WHO-PQ RECOMMENDED

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rifampicin 300 mg Capsules*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains rifampicin 300 mg

Excipients with known effect:
Each capsule contains:

- 0.7 mg of carmoisine (azorubine)
- 0.1728 mg of sodium methyl parahydroxybenzoate
- 0.0192 mg of sodium propyl parahydroxybenzoate
- 0.28 mg of sunset yellow (FD&C yellow #6)
- 0.196 mg ponceau 4R (cochineal red A)

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Scarlet/scarlet hard gelatin, size "0" capsule, filled with brick red powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Rifampicin 300 mg Capsules used in combination with other anti-tuberculosis drugs, is indicated for the treatment of tuberculosis caused by drug-susceptible *Mycobacterium tuberculosis.*

Consideration should be given to official treatment guidelines and recommendations for tuberculosis. Official guidance will normally include WHO and local health authorities guidance.

4.2 Posology and method of administration

Oral use.

Adults:

10mg/kg (8-12mg/kg) daily or 3 times weekly, maximum 600mg (2 capsules)

Children (only for children who can swallow capsules):

10-20mg/kg daily, maximum 600mg (2 capsules)

Rifampicin 300 mg Capsules should not be used for intermittent treatment regimens.
Rifampicin 300 mg Capsules should be taken on an empty stomach (at least one hour prior to or two hours after a meal) to ensure rapid and complete absorption.

*Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the trade/proprietary name is given as an example only.

Hepatic impairment:
Limited data indicate that the pharmacokinetics of rifampicin is altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of toxicity. Rifampicin 300 mg Capsules must not be used in patients with severe liver disease (see section 4.3).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Acute liver disease, icterus or severe liver impairment.

Co-administration of Rifampicin 300 mg Capsules is contraindicated with

- voriconazole

- any HIV protease inhibitor

- the following agents for therapy of hepatitis C: boceprevir, daclatasvir, ledipasvir and sofosbuvir (see section 4.5).

4.4 Special warnings and precautions for use

Liver toxicity: Rifampicin may cause hepatotoxicity (see section 4.8).

Whenever possible, the use of Rifampicin 300 mg Capsules should be avoided in patients with pre-existing hepatic impairment (ALT> 3 x ULN) due to the risk of liver toxicity. Patients should be strongly advised to restrict intake of alcoholic beverages while being treated with Rifampicin 300 mg Capsules. Patient groups especially at risk for developing hepatitis include:
- age> 35 years,
- daily users of alcohol (see section 4.5),
- patients with active chronic liver disease
- intravenous drug users.

Furthermore, the following patients should be carefully monitored:
- patients with concurrent use of any chronically administered medication (see section 4.5),
- existence of peripheral neuropathy or conditions predisposing to neuropathy,
- pregnant patients,
- HIV positive patients.

Patients should be instructed to immediately report signs or symptoms consistent with liver damage orother adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting,dark urine, icterus, rash, persistent paraesthesiae of the hands and feet, persistent fatigue orweakness of greater than 3 days duration or abdominal tenderness, especially of the right upperquadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, Rifampicin 300 mg Capsules should be discontinued promptly, since continued use in these cases may cause a more severe form of liver damage.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured prior to starting therapy with Rifampicin 300 mg Capsules and periodically throughout treatment.

Increased liver function tests are common during therapy with Rifampicin 300 mg Capsules. A cholestatic pattern is usually caused by rifampicin. These effect on liver function tests are usually mild to moderate, and will most commonly normalise spontaneously within three months, even with continued therapy.
If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of Rifampicin 300 mg Capsules should be strongly considered. Reinstitution of rifampicin therapy should only be performed when symptoms and laboratory abnormalities have subsided.

Hypersensitivity: Rifampicin may cause a hypersensitivity syndrome including 'flu-like' symptoms or organ manifestation. The risk is higher in intermittent therapy or if treatment is resumed after discontinuation. If severe, acute signs of rifampicin hypersensitivity do appear (e.g.thrombocytopenia, purpura, haemolyticanaemia, dyspnoea, shock or acute renal failure), Rifampicin 300 mg Capsules should immediately be discontinued. Such patients should not be rechallenged withrifampicin. If rifampicin therapy is temporarily discontinued, rifampicin should be restarted carefullyat a reduced dose, and with close monitoring. In this situation, Rifampicin 300 mg Capsules shouldnot be used.

