WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

Rifabutin 150 mg capsules for the treatment of TB in HIV-1 infected patients treated with Ritonavir-boosted Protease Inhibitor-containing antiretroviral therapy

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

Proposal for the inclusion of rifabutin 150 mg capsules in the WHO Model List of Essential Medicines for the treatment of diagnostic category I, II, III, and IV tuberculosis, as part of TB combination therapy, in HIV-infected patients treated with Ritonavir-boosted Protease-Inhibitor-containing antiretroviral therapy.

The principal reasons for requesting this inclusion are as follows:

1. Modern, standard TB therapy recommends the use of rifamycins, under normal circumstances, rifampicin, as part of short-course combination chemotherapy within the standardised DOTS strategy.

2. WHO-recommended anti-retroviral therapy (ART) recommends standardised sequencing of antiretroviral drugs with ritonavir-boosted Protease-Inhibitor (PI) based antiretroviral therapy reserved as the preferred therapeutic approach for patients requiring second-line therapy (i.e. patients no longer responding to first-line therapy) or as an alternative option in those with adverse reactions or contraindications to NNRTI’s used in standard first-line therapy.

3. ART in combination with WHO-recommended DOTS is an essential component of TB control and significantly improves survival in HIV/TB co-infected patients.

4. Problematic drug-interactions, between rifampicin and Protease Inhibitors, leading to sub-therapeutic concentrations of PIs mediated by CYP3A4, complicates the concomitant delivery of these essential medicines that form the backbone of successful TB and HIV treatment respectively, prohibiting large scale public-health delivery of these therapies in combination.

5. In contrast, rifabutin has little effect on PI serum concentrations allowing concomitant use of rifabutin and ritonavir-boosted PIs. When used in combination, rifabutin should be dose-reduced by 75%, with boosted-PI-containing therapy given at their standard dose.

6. Rifabutin is equally safe and effective as rifampicin for the treatment of TB, but the information from randomised clinical trials is dominated by HIV negative individuals. The evidence from observational cohort studies including in HIV-infected patients treated with ART does not point to inferior performance of rifabutin, but is less rigorous.
7. Rifabutin is not produced in fixed dose combination. Countries are urged to plan procurement of loose TB drug formulations to be used with rifabutin for patients who require it for use with PIs.

8. Although there is extensive experience with rifabutin for preventing and treating *Mycobacterium avium complex* (MAC) in people living with HIV, given the limited evidence of the safety profile of rifabutin for TB treatment in HIV infected patients, countries are advised to monitor side effects of rifabutin in combination with PI.

9. Rifabutin is cost-effective when used at the recommended 75% reduced dose, in combination with the standard dose of boosted-PI-containing ART.

10. A large-scale problem for HIV and TB co-therapy is emerging as a consequence of the rapid scale-up of ART [and subsequent need for PI-based therapy following failure of standard first-line ART], and the significant incidence of TB in patients on ART.

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

   Charles Gilks, WHO/HTM/HIV/ATC. Tel +41 22 791 4599

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

   Internally developed application

4. **International Non-proprietary Name (INN, generic name) of the medicine**

   Rifabutin

5. **Formulation proposed for inclusion; including adult and paediatric**

   150 mg capsule for adults

6. **International availability – sources, if possible manufacturers**

   Pfizer Inc., NYC, NY, USA; innovator (Mycobutin capsules 150 mg)

   Lupin laboratories Ltd. Mumbai (Bombay), India; generic capsules 150 mg: not prequalified

   Sichuan Med. Shine Pharmaceuticals, China; generic capsules 150 mg: not prequalified

   Macleods, India; generic capsules 150 mg, not prequalified

7. **Category of listing requested**

   Listing is requested as individual product as part of the therapeutic group of anti-tuberculosis therapy drugs

8. **Information supporting the public-health relevance (epidemiological information on disease burden, assessment of current use, target population)**

   10.1 *Epidemiological Information on the disease burden*
The global incidence of HIV/TB co-infection in 2006 was estimated at 700,000 [1]. TB is the most frequent life-threatening opportunistic disease in HIV-infected individuals, even in those receiving ART, and it remains a leading cause of death for people with HIV, with an estimated mortality of 231,000 in HIV/TB co-infected patients in 2006 [1]. Developing countries are the most affected in the world and the majority of high burden countries are in Sub-Saharan Africa. TB is more lethal in immune-compromised populations and ART has significantly reduced mortality in this population to about 5% [2, 3]. This underscores the importance of co-treatment for HIV and TB in this population.

