



**Application for addition of 3-FDC
rifampicin 150/isoniazid
75/ethambutol 275 mg (RHE) to the
WHO model list of essential medicines**

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

RHE Rifampicin 150/Isoniazid 75/Ethambutol 275 mg

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

Proposal for the inclusion of rifampicin 150/isoniazid 75/ethambutol 275 mg (R150/H75/E275) fixed dose, combination oral tablets in the WHO Model list of essential medicines for treatment of diagnostic category II tuberculosis. Fixed-dose combination, RHE, is not currently included in the formulary.

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

Hugo Vrakking, WHO/STB/TBP/GDF Tel: +41 22 791 4267

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

The International Union Against Tuberculosis and Lung Disease. Arnaud Trebucq, MD PhD
Medecins Sans Frontieres Myriam Hekens

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

(INN, BAN, USAN, DCF)

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

Oral tablet for adults

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

Fixed-dose combination RHE is part of the therapeutic group of antituberculosis therapy drugs.

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.

Improving access to medications and monitoring therapy through DOTS programs have effectively stemmed prevalence and death rates. Worldwide, the incidence rate decreased from 1.2% in 1997 to 0.6% in 2004, and prevalence and death rates have fallen in four out of the six WHO regions. However these rates have been rising in the African and Eastern Europe regions, with the highest rates of HIV infection and MDR-TB, respectively. 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. 66% of countries reported multidrug-resistant tuberculosis in 2004 totaling to 17,283 cases, with the majority of cases occurring in the European region. WHO estimates 460,000 MDR-TB cases occur each year; one-half among previously treated patients.

Proper administration and correct usage of antituberculosis medicines is essential to prevent failure of therapy and rise of MDR-TB cases among retreatment patient populations. Appropriate novel formulations of the drug improve accuracy of the treatment regimen, increase patient compliance, and increase simplicity and ease of anti-TB therapy. 3-FDC RHE is a component of standard therapy in Category II tuberculosis patients according to WHO treatment guidelines².

8.2 Assessment of current use

Fixed dose combinations

In addition to the proposed RHE fixed-dose combination, other 2-drug, 3-drug, and 4-drug combinations exist (see Table 1). Standardized DOTS strategy promotes administration of TB therapy in short-course, preferably fixed-dose treatment regimens. FDCs facilitate implementation of DOTS. Advantages of FDCs in treating TB as stated in the operational guide for tuberculosis control include³:

- Simplicity of treatment with minimal prescription errors;
- Increased patient acceptance and compliance with decreased likelihood of inadvertent medication errors;
- Increased health worker compliance to standardized and correct treatment;
- Improved drug management including ordering, procurement, distribution and dispensing/handling at different levels of the national programs;
- Lowered risk of misuse of single drugs and of emergence of drug-resistant TB due to reduced use of monotherapy.

Fixed-dose combinations (FDCs) are advantageous in tuberculosis treatment, reducing noncompliance and development of multi-drug resistance. Current fixed-dose combination therapies are presented below.

Fixed-dose combinations from the WHO Model List of Essential Medicines

Drug	Dose form	Strength for Daily use	Strength for intermittent use 3 times per week
rifampicin + isoniazid [RH]	Tablet	150 mg + 75 mg 300 mg + 150 mg	150 mg + 150 mg
	Tablet or pack of granules*	60 mg + 30 mg	60 mg + 60 mg
ethambutol + isoniazid [EH]	Tablet	400 mg + 150 mg	-
isoniazid + thioacetazone [HT]**	Tablet	100 mg + 50 mg	-
		300 mg + 150 mg	-
rifampicin + isoniazid + pyrazinamide [RHZ]	Tablet	150 mg + 75 mg + 400 mg	150 mg + 150 mg + 500 mg
	Tablet or pack of granules*	60 mg + 30 mg + 150 mg	-
rifampicin + isoniazid + pyrazinamide + ethambutol [RHZE]	Tablet	150 mg + 75 mg + 400 mg + 275 mg	- -

* For paediatric use

** Although used in some programmes, WHO does not recommend the use of thioacetazone (T) because of the risk of severe toxicity, particularly in HIV infected individuals. In general, thioacetazone should be replaced by ethambutol.

Source: Operational guide for national tuberculosis control programmes³

In the continuation phase of category II treatment, RHE are taken concurrently, therefore this application supports inclusion of the 3-drug FDC tablet. 2-drug FDC RH is available in 60/30, 150/75; 300/150; and 60/60mg strengths. Single dose ethambutol is available as 100 and 400mg tablets. It is proposed that 3-drug FDC of R150/H75/E275 be included on the WHO model list.