Haematological toxicity: Since rifampicin treatment has been associated with haemolyticanaemia, leucopenia and thrombocytopenia, full blood count should be monitored regularly throughout therapy with Rifampicin 300 mg Capsules. In case of severe haematological disturbances, Rifampicin 300 mg Capsules must be discontinued.

Drug interactions
Rifampicin is a strong inducer of hepatic drug metabolism. Therefore Rifampicin 300 mg Capsules may reduce exposure and efficacy of many therapeutic drugs, including antiviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives (see sections 4.3 and 4.5).

Contraception:
Oral contraceptives do not provide adequate protection against conception when co-administered with Rifampicin 300 mg Capsules. This probably also pertains to other forms of hormonal contraceptives (e.g. patches, transdermal implants). Barrier or other non-hormonal methods of contraception should be used.

Corticosteroids:
Rifampicin 300 mg Capsules may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

Other anti-tuberculosis drugs:
If p-aminosalicylic acid and rifampicin are both included in the treatment regimen, they should be given not less than eight hours apart to ensure satisfactory blood levels.

When rifampicin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampicin and halothane should be avoided. Patients receiving both rifampicin and isoniazid should be monitored closely for hepatotoxicity.

Porphyria: Rifampicin 300 mg Capsules should be used with caution in patients with porphyria, since the enzyme induction by rifampicin may cause symptoms.

Discoloration of body fluids: Rifampicin 300 mg Capsules may cause a reddish-orange discoloration of body fluids such as urine, sputum and tears.

Laboratory monitoring: Full blood count and liver function should be monitored prior to and at regular intervals during treatment with Rifampicin 300 mg Capsules.

Excipients:
Rifampicin 300 mg Capsules containscarmoisine (azorubine); sodium methyl parahydroxybenzoate; sodium propyl parahydroxybenzoate; sunset yellow (FD&C yellow #6); and Ponceau 4R (cochineal red A) which may cause allergic reactions

4.5 Interactions with other medicinal products and other forms of interaction

Rifampicin is a very potent inducer of the hepatic and intestinal cytochrome P-450 enzyme system, as well as of glucuronidation and the P-glycoprotein transport system**.** Administration of rifampicin with drugs that undergo biotransformation through these metabolic pathways is likely to accelerate elimination of co-administered drugs. These effects approach their maximum after about 10 days of treatment, and gradually return to normal within 2 or more weeks after discontinuation. This must be taken into account when co-treating with other drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping the concomitant administration of Rifampicin 300 mg Capsules.

Rifampicin 300 mg Capsules may interact with a very large number of other drugs, primarily by reducing the exposure to co-administered agents, reducing their efficacy and increasing the risk of therapeutic failure. For many important therapeutic agents, no interaction data with rifampicin are available. However, clinically significant reductions in drug exposure may occur. Whenever co-prescribing any drug together with Rifampicin 300 mg Capsules, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with Rifampicin 300 mg Capsules is not exhaustive, but is a selection of interactions of putative importance. The scope of the table is largely based on the WHO Essential Medicines List.

Drugs by Therapeutic Area	**Interaction**	**Recommendations on co-administration**
INFECTION *Antiretrovirals: nucleoside analogues*		
Zidovudine	Zidovudine AUC ↓ 47%	The clinical significance of the lowered zidovudine exposure is unknown. Dose modification of zidovudine in this situation has not been formally evaluated.
Stavudine **Didanosine** **Lamivudine** **Emtricitabine**	No interaction expected	No dose adjustment required
Tenofovirdisoproxilfumarate	Tenofovir AUC ↓ 13%	No dose adjustment required
Abacavir	Empirical data are lacking, but rifampicin may decrease abacavirconcentrationby inducingglucuronidation	Efficacy of abacavir should be closely monitored in co-treatment
Antiretrovirals: non-nucleoside analogues		
Efavirenz	Efavirenz AUC ↓ 26%	When co-treating with Rifampicin 300 mgCapsules, consideration may be given to increasing theefavirenz dose(to 800 mg once daily in adults)