The WHO “Antiretroviral Therapy for HIV Infection in Adults and Adolescents” Guidelines (2006 revision) recommend a combination of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) as the preferred first-line options in developing countries and (ritonavir-boosted) PI-based therapy as preferred second-line therapy in patients no longer receiving benefit from their first-line HIV therapy [4].

The scale up of ART is rapidly expanding at a rate of 80,000 per month, with an estimated 3.0 million people receiving ART at the end of 2007 [5]. The rapid scale-up will lead to increasing numbers of patients failing first-line ART and needing (ritonavir-boosted) PI based therapy. Currently, in low income settings with recently established ART programs, the annual migration from first to second-line therapy is ~ 2%, and in countries with more mature ART programs (i.e. Brazil, Mexico, Thailand), this rate is around 4% per year [6, 7]. Using UNAIDS/WHO projections regarding the pace of ART scale-up, we estimated the number of patients that will develop TB between 2008 and 2015, whilst on PI-based second-line ART, and approximated the total to be between 221,580 and 508,550 with a 2% annual migration, and between 392,760 and 901,810 with a 4% annual migration (see appendix). These totals are based on the most conservative UNAIDS/WHO “projected, based on 2007 actual” ART roll-out scenario [8] that takes into account the 2007/2008 revised estimates of the epidemic [5].

Annual TB rates during ART are almost entirely dependent upon the current CD4 cell count at any given time but are generally thought to be around 3-7%. According to preliminary reports, approximately 15% of patients initiating second-line therapy need treatment for TB disease. For example, in the Gugulethu cohort in Cape Town, South-Africa, the rates according to current CD4 count are as follows: "During cumulative person-time within the 0-100, 101-200, 201-300, 301-400, 401-500 and >500 cells/μL CD4-strata, unadjusted TB incidence rates were 16.8, 9.3, 5.5, 4.6, 4.2 and 1.5 cases/100PYs, respectively (p<0.001). Detectable viral load is also less strongly predictive, but baseline patient characteristics, history of TB etc were not associated”. (Stephen Lawn, personal communication, manuscript submitted). Therefore, once established on PI based therapy with average CD4 counts between 100 and 500 during the course of treatment, incidence rates between 4.2 and 9.3 cases/100 PY would be expected. To allow for lower burden settings a yearly TB incidence of 3-7 % is a realistic estimate of TB disease whilst on PI-based therapy. In the setting of maturing disease programs in low-income settings with 4% annual migration to second-line therapy, this
range would result in 392,760 to 901,810 patients requiring TB treatment whilst on PI-based therapy (see appendix).

Proper dosing and correct usage of anti-TB drugs and ART is essential to prevent failure of therapy and rise of multi-drug resistant TB strains and HIV resistance. Problematic drug-interactions, between rifampicin and PIs, leading to sub-therapeutic concentrations of PIs mediated by CYP3A4, complicates the concomitant delivery of these essential medicines that form the backbone of successful TB and HIV treatment respectively, prohibiting large scale public-health delivery of these therapies in combination. In contrast, rifabutin has little effect on PI serum concentrations allowing concomitant use of rifabutin and PIs in a standardised programmatic approach. It should be noted that when rifabutin is substituted for rifampicin, that programmatic delivery in TB programs that rely upon FDCs is complicated and ordering of loose anti-TB drugs may be needed.

Thus, inclusion of rifabutin on the WHO model list is sought for the treatment of TB in patients treated with a HIV protease inhibitor. The application is supported by an emerging public-health program of scale, demonstrated efficacy and safety of rifabutin for the treatment of TB infection including in HIV infected patients treated with protease inhibitors (section 10 and 11) and cost-effectiveness in combination with PIs (section 12).