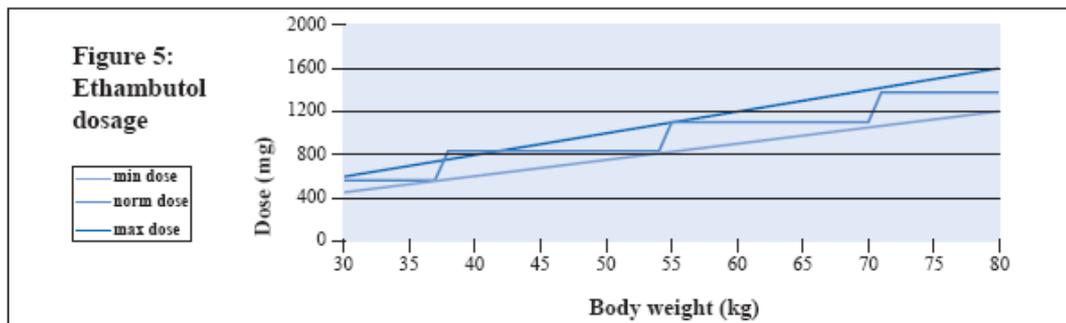
- RHE eases the logistics of treatment.
 - less quantity of pills to consume (4 vs. 10 per day)
 - increased patient compliance
 - increased health worker accuracy of administration
 - easier distribution and supply of single FDC

- RHE is indicated in treatment of Category II TB to prevent development of resistance. Cures patients who may be excreting bacilli resistant to isoniazid and/or streptomycin (TX handbook). Category II retreatment patients are those most likely to develop MDR-TB.
- R150/H75/E275 is based on 2:1:3 dosing guidelines (IAP, Indian Pediatrics.net). Reduced dose E275 allows for more accurate dosing than E400mg (and E100mg)
- E275 complements R150/H75, which are currently available only as separate formulations.
- Although 4-FDC RHZE is currently included on the EML, and is indicated for initial phase therapy in Category II TB, this formulation is not appropriate for the continuation phase, because PZ is no longer effective beyond 2 months of treatment (initiation phase).
- E275 is appropriate for daily dosing, as demonstrated by the following pharmacokinetic assessment. The graph demonstrates that plasma concentrations stay within MEC range for least occurrence of toxicity and longest duration of effectiveness.

OPERATIONAL GUIDE FOR NATIONAL TUBERCULOSIS CONTROL PROGRAMMES ON THE INTRODUCTION AND USE OF FIXED-DOSE COMBINATION DRUGS

Figures 2-5: Dose distributions of the four FDC drugs

(rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, ethambutol 275 mg) recommended by WHO (by body weight cut-off points of 30-37 kg, 38-54 kg, 55-70 kg, 71 kg and above).



Source: Operational guide for national tuberculosis control programmes³

8.3 Target population

Category II tuberculosis

One-half of MDR-TB cases occur among patients who were treated previously. Patients who had previously taken a treatment regimen for tuberculosis, and are therefore at risk for developing MDR-TB, are treated as diagnostic category II tuberculosis patients. These are patients who were previously diagnosed and treated for smear-positive pulmonary-tuberculosis. Retreatment is initiated in these patients after relapse, treatment interruption, or treatment failure. Previously treated patients are more likely to be resistant, with resistance to multiple drugs. The proposed RHE combination is recommended for use in long-term treatment of diagnostic category II patients, to decrease potential development of drug resistance.

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

Tuberculosis infection is caused by *Mycobacterium tuberculosis* bacterium. Primary infection is usually asymptomatic, or latent, with development into the lungs, the main organ affected (80% of adult cases). Antituberculosis treatment regimens consist of a combination of medications which may include isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol and thioacetazone, which attack mycobacterium by varying methods including sterilization, bacteriostatic, and bactericidal methods. Monotherapy is not used, to avoid development of resistant strains of TB. Isoniazid and rifampicin are the most powerful bactericidal drugs against all strains of TB bacilli. Rifampicin is the most potent sterilizing drug available, and pyrazinamide and streptomycin are also bactericidal in certain populations of TB bacilli. Streptomycin is bactericidal against rapidly multiplying TB bacilli. Ethambutol and thioacetazone are used in combination with more powerful drugs to prevent the emergence of resistant bacilli. Standard 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% effective.