Drugs by Therapeutic Area	Interaction	Recommendations on co-administration
Nevirapine	Nevirapine: AUC ↓ 58%	Since neither the appropriate nevirapine dose when given with rifampicin, nor the safety of the combination has been established, concomitant use of Rifampicin 300 mg Capsules and nevirapine is not recommended
Etravirine	Rifampicin is likely to significantly reduce etravirine concentration	Concomitant treatment of Rifampicin 300mg Capsules with etravirine should be avoided
Rilpivirine	Rilpivirine AUC ↓ 80%	Rifampicin 300 mg Capsules must not be co-administered with rilpivirine
Antiretrovirals: protease inhibitors		
Atazanavir(also atazanavir with cobicistat) **Darunavir**(also darunavir with cobicistat) **Fosamprenavir** **Indinavir** **Lopinavir** **Nelfinavir** **Ritonavir** **Saquinavir** **Tipranavir**	Protease inhibitor exposure will be reduced to sub-therapeutic level due to interaction with rifampicin. Rifampicin also reduces levels ofcobicistat (used for boostingatazanavir and darunavir) and can lead to loss of therapeutic effect and possible development of resistance	Rifampicin 300 mg Capsules must not be co-administered with protease inhibitors. (See section 4.3).
Other antiretrovirals		
Bictegravir	Bictegravir AUC ↓ 75%	Rifampicin 300mg Capsules must not be co-administered with bictegravir
Dolutegravir	Dolutegravir AUC ↓ 54% Cmax↓ 43% Cτ↓ 72%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin. Children should receive the weight-based dose of dolutegravir twice daily
Elvitegravir with cobicistat	Rifampicin significantly reduces levels of elvitegravir and cobicistat and can lead to loss of therapeutic effect and possible development of resistance	Rifampicin 300 mg Capsules must not be co-administered with elvitegravir and cobicistat
Raltegravir	Raltegravir AUC ↓ 40%	If co-treatment is necessary, increasing the raltegravir dose (to 600 mg twice daily in adults) should be considered
Maraviroc	Maraviroc AUC ↓ 63%	Co-treatment should be avoided. If maraviroc is necessary, the dose should be increased (to 600 mg twice daily in adults)

Drugs by Therapeutic Area	Interaction	Recommendations on co-administration
Antivirals for treating chronic hepatitis C		
Daclatasvir	↓ Daclatasvir AUC: 0.21 (0.19, 0.23) Cmax: 0.44 (0.40, 0.48)	Co-administration with daclatasvir is contraindicated (see section 4.3)
Simeprevir	Simeprevir AUC 0.52 (0.41-0.67) ↓ Simeprevir Cmax 1.31 (1.03-1.66) ↑ Simeprevir Cmin 0.08 (0.06-0.11) ↓	It is not recommended to coadminister simeprevir with rifampicin as coadministration may result in loss of therapeutic effect of simeprevir.
Boceprevir	No data are available. The concomitant use may significantly reduce the plasma exposure of boceprevir through induction of CYP.	The combination of rifampicin with boceprevir is contraindicated (see section 4.3)
Ledipasvir	Ledipasvir ↓ Cmax 0.65 (0.56, 0.76) ↓ AUC 0.41 (0.36, 0.48)	Coadministration with ledipasvir is contraindicated (see section 4.3)
Sofosbuvir	Sofosbuvir ↓ Cmax 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) Cmin (NA) GS-331007 ↔ Cmax 1.23 (1.14, 1.34) ↔ AUC 0.95 (0.88, 1.03) Cmin (NA)	Coadministration with sofosbuvir is contraindicated (see section 4.3).
Antifungals		
Ketoconazole	Ketoconazole AUC ↓ 80%	Co-administration should be avoided but if necessary, a higher dose of ketoconazole may be required
Fluconazole	Fluconazole AUC ↓ 23%	Efficacy should be monitored. A higher dose of fluconazole may be required
Itraconazole	Itraconazole AUC ↓ 64–88% (or more)	Co-administration should be avoided
Voriconazole	Voriconazole AUC ↓ 96%	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.