10.2 Assessment of current use

Rifabutin is currently not used as standard therapy for TB infection. In addition, the clinical experience with rifabutin for TB disease in resource-constrained settings is limited, especially in the context of the PIs currently recommended in WHO, and other HIV-treatment guidelines. These limitations in the data have hampered the development of clear WHO policy recommendations regarding the programmatic indications and advisability of including rifabutin on the Essential Medicine List (EML). Listing rifabutin on the EML, as a first step toward EOI and PQ, would likely serve to increase the availability of rifabutin for large scale use at affordable cost in the resource-limited settings. The high cost of rifabutin when compared with rifampicin has rendered it thus far inaccessible to tuberculosis control programs in resource-limited settings.

Rifamycins are essential components of TB therapy, and rifampicin is currently recommended by WHO in Category 1, 2 and 3 anti-TB regimens for the duration of treatment [9]. There is consensus that regimens that do not contain rifamycins are inferior to rifamycin-containing regimens [10]. However, despite its efficacy, rifampicin increases the metabolism of many antiretroviral drugs (ARV), leading to sub-therapeutic concentrations of PIs in particular [11]. Recently, consensus was reached on atazanavir (ATV) or lopinavir (LPV) boosted with ritonavir (r) as preferred PIs in second-line ART [12]. Rifampicin is contraindicated for use in combination with ATZ/r due to a greater than 90% reduction of plasma levels during co-administration [13-15]. Rifampicin can only be used in combination with LPV boosted with high-doses of ritonavir (eg. “super-boosting” with ritonavir 400 mg twice daily). This regimen, including the new heat-stable LPV/r tablets, has been associated with high levels of toxicity [16, 17] and is therefore
9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

9.1 Dosage regimen and duration in category I, II, III and IV tuberculosis treatment

Treatment regimens for TB are differentiated according to 4 different treatment categories, with category IV consisting of patients with chronic and MDR-TB cases who are unimproved after re-treatment.


Inclusion of rifabutin on the essential medicines list is sought as a substitute for rifampicin in HIV patients that are on concomitant ART that includes a PI. Therefore, with the use of rifabutin the TB treatment will be able to follow standard drug combinations, as outlined in the WHO guidelines on “Treatment of Tuberculosis: Guidelines for National Programs”, for category I, II, and III TB will apply. The only difference is that rifabutin can be substituted for rifampicin.

In regimens for category I, II and III TB, rifabutin will substitute rifampicin at a standard dose of rifabutin 150 mg 3x/week as part of the recommended short-course multi-drug TB regimens, in combination with the standard dose of the recommended ritonavir-boosted PI-based ART. The dosing of other TB drugs will remain unchanged.

An important advantage of rifabutin is that a 75% dose reduction of the standard 300 mg QD is recommended, when used in combination with all boosted PIs given at their standard dose. The dosing information for rifabutin co-administered with the PIs recommended as preferred options in WHO and other major guidelines (CDC, US-DHHS), dosing information is based on PK interaction studies in healthy volunteers [18-20]. These studies indicate that rifabutin should be used with the recommended standard doses of LPV/r, ATV/r DRV/r and FPV/r [18-20]. However, as PIs inhibit the metabolism of rifabutin, a dosing reduction of rifabutin of ≥75% of the standard dose of 300 mg once daily is required [18-20]. The recommendation translates in a 75 mg daily dose for use with all boosted PIs. However, due to the lack of a 75 mg formulation, rifabutin 150 mg 3x/week or QOD is currently recommended. This translates in a recommendation of 150 mg rifabutin 3x/week or every-other-day (QOD) in combination with these boosted PIs [21, 22].

9.2 Reference to WHO and other clinical guidelines

not suitable for large scale programmatic delivery outside specialist centers of excellence.

10.3 Target Population

HIV-infected patients with category 1, 2 and 3 TB that qualify for TB therapy whilst qualifying for treatment with PI-based ART. Patients that qualify for PI-based ART are those that experience treatment failure on a first-line ART regimen on clinical, immunological or virological failure criteria as defined in WHO guidelines [4], and those with contraindications for NNRTI’s.
Rifabutin is not included in WHO treatment guidelines but referred to for consideration in combination with ART in 5 WHO publications [4, 12, 23-25].

