg (max 1500mg) Administration: oral, R120/H50/Z300 capsules given to older children, otherwise rifampicin suspension followed by crushed isoniazid and	Clinical adverse effects: gastrointestinal, rash, arthralgia, hepatotoxicity (ALT >45U/L), hyperuricemia: (uric acid >7.5 mg/dL), other symptoms Laboratory: blood cell counts, ERS, AST, ALT, serum uric acid	Abdominal pain 2/114; vomiting and anorexia 3/114; Fever 3/114; increased ALT after 1 to 5 months therapy 11/56, none showed clinical signs of hepatotoxicity; uric acid increased in most children evaluated, none developed arthralgia or gout

				pyrazinamide together; all treatment after overnight fasting		
Corrigan 1999 ¹⁸ UK	Monitor liver function in children during triple drug therapy for TB	Cohort study; liver function tests (LFTs) before and during treatment (median of 5 times, range 1, 23)	43 children with TB infection (8) or disease (35); median age 6.6 years (range 0.7, 15.1); 21 male; 31 Caucasian; 1 had mildly abnormal LFTs pretreatment Exclusion criteria: other hepatotoxic drugs	Pyrazinamide, rifampicin, and isoniazid triple drug therapy in standard recommended doses	AST, ALT, bilirubin (abnormal defined as > mean + 2 SD)	13 developed abnormal LFTs, enzyme elevation occurred at median 1.65 weeks (0.6, 16.6); 2 children had symptoms, 1 pruritus, 1 jaundice; treatment of the child with jaundice was stopped temporarily, other LFTs normalized without interrupting treatment
Mukadi 1997 ¹⁹ Côte d'Ivoire	Assess impact of HIV on development and outcome of TB in children	Prospective cohort study; 1994 to 1995; children evaluated at 2, 4 and 6 months (also reports a case- control analysis of risk factors for TB)	161 children with PTB (119) or EPTB (42); median age 49 months (range 3, 116); 84 male; 31 HIV positive, 129 HIV negative (1 not tested)	Standard 6 months therapy with 2RHZ/4RH	Mortality, failure, side effects and compliance with preventive therapy (also reports on risk factors for TB and clinical presentation)	Mortality: 7/31 HIV positive, 5/129 HIV negative Failure: 1 HIV positive Side effects: minor skin rash 13% HIV positive, 7% HIV negative (not significantly different)

11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to date

Pyrazinamide became available in 1954, and has been used commonly in standard tuberculosis treatment.

11.2 Description of adverse effects/reactions

Side Effect Table	
Main Effects	Rare Effects
Arthralgia-itching, skin rash	Cutaneous reactions
Hepatitis	Sideroblastic anemia
Gastrointestinal-anorexia, nausea, abdominal pain	

Major side effects are hepatotoxicity and polyarthralgias. Pyrazinamide-induced hepatotoxicity is usually 2% with standard dosing. Pyrazinamide is the most hepatotoxic of all essential antituberculosis drugs, especially in doses > 30mg/kg/day. However, children are most tolerant of higher doses of the drug, with less toxic adverse effects. Polyarthralgias occur in up to 40% of patients but are treatable with aspirin or nonsteroidal anti-inflammatory agents. Other side effects are nausea, vomiting, acute gouty arthritis, and photosensitive dermatitis¹⁰.

Tolerance to pyrazinamide was reportedly good in a prospective series of 114 children in Spain given short course combination therapy for pulmonary tuberculosis between 1985 and 1995¹⁷. Children received a 20 to 25 mg/kg daily dose of pyrazinamide (maximum 1500mg) with rifampicin 15mg/kg and isoniazid 10mg/kg. Older children received R120/H50/Z300 capsules while others were given rifampicin in suspension followed by isoniazid and pyrazinamide crushed and not mixed with food. Clinical adverse effects in the form of gastrointestinal disturbances and fever were uncommon and mild. None of the children developed clinical symptoms of hepatotoxicity, although ALT increased with pyrazinamide medication in 11 out of 56 children evaluated, exceeding 65U/L in four cases, treatment was not interrupted. Most children had increased serum uric acid during treatment, exceeding the normal range in 9.8% of those evaluated, however, none developed clinical symptoms of arthralgia or gout and treatment was not interrupted.

Elevation of liver enzymes was not uncommon among 43 children receiving RHZ therapy for tuberculosis infection or disease in the UK however this generally occurred within the first two weeks and normalized within two months without interrupting treatment¹⁸. Clinical symptoms were rare, once case of pruritis and one of jaundice, with treatment stopped temporarily for the child who developed jaundice. In a randomized trial in India one child out of 69 treated with intermittent RHZ developed jaundice, treatment was changed temporarily until liver function tests became normal at which time treatment with RHZ was resumed (children with evidence of hepatic disease were not enrolled in the trial)¹³. A prospective cohort study in Côte d'Ivoire reported that minor skin rashes were the only side effects of RHZ therapy observed among 161 children treated for tuberculosis and that these were more frequent among children who were HIV positive¹⁹.

Adverse drug reactions were less common in children than adults receiving combination therapy during a population pharmacokinetic study of pyrazinamide in the United States¹⁴. Fewer children (1/21) than adults (8/42) experienced adverse effects that included nausea, vomiting, diarrhoea, itching, blurred vision, joint pain, stomach upset and elevated liver enzymes.

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

11.4 Summary of comparative safety against comparators

The previous studies demonstrate safety of pyrazinamide use in children. It is well tolerated in both children and adults. Pyrazinamide is advantageous compared to previous treatment regimens, because it reduces the length of therapy, allows for improved patient compliance, and therefore it is more likely for therapy to be effective. Use of pyrazinamide has already been approved and it is a standard component of WHO antituberculosis treatment guidelines.

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\$)
Pyrazinamide 150mg	0.0129/Tab-cap	0.0129/Tab-cap	0.0129/Tab-cap

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

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 Child Dose	Cost per tablet (US\$)	Total cost per day treatment (US\$)	Total cost per 60 day treatment (short-course) US\$
Pyrazinamide 150mg	2000 mg	0.0129/Tab-cap	0.0172	1.03

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

Formulation registered in India.

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

Not known.

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

To be added.

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