Drugs by Therapeutic Area	Interaction	Recommendations on co-administration
Antibacterials including antituberculosis antibacterials		
Clarithromycin	Clarithromycin mean serum concentration ↓ 85%. 14-OH clarithromycin levels unchanged	Co-administration should be avoided
Chloramphenicol	Case reports indicate > 60–80% reduction of chloramphenicol exposure.	Co-administration should be avoided
Ciprofloxacin	No significant interaction	No dose adjustment required
Doxycycline	Doxycycline AUC ↓ 50–60%	If co-treatment is considered necessary, the dose of doxycycline should be doubled
Metronidazole	Metronidazole AUC (intravenous) ↓ 33%	The clinical relevance of the interaction is unknown. No dose adjustment is recommended. Efficacy should be monitored
Sulfamethoxazole	Sulfamethoxazole AUC ↓ 23%	Interaction probably not clinically significant. Efficacy of sulfamethoxazole should be monitored
Trimethoprim	Trimethoprim AUC ↓ 47%	A dose increase of trimethoprim may be required. Efficacy should be monitored
Ethionamide		Rifampicin and ethionamide should not be co-administered, due to increased risk of hepatotoxicity
P-aminosalicylic acid	In vitro data show reduced uptake of P-aminosalicylic acid by the OATP1B1 transporter due to inhibition by rifampicin.	If p-aminosalicylic acid and rifampicin are both included in the treatment regimen, they should be given not less than eight hours apart to ensure satisfactory blood levels
Antimalarials		
Chloroquine		Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifampicin co-therapy. Co-administration should be avoided
Atovaquone	Atovaquone AUC ↓ 50% Rifampicin AUC ↑ 30%	Co-administration should be avoided
Mefloquine	Mefloquine AUC ↓ 68%	Co-administration should be avoided
Amodiaquine	Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is likely that clearance is increased when co-treating with rifampicin.	Co-administration should be avoided

Drugs by Therapeutic Area	Interaction	Recommendations on co-administration
Quinine	Quinine AUC ↓ ≈ 80%. This has been associated with significantly higher recrudescence rates.	Co-administration should be avoided. If co-administration is necessary, a higher dose of quinine should be considered
Lumefantrine	Empirical data are not available. Since lumefantrine is metabolised by CYP3A, lower levels are expected with rifampicin co-treatment.	Co-administration should be avoided
Artemisinin and derivatives	Empirical data are not available. During co-treatment with rifampicin, lower levels of artemisinin and its derivatives may be expected.	Co-administration should be avoided
ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS		
Morphine	Morphine AUC (by mouth)↓ 30%	If co-administration necessary, efficacy should be monitored and the dose may need to be increased
Codeine	Plasma level of morphine, an active metabolite of codeine, is likely to be substantially reduced.	Efficacy should be monitored and codeine dose increased if necessary
Methadone	Methadone AUC ↓ 33–66%	Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate
Paracetamol (acetaminophen)	Rifampicin may increase the glucuronidation of paracetamol and decrease its efficacy	Co-administration of Rifampicin 300 mg Capsules and paracetamol (acetaminophen)should be avoided
ANTICONVULSANTS		
Carbamazepine	Rifampicin is expected to decrease the serum concentration of carbamazepine.	Co-administration of Rifampicin 300 mg Capsules and carbamazepine should be avoided
Phenobarbital	Phenobarbital and rifampicin are both strong hepatic enzyme inducers, and each may lower the plasma concentrations of the other.	Co-administration of Rifampicin 300 mg Capsules and phenobarbital should be undertaken with caution, with monitoring of clinical effects and, if possible, plasma drug concentrations