The problematic drug interactions and patient-safety risks of co-administration of rifampicin and PIs are reflected in the CDC, Australian (ASHM), and the US-DHHS treatment guidelines that now recommend rifabutin as first-choice rifamycin in combination with PI-containing therapy [21, 22, 26, 27].

9.3 Need for special diagnostic or treatment facilities and skills

Standard diagnostic procedures for TB in HIV-infected patients will apply.

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

10.1 Identification of clinical evidence

10.1.1 Search Strategy

The following databases were searched in July/August 2008: Pubmed, EMBASE and CAB abstracts using MeSH/EMTREE terms for “HIV protease inhibitors”, “rifabutin” and “tuberculosis”. Additional searches were conducted iteratively in Pubmed and Scholar-Google using a combination of terms and text words. The program and abstracts of the First International Workshop on Clinical Pharmacology of TB Drugs, Toronto, 2008, and 17th International AIDS Conference, Mexico-City, 2008, were reviewed. Additional articles were retrieved by reviewing the citations of articles selected. The abstracts and articles identified were rejected if preclinical, not related to tuberculosis, or outdated general reviews and opinions.

10.1.2 Systematic reviews included

A systematic review on rifabutin for the treatment of TB prepared by the Cochrane library [28], and a review on Drug Interactions in the Treatment of HIV-Related Tuberculosis were included [21].

10.1.3 Selection/exclusion of particular data

Eleven clinical studies assessing efficacy and/or safety outcomes of rifabutin in TB infection were identified from the literature. The study characteristics are summarised in table 1.

Six randomised controlled trails (RCT) were identified. Five of these compared rifabutin with rifampicin [29-33]. The sixth RCT was a phase-II safety study comparing different doses of rifabutin in latent TB infection [34]. Only one RCT was conducted in HIV infected individuals in the resource-limited setting [33] (see table 1).

In addition, five cohort studies were identified. Of these, three observational cohort studies included exclusively HIV infected patients treated with rifabutin [35-37], and two retrospective cohort studies included both rifabutin and rifampicin treated patients and included both HIV+ and HIV- individuals [38, 39] (see table 1).
10.2 Summary of available data (appraisal of quality, outcome measures, summary of results)

The eleven clinical studies with rifabutin for the treatment of TB included a total of 1103 patients (585 HIV+) that were treated with rifabutin-based regimens, and an additional 440 (395 HIV+) that received both rifabutin and rifampicin during the course of TB treatment (see table 1). The studies employed various different dosing regimens and differed in objectives and outcome measures (see table 1).

The five RCTs comparing rifampicin and rifabutin for treating pulmonary TB [29-33] were included in a recent review prepared by the Cochrane library [28]. The studies included 924 participants of which 5% were HIV positive. No further randomised comparisons have been reported since the review. Only two of the trials selected for review were moderately large and contributed 89% of the patient total of the five studies [30, 31]. In these two studies two different rifabutin doses were employed, 150 mg and 300 mg once-a-day (QD), and compared to the standard rifampicin dose of 600 mg QD. One study small RCT included in the review was conducted HIV+ patients. The review of the five studies found no differences in cure and relapse of TB between rifampicin and either of two doses of rifabutin. They found no evidence for using the higher dose of rifabutin and that 150 mg QD was safe and effective. However the authors note that HIV-infected individuals “were under-represented in the included trials and are the group most likely to benefit from substitution of rifampicin with rifabutin due to its lack of interaction with antiretroviral drugs” [28].

The five cohort studies included the vast majority (93%) of HIV-infected individuals in the 11 studies. Due to methodological issues (the retrospective cohort studies only included patients completing therapy), no rigorous efficacy assessment from these studies is possible, but there were no findings that would point to inferior performance of rifabutin. The studies included a total of 313 patients on HIV and rifabutin co-therapy, of which 125 received a PI. No specific efficacy concerns were identified for this subset of patients. In HIV-infected individuals, rifabutin was not associated with a higher risk of acquired rifamycin resistance (ARR) related treatment relapse or failure but related to twice weekly therapy in some studies. Proportionally, less patients treated with rifabutin developed failure or ARR, but the number of events was small and points to successful TB treatment in this difficult to treat population. However, these studies were conducted more than 10 years ago and did not include patients on currently recommended PIs. To date, there are no published efficacy studies of rifabutin in combination with these newer boosted PIs.