Once TB infection is diagnosed, treatment should begin immediately to avoid dissemination into life-threatening disease. 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.

9.1 Dosage regimen in category II tuberculosis treatment

Treatment regimens are differentiated according to 4 treatment categories, in order of prioritization for treatment intervention. Category I patients are new smear-positive patients, new smear-negative PTB

patients with parenchymal involvement, HIV positive patients, or severe EPTB patients. Category II patients are previously treated smear-positive PTB cases that have relapsed, treatment was interrupted, or treatment failed. Category III patients are less severe smear-negative cases and forms of EPTB. Category IV are chronic and MDR-TB cases who are unimproved after re-treatment. Medical treatment of Category I patients has the most impact and cost-effectiveness, while Category IV has the least.

Previously treated patients with Category II diagnosis have increased potential to acquire drug resistance. They are more likely than new patients to harbor bacilli resistant to at least isoniazid treatment. The re-treatment regimen consists of initially 5 drugs, with 3 drugs in the continuation phase: rifampicin, isoniazid and ethambutol (RHE). RHE is administered for the entire duration of treatment. This reduces the risk of acquiring further resistance. The patient receives at least 2 drugs in the initial phase which are still effective. Sputum smear examination should be performed at the end of the initial phase of treatment (third month), during continuation phase (fifth month) and at the end of treatment.

Table: Sample regimens for treatment of category II tuberculosis. Sample regimens with fixed-dose combinations of antituberculosis drugs in adults^a From Treatment of Tuberculosis Guidelines 2003.

	WEIGHT IN KG			
	30-39	40-54	55-70	>70
Initial phase - daily				
HRZE (75 mg + 150 mg + 400 mg + 275 mg)	2	3	4	5
or: HRZ (75 mg + 150 mg + 400 mg)	2	3	4	5
Category II: add S (vial 1 g) for 2 months	0.5	0.75	1	1
Continuation phase - daily				
either HR (75 mg + 150 mg)	2	3	4	5
Category II: add E (400 mg)	1.5	2	3	3
or HE (150 mg + 400 mg)	1.5	2	3	3
Continuation phase - 3 times weekly				
HR (150 mg + 150 mg)	2	3	4	5
Category II: add E 400 mg	2	4	6	6

^a Adapted from Blomberg B et al. *Informal consultation on 4-drug fixed-dose combinations compliant with the WHO model list of essential drugs, Geneva, 15-17 August 2002.* Geneva, World Health Organization (unpublished).

Source: WHO Treatment Guidelines²

9.2 WHO treatment guidelines

RHE is a component of short-course treatment currently recommended by the WHO for category II tuberculosis. HRZES for 2 months or HRZE for 1 month, followed by HRE for 5 months. The combination therapy can be given daily or 3 times weekly.

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

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. Positive Mantoux skin test only indicates infection, not necessarily TB.

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 search of the published literature failed to identify any studies of treatment with 3-FDC RHE in diagnostic Category II patients for whom the standard re-treatment regimen with RHE throughout is recommended². Formulations of R150/H75/E275 have been shown to reach adequate therapeutic plasma concentrations of rifampicin in healthy volunteers⁶. The data are summarized in the Evidence Table.

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

An *in vitro* evaluation and bioequivalence assessment of two formulations of 3-FDC R150/H75/E275 measured rifampicin pharmacokinetic parameters in 20 healthy male adult volunteers⁶. Participants swallowed 3 tablets of each formulation with 200ml water after overnight fasting in a randomized cross-over sequence with a one week washout period. The rifampicin C_{max} value was above the minimum therapeutic plasma concentration with both formulations at 7.74 μ g/ml (SD 1.39) and 7.36 μ g/ml (SD 1.24) respectively. There was no statistically significant difference between the formulations in AUC_{0-24} or C_{max} values for rifampicin and desacetyl-rifampicin. The upper limit of the rifampicin T_{max} 90% CI was the only value outside the acceptable range for bioequivalence (0.80, 1.25). Both formulations passed quality control tests of weight variation, hardness, friability, disintegration time, assay and a dissolution test in 0.01N HCl. One formulation, Akurit-3, failed the dissolution test at pH6.8⁶.

10. 3 Summary of available estimates of comparative effectiveness

A literature search failed to identify published estimates of effectiveness comparing 3-FDC RHE treatment with alternative combination and/or single drug formulations in diagnostic Category II tuberculosis. Pharmacokinetic data comparing 3-FDC RHE with alternative formulations were not found in the published literature.