Drugs by Therapeutic Area	Interaction	Recommendations on co-administration
Phenytoin	Phenytoin AUC (intravenous)↓ 42%	Co-treatment with phenytoin and Rifampicin 300 mg Capsules should be avoided
Valproic acid	Since valproic acid is eliminated through hepatic metabolism, including glucuronidation, rifampicin is likely toreduce plasma level of valproic acid	Co-treatment should be avoided. If necessary, efficacy and, if possible, plasma concentrations of valproic acid, should be monitored
Lamotrigine	Lamotrigine AUC ↓ 45%	Co-treatment should be avoided but if necessary, lamotrigine dose should be increased.
IMMUNOSUPPRESSIVES		
Cyclosporine	Rifampicin can substantially increase cyclosporine clearance	Co-administration should be avoided but if necessary, plasma concentration of cyclosporine should be monitored and doses adapted accordingly (3–5 fold increases in cyclosporine dose have been required).
Tacrolimus	Tacrolimus AUC (intravenous) ↓ 35%; AUC (oral) ↓ 70%	Co-administration of Rifampicin 300 mg Capsules and tacrolimus should be avoided but if necessary, plasma concentrations of tacrolimus should be monitored, and the dose increased as appropriate
CARDIOVASCULAR MEDICINES		
Warfarin	Warfarin AUC ↓ 85%	Co-administration should be avoided
Atenolol	Atenolol AUC ↓ 19%	No dose adjustment required
Verapamil	S-verapamil (oral) CL/F ↑ 32-fold. With (intravenous) S-verapamil, CL ↑ 1.3-fold	Rifampicin 300 mg Capsules and oral verapamil should not be co-administered. If verapamil is given intravenously, the therapeutic effect should be carefully monitored; dose adjustment may be required
Digoxin	AUC (oral)↓ 30%	When co-administering Rifampicin 300 mg Capsules with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required
Lidocaine	Lidocaine CL (intravenous) ↑ 15%	No dose adjustment required
Amlodipine	Amlodipine, like other calcium-channel blockers, is metabolised by CYP3A; lower exposure is expected when co-treating with rifampicin	Efficacy should be monitored

Drugs by Therapeutic Area	Interaction	Recommendations on co-administration
Enalapril	No interaction expected	No dose adjustment required
Simvastatin	Simvastatin AUC ↓ 87% Simvastatin acid AUC ↓ 93%	Co-administration is not recommended
GASTROINTESTINAL MEDICINES		
Ranitidine	Ranitidine AUC ↓ 52%	Efficacy should be monitored, and ranitidine dose increased if necessary
Antacids	Antacids may reduce the bioavailability of rifampicin by up to one-third	The clinical importance is unknown Acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used, if co-treatment with Rifampicin 300 mg Capsules is necessary
PSYCHOTHERAPEUTIC MEDICINES		
Diazepam	Diazepam AUC ↓> 70%	Co-treatment is not recommended. If deemed necessary, diazepam doses may need to be increased
Chlorpromazine	Rifampicin may reduce chlorpromazine exposure.	Co-administration should be avoided. If considered necessary, patients should be carefully monitored for isoniazid toxicity
Haloperidol	Rifampicin substantially increases haloperidol clearance	If co-treatment of Rifampicin 300 mg Capsules with haloperidol is necessary, efficacy of haloperidol should be monitored. A dose increase may be required
Amitriptyline	Case reports (and theoretical considerations) suggest that rifampicin considerably increases amitriptyline clearance	Co-treatment should be avoided. If necessary, efficacy and, if possible, plasma concentrations of amitriptyline should be monitored.
HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES		
Prednisolone and other systemically administered corticosteroids	Prednisolone AUC ↓ 66% Also for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifampicin.	Co-administration of Rifampicin 300 mg Capsules with corticosteroids should be avoided. If deemed necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses adjusted as needed
Glibenclamide	Glibenclamide AUC ↓ 34%	Blood glucose levels should be closely monitored. The dose of glibenclamide may need to be increased
Insulin	No interaction expected	No dose adjustment required.

Drugs by Therapeutic Area	Interaction	Recommendations on co-administration
Levothyroxine	Rifampicin may decrease the effect of levothyroxine.	TSH levels should be monitored
Ethinylestradiol	Ethinylestradiol AUC ↓ 66%	Co-administration with Rifampicin 300 mg Capsules may decrease contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used
Norethisterone	Norethisterone AUC ↓ 51%	Co-administration with Rifampicin 300 mg Capsules may decrease contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used
OTHER MEDICINES		
Praziquantel	Praziquantel AUC ↓ 80–99%	Co-treatment with Rifampicin 300 mg Capsules should be avoided

Interference with laboratory and diagnostic tests
Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Thus alternative assay methods should be considered. Transient elevation of BSP and serum bilirubin has been reported. Rifampicin may impair biliary excretion of contrast media used for visualization of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of rifampicin.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although rifampicin has been reported to cross the placental barrier and appear in the cord blood, the effect of rifampicin, alone or in combination with other antituberculosis drugs, on the human fetus is not known. Rifampicin 300 mg Capsules should be used in pregnancy only if the benefits are considered to outweigh the risks. When rifampicin is administered during the last few weeks of pregnancy it may cause post-natal haemorrhage in the mother and infant for which treatment with vitamin K1 may be indicated.