10.3 Summary of available estimates of comparative effectiveness

The evidence from the RCTs, dominated by HIV negative individuals, suggests that rifabutin is as effective as rifampicin for the treatment of TB infection. The Cochrane review [28] of five RCT found no statistical difference between the two rifamycins with a relative risk (RR) of 1.00 (95% CI: 0.96 - 1.04) for cure of TB, a RR of 1.23 (95%CI: 0.45 – 3.35) favouring rifampicin for relapse, and a RR of 1.05 (95% CI: 0.96 – 1.15) favouring rifabutin, and 1.00 (95% CI: 0.98 – 1.03), for culture status at 2 and 3 month respectively. The only comparative RCT in HIV positive patients found both rifamycins to
be safe and effective and demonstrated more rapid clearance of acid-fast bacilli in the rifabutin arm (log rank p< 0.05) [33].

11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to date

Estimates of total patient exposure of rifabutin are not available. Rifabutin was licensed in 1992 and widely used for the treatment of *Mycobacterium Avium Intracellulare* Complex in severely immune-compromised HIV-infected patients. In most countries, rifabutin is also registered for TB treatment, and in addition there is evidence (including from observational studies) that rifabutin is used off-label for the treatment of TB in HIV infected patients treated with ART, in the US and very recently in a study from Lilongwe, Malawi, of which 9/60 patients that were switched to second-line ART needed rifabutin for the treatment of TB disease whilst treated with concomitant PI-based ART [40].

11.2 Description of adverse events

The side effects of rifabutin are well described in standard texts. The most common side effects are neutropenia, leucopenia, ALAT/ASAT elevations, rash and upper gastrointestinal complaints, and more rarely uveitis. No unexpected side effects and no cases of uveitis were reported in the eleven reviewed studies but these mostly include HIV negative cohorts. Anecdotal case reports of HIV positive patients show higher rates on pancytopenia and uveitis.., Due to methodological issues, no rigorous assessment of adverse events is possible from the cohort studies. The available evidence suggests that rifabutin is generally well tolerated and in one study rifabutin caused less hepatotoxicity than rifampicin [31]. Greater than 5-fold liver-enzyme elevations were reported in up to 8% of patients [36, 41] and associated with hepatitis-C co-infection in one of the studies [36]. Discontinuation due to adverse events was uncommon. An additional literature search revealed only one case report on uveitis in combination with a PI [42].

The Cochrane review did not find a difference in tolerability between rifampicin and rifabutin but noted a trend for more adverse events with 300 mg QD: the RR of adverse events with the 150 mg dose was 0.98 (95% CI: 0.45 – 2.12), but the RR increased to 1.78 (95% CI: 0.94 – 3.34) favouring rifampicin with higher rifabutin dose [28].

In summary, the evidence suggests that rifabutin is equally safe as rifampicin can be used instead of rifampicin in TB-combination therapy. In one report, rifabutin has been proposed for patients intolerant for rifampicin [43]. However, it is worth noting that the information from randomised clinical trials is dominated by HIV negative cohorts.

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

12.1 Range of cost of the proposed medicine
**Lupin** (provided by Barbara Milani, see below): EX WORK price for one capsule rifabutin 150 mg: 0.84 USD. Estimated EX WORK prices of 6 months rifabutin regimen is around 70 USD, of with > 95% of the cost is due to rifabutin.

**MedShine (RisingPharm):** $3 per dose (information communicated to the Clinton foundation)

The **Pfizer** product cost is $4.86 per dose. This is from the price guide at the following link: [http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2006_En.pdf](http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2006_En.pdf)

**Macleods:** pricing information not available

### 12.2 Comparative cost-effectiveness presented as range of cost per routine outcome

NB. The cost-comparison is here presented as the total cost of the standard recommended dose of 6 month HIV and TB treatment in combination, eg. comparing rifabutin-based TB therapy plus (standard) PI-based ART versus Rifampicin-based TB therapy plus (super-boosted) PI based therapy. This approach is chosen as inclusion of rifabutin in the EML is only sought for use in combination with PI-based ART. Rifabutin (75% dose-reduced) allows for concomitant use of the standard ritonavir-boosted PI dose (ritonavir 100 mg twice daily), and eliminates the need for “super-boosting” with 400 mg ritonavir twice daily, thereby achieving significant cost savings in the ART component of the treatments. Additional cost savings that will arise from standard programmatic delivery [of rifabutin-containing therapy with standard PI-based ART], instead of closely monitored delivery [of rifampicin-containing therapy with super-boosted PI-containing ART] in specialist training centres are not available and not included in the analysis.