Evidence table

Study	Aim	Methods	Population	Intervention	Outcome measures	Results
Ashokraj 2005 ⁶ India	Investigate the feasibility of FDC formulations as reference products for bioequivalence studies of rifampicin	<i>In vitro</i> evaluation and <i>in vivo</i> randomized cross-over study with 1 week washout; HPLC analysis of rifampicin and desacetyl-rifampicin in blood sampled at 1, 2, 3, 4, 6, 8, 12, 24h	22 healthy adult male volunteers; 20 completed the study Inclusion criteria: 18 to 55 years old, within +/-15% of average ideal body weight	3-FDC R150/H75/E275 Reference formulation Akurit-3 (Lupin Laboratories Ltd, Mumbai) and Test formulation (Svizera Laboratories, Mumbai) Single dose, 3 tablets taken with 200ml water after overnight fasting	<i>In vivo</i> : AUC ₀₋₂₄ , C _{max} , T _{max} , t _{1/2} , elimination rate (<i>k</i>), absorption efficiency <i>In vitro</i> : weight, hardness, friability, disintegration time, assay, dissolution	Both formulations achieved effective therapeutic plasma concentrations of rifampicin: C _{max} 7.74 (SD 1.39) and 7.36 (SD 1.24). There was no statistically significant difference in AUC ₀₋₂₄ or C _{max} values but the upper limits of the normal and log transformed rifampicin T _{max} 90% CIs were outside the bioequivalence limit of 1.25 Both formulations passed all <i>in vitro</i> tests except that Akurit-3 failed the pH6.8 dissolution test

11. Summary of comparative evidence on safety Studies

11.1 Estimate of total patient exposure to date

An estimated of 125 millions of tablets have been supplied by the Global TB Drug Facility, the past 2 years. No side effects have been reported except the ones described in standard texts.

11.2 Description of adverse effects/reactions

Adverse effects of rifampicin, isoniazid and ethambutol have been described in standard texts.

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

The cost of category II treatment regimens have been provided for comparison. The currently available separate fixed-dose RH and single-dose E regimen is given in grey, and the second proposed 3-drug RHE combination, is given in white. The cost savings of RHE fixed-dose combination is presented.

Drug	Highest Cost US\$	Lowest Cost (US\$)	Median Cost (US\$)
R+H 150/75	0.0267/Tab-cap	0.0167/Tab-cap	0.0224/Tab-cap
Ethambutol 400	0.0310/Tab-cap	0.0151/Tab-cap	0.0186/Tab-cap
R+H+E 150/75/275	0.0423/Tab-cap	0.0400/Tab-cap	0.0412/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 Dose	Cost per tablet (US\$)	Total cost per day treatment (US\$)	Total cost per 150 day treatment (continuation phase) US\$
R+H 150/75	4 tabs	0.0224/Tab-cap	0.0896	13.44
Ethambutol 400	6 tabs	0.0186/Tab-cap	0.1116	16.74
R+H+E 150/75/275	4 tabs 600/300/2500	0.0412/Tab-cap	0.1648	24.72

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

The triple FDC is registered in Ethiopia, Georgia, India, Kenya, Malawi, Myanmar, Nigeria and Vietnam.

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

The Rifampicin, Isoniazid, Ethambutol HCL is listed in the BP 2005.

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

Rifampicin, isoniazid and ethambutol

Tablets: Rifampicin 150mg, isoniazid 75mg and ethambutol 275mg

Use: For treatment of tuberculosis - this fixed-dose combination of 3 drugs (intended to promote adherence) is used as the continuation phase of treatment of adult tuberculosis patients in diagnostic category II (i.e. retreatment regimen). It is essential that all such products be shown to have adequate bioavailability.

Contraindications: see Rifampicin, Isoniazid and Ethambutol

Precautions: see Rifampicin, Isoniazid and Ethambutol

Dosage: Rifampicin 10mg/kg, isoniazid 5mg/kg, and ethambutol 15mg/kg daily; rifampicin 10mg/kg, isoniazid 10mg/kg and ethambutol 30mg/kg three times a week.

Adverse effects: see Rifampicin, Isoniazid and Ethambutol

References

1. World Health Organization. Global tuberculosis control: WHO report 2006. WHO/HTM/TB/2006.362. Geneva: WHO, 2006.
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5. McFayden JE. International Drug Price Indicator Guide. Arlington: Management sciences for health, 2005.
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