Breast-feeding
Rifampicin is excreted in the breast milk of lactating mothers. However, concentrations in breast milk are so low, that breast-feeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants. No adverse effects in the baby have been reported.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most important adverse reactions of rifampicin are hepatotoxicity, particularly cholestatic reactions, and skin reactions. Rifampicin may cause subclinical, unconjugated hyperbilirubinaemia or jaundice without hepatocellular damage, but occasionally causes

hepatocellular injury. It can also potentiate the hepatotoxicity of the other anti-tuberculosis medications.

Cutaneous reactions which are mild and self-limiting may occur and do not appear to be hypersensitivity reactions. Typically, they consist of flushing and itching with or without a rash. Urticaria and more serious hypersensitivity cutaneous reactions have occurred but are uncommon. Exfoliate dermatitis, pemphigoid reaction, erythema multiforme including Stevens-Johnson syndrome, Lyells syndrome and vasculitis have been reported rarely.

Gastrointestinal reactions consist of anorexia, nausea, vomiting, abdominal discomfort, and diarrhoea. Pseudomembranous colitis has been reported with rifampicin therapy.

Hepatitis can be caused by rifampicin and liver function tests should be monitored (see section 4.4).

Central Nervous system: Psychoses have been rarely reported.

Thrombocytopenia with or without purpura may occur, usually associated with intermittent therapy, but is reversible if drug is discontinued as soon as purpura occurs. Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.

Disseminated intravascular coagulation has also been rarely reported.
Eosinophilia, leucopenia, oedema, muscle weakness, and myopathy have been reported to occur in a small percentage of patients treated with rifampicin. Agranulocytosis has been very rarely reported.

Rare reports of adrenal insufficiency in patient with compromised adrenal function have been observed.

Reactions usually occurring with intermittent dosage regimens and most probably of immunological origin include:
- 'Flu Syndrome' consisting of episodes of fever, chills, headache, dizziness, and bone pain appearing most commonly during the 3rd to the 6th month of therapy. The frequency of the syndrome varies but may occur in up to 50% of patients given once-weekly regimens with a dose of rifampicin of 25mg/kg or more.
- Shortness of breath and wheezing
- Decrease in blood pressure and shock
- Anaphylaxis
- Acute haemolyticanaemia
- Acute renal failure usually due to acute tubular necrosis or to acute interstitial nephritis.

If serious complications arise, e.g. renal failure, thrombocytopenia or haemolyticanaemia, rifampicin should be stopped and never restarted.

Occasional disturbances of the menstrual cycle have been reported in women receiving long term antituberculosis therapy with regimens containing rifampicin.

Rifampicin may produce a reddish discolouration of the urine, sweat, sputum and tears. The patient should be forewarned of this. Soft contact lenses may be permanently stained.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Symptoms

When overdosed, rifampicin may cause a reddish-orange discolouration of the skin ('red man syndrome'). Further symptoms include hypotension, sinus tachycardia, ventricular arrhythmias, seizures, facial oedema, pruritus, nausea, vomiting and abdominal tenderness. In adults, a total dose of14 g has caused cardiopulmonary arrest.

Treatment

Intensive supportive measures should be instituted and individual symptoms treated as they arise. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis. Following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting. Active diuresis (with measured intake and output) will help promote excretion of the drug. Haemodialysis may be of value in some patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, antibiotics ATC Code: J04AB02.

Mechanism of action

In vitro, rifampicin is bactericidal against a wide range of organisms, including *Mycobacterium tuberculosis*. It inhibits DNA-dependent RNA polymerase, inhibiting transcription. In tuberculosis, rifampicin is bactericidal for both intracellular and extracellular microorganisms. The bacteria may develop resistance as a result of alterations in the target enzyme (RNA polymerase).