In March/April 2007 a cost analysis of PI-based ART with rifampicin or rifabutin based TB regimens was performed. The PIs used in this study were lopinavir (LPV) and saquinavir. For completeness, this is attached as an appendix at the end of the document, but it should be noted that saquinavir is no longer recommended in WHO guidelines. WHO currently recommends LPV/r or ATZ/r as preferred PIs, but ATZ/r is contraindicated for use with standard rifampicin-containing TB therapy. Thus, a cost-comparison of rifabutin and rifampicin in combination with ATZ/r is not relevant and this section will summarise the results comparative cost-effectiveness for rifabutin with LPV/r only.

The cost analysis compares the cost of super-boosted LPV/r plus daily rifampicin and standard LPV/r dose plus rifabutin 150 mg 3x/week (see appendix)

Price data have been extrapolated by the WHO database Global Price reporting mechanism that stores transacted prices by countries on ARVs. Main carriage paid prices for saquinavir, ritonavir, lopinavir/ritonavir have been extracted, cleaned and elaborated for the purpose of this analysis. The estimation has been built for two country categories, Low income countries and Middle income countries. The calculations based on median values of main carriage paid prices for lopinavir/ritonavir during 6 months regimen during TB treatment with rifampicin resulted in a projection of
453.6 USD for Low Income Countries and 2764.8 USD for Middle Income Countries. With rifabutin, the cost projection for lopinavir/ritonavir is of 270 USD for Low Income Countries and 1846.8 USD for Middle Income Countries. This represents a cost saving per regimen of 183.6 USD (40.5%) in Low Income Countries and of 918 USD (33.2 %) in Middle Income countries when rifabutin is used.

The cost for 6 month rifabutin was estimated to be 70 USD compared to 21 USD for rifampicin. This means that the total combined cost HIV and TB therapies using rifabutin is cheaper that that with rifampicin, costing 340 or 1961 USD compared to 474 or 2785 USD in low or middle-income settings respectively, making rifabutin in combination a cost effective treatment option in patients treated with concomitant PI-based ART.

13. Summary of regulatory status

Rifabutin is off-patent [44].

A list of all countries that have registered Pfizer’s Mycobutin® is available. In all countries in which is registered it is registered for the treatment of Mycobacterium Avium disease and Tuberculosis, except Canada, USA, Japan, Taiwan and South-Africa in which is only registered for the treatment Mycobacterium Avium. In Belarus and Ireland it is exclusively registered for treatment of tuberculosis

The following information has been provided by the Clinton Foundation: Lupin’s product is not approved by a stringent authority, and bioequivalence has not been run on their product. It is manufactured in an FDA approved facility that manufactures other TB products, and is manufactured under GMP. Rifabutin does not qualify for a BCS biowaver based on dissolution data, so bioequivalence will be required for stringent authority approval. It does qualify for GFATM funded purchases in the c(ii) category. Medshine’s product is SFDA approved and available in China. It is not known whether the facility has been inspected by an SRA. Bioequivalence has not been run on this product. Macleods product is available in India. Information on the regulatory status is not available but their product has not gone through bioequivalence studies either.

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

Rifabutin is listed in the US Pharmacopeia 2007. It is not listed in the International Pharmacopeia.

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

Description:

Rifabutin is a wide spectrum, semi-synthetic ansamycin antibiotic particularly active on acid-fast bacilli, including atypical and multidrug-resistant mycobacteria.

It is supplied in capsules for oral administration: Rifabutin 150 mg.

Use:
Rifabutin is indicated for the treatment of tuberculosis in HIV-infected patients treated with a concomitant ritonavir-boosted protease inhibitor – rifabutin is used as a substitute for rifampicin as part of multi-drug anti-tuberculosis chemotherapy in HIV-infected patients with concomitant use of protease-inhibitor-containing anti-retroviral therapy.

Contraindications:

Rifabutin is contraindicated in patients with a history of hypersensitivity to rifabutin or other rifamycins (e.g. rifampicin).

Delavirdine should not be coadministered with rifabutin.

Precautions:

Rifabutin may impart a red-orange colour to the urine and possibly to skin and body secretions. Contact lenses, especially the soft variety, may be permanently stained.

In accordance with the commonly accepted criteria for the treatment of mycobacterial infections, rifabutin should always be given in combination with other anti-mycobacterial drugs not belonging to the family of rifamycins.

Consideration should be given to monitoring white blood cell and platelet counts and liver enzymes during long term treatment with multidrug regimens that include rifabutin because rifabutin may be associated with neutropenia and, more rarely, thrombocytopenia.

Rifamycins have been associated with drug-induced hepatic breakdown of vitamin K in pregnant women and their offspring (see Use in Pregnancy).

*Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifabutin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile*.

**Hepatic Impairment:** Rifabutin should be used with caution in cases of liver insufficiency. For patients with severe liver insufficiency a dose reduction should be considered. Mild hepatic impairment does not require a dose modification.

**Renal Impairment**
Mild to moderate renal impairment does not require any dosage adjustment. Severe renal impairment (creatinine clearance below 30 mL/min) requires a dosage reduction of 50%

**Uveitis**
When rifabutin is given in association with clarithromycin, the dosage of rifabutin should be reduced to 300 mg (see Adverse Reactions). Because of the possibility of occurrence of uveitis, patients should be carefully monitored when rifabutin is given in combination with clarithromycin (or other macrolides) and/or fluconazole (and related compounds). If uveitis occurs, the patient should be referred to an ophthalmologist. If considered necessary rifabutin treatment should be discontinued and appropriate treatment given.

**Use in Pregnancy** - Category C
Reproduction studies have been carried out in rats and rabbits. Teratogenicity was not observed in either species. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, rifabutin should be used in pregnant women only if the potential benefit justifies the potential risk to the foetus.

During the late stages of pregnancy, rifampicin has been associated with serious vitamin K deficiency in mother and neonate, resulting in haemorrhagic disturbances. Rifabutin has not been studied in pregnancy. This should be borne in mind if, in exceptional cases, the physician considers the benefit of treatment outweighs the risk and wishes to treat a pregnant woman with rifabutin.

Use in Lactation
It is not known whether rifabutin is excreted in human breast milk. Because many drugs are excreted in human milk and the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Malabsorption
Gastric pH alteration due to progressing HIV disease has been linked with malabsorption of some drugs used in HIV-positive patients (eg rifampin, isoniazid). Drug serum concentration data from AIDS patients with varying disease severity (based on CD4+ counts) suggest that rifabutin absorption is not influenced by progressing HIV disease.

Drug interactions
Rifabutin is metabolized by the cytochrome P450 system. Although structurally similar to rifampicin, rifabutin appears to induce enzymes of the P450 system to a lesser extent. Therefore, as rifabutin has been shown to induce the enzymes of the cytochrome P450 3A subfamily, rifabutin may alter the metabolism of some drugs metabolized by the enzymes belonging to that subfamily (as is seen with rifampicin).

Rifabutin accelerates the metabolism of: Fluconazole, Oral contraceptives, Methadone, Phenytoin,

Rifabutin decreases the concentration of: Atovaquone, Sulfamethoxazole, Benzodiazepines, Tacrolimus, Opiate analgesics, Trimethoprim

Rifabutin accelerates the metabolism and may decrease plasma concentrations of: Astemizole, Lovastatin, Calcium channel blockers, Midazolam, Cisapride, Nevirapine, Clarithromycin, Oestrogens, Corticosteroids, Quinidine, Cyclosporin, Ritonavir, Delavirdine, Saquinavir, Erythromycin, Terfenadine, Indinavir, Theophylline, Itraconazole Triazolam, Ketoconazole, Warfarin, Lvidocaine, Zidovudine

In addition, some drugs increase the concentration of rifabutin and these include the following: Ciprofloxacin, Clarithromycin, Itraconazole, Enoxacin, etoconazole, Erythromycin, Fluconazole, and Protease Inhibitors.