5.2 Pharmacokinetic Properties

Absorption

Rifampicin is rapidly absorbed from the gastrointestinal tract. Its bioavailability is 90–95% in adults, but may be lower in children. Concomitant intake of food delays absorption and reduces the peak concentration, but does not decrease bioavailability.

Following single dose administration of 1 × Rifampicin 300 mg Capsules in healthy volunteers, used for comparing the bioavailability of this product with the same dose of the reference formulation, the mean (±SD) rifampicin C_{max} value was 6.56 (±1.68)µg/ml, and the corresponding value for AUC was 36.8 (±10.7)µg·hour/ml. The mean (±SD) rifampicin t_{max} value was 1.46 (±0.44) hours.

Distribution

Rifampicin is 60–90% bound to plasma proteins and has a volume of distribution of approximately 0.9 litre/kg. CSF concentrations are of the same order of magnitude as the unbound concentrations in plasma. Rifampicin readily crosses the placenta.

Metabolism

Rifampicin is metabolised by hydrolysis and desacetylation into several metabolites, including the active metabolite desacetylrifampicin. Rifampicin induces its own metabolism; after repeat doses bioavailability is reduced to approximately 70% and apparent clearance is increased.

Excretion

The half-life of rifampicin after a single dose is approximately three hours. After repeat doses this is reduced to approximately 1–2 hours. Rifampicin and its metabolites are mainly excreted

in bile, and rifampicin undergoes enterohepatic recirculation. Approximately 25% of a dose is excreted in the urine.

Special populations

The half-life of rifampicin has been reported to be longer in patients with liver impairment or biliary obstruction.

5.3 Preclinical safety data

After oral administration of 100 mg/kg bodyweight rifampicin for 6 months in rats no toxic effects were observed. After chronic administration of 200 mg/kg, swelling and hydropic degeneration of the liver were observed. In monkeys, vomiting, anorexia and weight loss were observed at chronic doses of 105 mg/kg/day.

Only limited evidence is available for the carcinogenicity of rifampicin in mice, and in the absence of epidemiological studies, the carcinogenicity of rifampicin in humans cannot be evaluated.

The available studies on mutagenicity indicate an absence of a mutagenic effect.

Rifampicin concentrations in cord blood reach 12–33% of maternal blood concentrations.

Teratogenic effects occurred in rodents treated with high doses. 100–150 mg/kg daily in rodents have been reported to cause cleft palate and spina bifida. In rats neither fertility nor perinatal or postnatal development was impaired.

Malformation and death in infants born to mothers exposed to rifampicin, were reported at the same frequency as in the general population.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill: microcrystalline cellulose, povidone, maize starch, sodium lauryl sulfate, purified talc, magnesium stearate

Capsule shell: gelatin; sodium methylparahydroxybenzoate (E219); sodium propyl parahydroxybenzoate (E217); sodium lauryl sulphate; titanium dioxide (E171), sunset yellow/ FD&C Yellow #6 (E110); carmoisine/azorubine (E122); and ponceau 4R /cochineal red A (E124).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at a temperature not exceeding 25°C.Store in a dry place, protected from light. Dispense in tight container.

Blister pack: Store capsules in blisters in the provided carton.

6.5 Nature and contents of container

Blister packs of 10 x 10 capsules
10 capsules packed in clear PVC-Alu blister cards. Such 10 blister cards are packed in a box (carton) along with the patient information leaflet.

Strip packs of 10 x 10 capsules
10 capsules packed in Alu-Alu strips. Such 10 strips are packed in a box (carton) along with the patient information leaflet.

Bottle pack of 100 capsules
100 capsules packed in a self-sealing LDPE bag, put in a plain triple laminated sachet (LDPE/PET-Alu); the triple laminated sachet is kept in a round, wide mouth, opaque, milky white HDPE container sealed with tagger and closed with screw thread cap (HDPE) along with the patient information leaflet.

6.6 Instructions for use and handling and disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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9. DATE OF FIRST PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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References

General references

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References for specific sections of the SmPC

Section 4.4

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