Protease inhibitors act as substrates or inhibitors of cyp450 IIIA4 mediated metabolism. Due to significant drug-drug interactions between protease inhibitors and rifabutin, rifabutin should be dose reduced during concomitant use. When administered with ritonavir-boosted protease inhibitors, lopinavir (LPV/r), atazanavir (ATZ/r), fosamprenavir (FPV/r) or
In regimen, shown recommended clearly Blood (approximately 4% to 12%). Nelfinavir, indinavir, saquinavir and ritonavir significantly increase rifabutin. Rifabutin should be dose reduced and their concomitant use of should be carefully monitored and the combination only used if clearly indicated and no other options are available. Concomitant use of rifabutin and ritonavir, in high dose as a single agent, is contraindicated.

Although pharmacokinetic data have shown that rifabutin, when given in combination with zidovudine, reduces the plasma levels of the latter, a large, controlled clinical study has shown that these changes are of no clinical relevance.

In contrast, no significant interactions may be expected with ethambutol, pyrazinamide, theophylline, sulfonamides and zalcitabine (DDC).

Clinical studies have shown that rifabutin does not affect the pharmacokinetics of didanosine (DDI), isoniazid and fluconazole: fluconazole however increases rifabutin plasma levels. Zidovudine and DDI were shown not to affect the pharmacokinetics of rifabutin.

There are insufficient data to assess whether dose adjustments are necessary when nevirapine and rifabutin are coadministered. Concomitant use of these drugs should be carefully monitored and the combination only used if clearly indicated.

When rifabutin is used concomitantly with clarithromycin, a decreased dose of rifabutin is recommended due to the increase in plasma concentrations of rifabutin. Other macrolide antibiotics may also inhibit metabolism of rifabutin.

**Adverse Effects (from Mycobutin®)**

The tolerability of rifabutin in multiple drug regimens was assessed in both immunocompetent and immunocompromised patients suffering from tuberculosis and nontuberculous mycobacteriosis in long-term studies with daily dosages up to 600 mg. Bearing in mind that rifabutin was often given in these studies as part of a multidrug regimen, it is not possible to define with certainty a drug-event relationship.

The most commonly reported adverse events, in decreasing rank of frequency, were primarily related to:

**Gastrointestinal system:** Such as nausea, vomiting, increase of liver enzymes, jaundice (approximately 8-12%).

**Blood and lymphatic system:** Such as leucopenia, thrombocytopenia and anaemia (approximately 4-9%). The frequency and severity of haematological reactions may be increased by combined administration of isoniazid.

**Musculo-skeletal system:** Arthralgia and myalgia (approximately 3%). Also fever (approximately 2-4%), rash (approximately 3-4%) and, rarely (<1%), other hypersensitivity reactions such as eosinophilia, bronchospasm and shock might occur, as has been seen with other antibiotics.

**Dermatological:** Limited numbers of cases of skin discoloration have been reported.

**Ocular:** Mild to severe, reversible uveitis has been reported. The risk is very low when rifabutin is used at 300 mg as monotherapy in MAC prophylaxis, but increases when rifabutin is administered at higher doses in combination with clarithromycin for MAC treatment (see Precautions). The possible role of fluconazole (and related compounds) in increasing the risk of uveitis has not yet been established. Uveitis has not been reported in
patients treated with rifabutin (150 to 600 mg daily) in combination with other drugs for primary pulmonary tuberculosis.

Dosage:

For the treatment of tuberculosis in HIV-infected patients in combination with the ritonavir boosted protease inhibitors lopinavir (LPV/r), atazanavir (ATZ/r), fosamprenavir (FPV/r) and darunavir (DRV/r): Rifabutin 150 mg three times per week, or Rifabutin 150 mg every-other-day, at any time independent of meals.

Caution should be applied when rifabutin is coadministered with any of the other drugs listed in the "Interactions with Other Drugs" section. Dosages of either drug may need to be adjusted on a case-by-case basis.

16. References


