National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

RIFAXCIN CAPSULES– RIFAMPICIN CAPSULES BP 300 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

S.N.	Name of active ingredient(s)*	Reference	Quantity / Batch in kg	Quantity / Capsule in mg	Function
1	Rifampicin	BP	150.000	300	Active
2	Starch	BP	70.203	140.406	Diluent
3	Talcum	BP	7.839	15.678	Lubricant
4	Magnesium Stearate	BP	1.956	3.912	Lubricant
5	E.H.G capsules , Size '0' Scarlet RED / Scarlet RED	IH	500000		
	Total		229.998=230.00	459.996=460.0	

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3. PHARMACEUTICAL FORM

Hard Gelatine Capsules

Description: Scarlet/ Scarlet coloured hard gelatin capsules, size "0" printed 'Rifa 300'on cap & logo of Maxheal pharmaceuticals on body, containing red coloured powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tuberculosis: Rifampicin, used in combination with other active anti-tuberculosis drugs, is indicated in the treatment of all forms of tuberculosis, including fresh, advanced, chronic and drug-resistant cases. Rifampicin is also effective against most atypical strains of mycobacteria.

Prophylaxis of meningococcal meningitis: Prophylaxis of meningococcal meningitis in close contact adult and paediatric patients.

Leprosy: Rifampicin is indicated in the combination treatment of multibacillary and paucibacillary leprosy in patients of all age groups.

Haemophilus influenza: Propylaxis of Haemophilus influenzae type b disease in close contacts.

Other infections: Rifampicin is indicated in the treatment of brucellosis, legionnaires disease, and serious staphylococcal infections. Rifampicin should be used in combination with another appropriate antibiotic to prevent emergence of resistant strains of the infecting organism.

4.2 Posology and method of administration

Posology

Tuberculosis

Rifampicin should be given with other effective anti-tuberculosis drugs to prevent the possible emergence of rifampicin resistant strains of mycobacteria.

Adults: The recommended single daily dose in tuberculosis is 8-12mg/kg.

Usual daily dose:

Patients weighing less than 50kg – 450mg

Patients weighing 50kg or more – 600mg

Paediatric patients:

Children above 3 months: Oral doses of 15 (10-20) mg/kg body weight daily are recommended, although a total daily dose should not usually exceed 600mg.

Prophylaxis of Meningococcal Meningitis

Adults: 600mg twice daily for 2 days.

Paediatric patients:

Meningococcal Carriers: Dose must not exceed 600 mg/ dose.

For children ≥1 month of age the recommended dose is 10 mg/kg every 12 hours for 2 days.

For children <1 month of age, the recommended dose is 5 mg/kg every 12 hours for 2 days.

Leprosy

Rifampicin should always be used in conjunction with at least one other anti-leprosy drug to treat the disease.

Adults: 600mg of rifampicin should be given once per month. If a daily dose regime is indicated then the recommended single dose is 10mg/kg. The usual daily dose for patients less than 50kg is 450mg and for patients 50kg or more, the usual daily dose is 600mg.

Paediatric patients:

Rifampicin should always be administered with dapsone in case of paucibacillary forms and with dapsone and clofazimine in case of multibacillary forms.

For children over 10 years, the recommended dose for rifampicin is 450 mg once a month.

For children less than 10 years, the recommended dose for rifampicin is 10 to 20 mg/kg rifampicin

once a month.

The duration of treatment is 6 months for paucibacillary and 12 months multibacillary forms.

Prophylaxis of Haemophilus Influenzae

Adults and children ≥1 month of age: For members of a household exposed to H. Influenzae B disease when the household contains a child 4 years old or younger, it is recommended that all members (including the child) receive 20mg/kg once daily (maximum daily dose of 600mg) for 4 days.

Index cases should be treated prior to discharge from hospital.

For children <1 month of age: 10mg/kg once daily for 4 days

Brucellosis, Legionnaires Disease or Serious Staphylococcal Infections

Adults: The recommended daily dose is 600mg to 1200mg given in 2 to 4 divided doses, together with another appropriate antibiotic to prevent the emergence of resistant strains of the infecting organism.

Patients with impaired liver function

A daily dose of 8mg/kg should not be exceeded in patients with impaired liver function.

Use in the Elderly

In elderly patients, the renal excretion of rifampicin is decreased proportionally with physiological decrease of renal function; due to compensatory increase of liver excretion, the serum terminal half-life is similar to that of younger patients. However, as increased blood levels have been noted in one study of rifampicin in elderly patients, caution should be exercised in using rifampicin in such patients, especially if there is evidence of liver function impairment.

Method of administration

For oral administration only.

The daily dose of rifampicin, calculated from the patient's body weight, should preferably be taken on an empty stomach or at least 30 minutes before a meal or 2 hours after a meal to ensure rapid and complete absorption.

4.3 Contraindications

Rifampicin is contraindicated in the presence of jaundice, and in patients who are hypersensitive to the active substance, rifampicin or any of the excipients listed in section 6.1.

Rifampicin is contraindicated when given concurrently with the combination of saquinavir/ ritonavir (see section 4.5).

4.4 Special warnings and precautions for use

Rifampicin should be given under the supervision of a respiratory or other suitably qualified physician.

Cautions should be taken in case of renal impairment if dose > 600 mg/day.

All tuberculosis patients should have pre-treatment measurements of liver function.

Adults treated for tuberculosis with rifampicin should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count, and a platelet count (or estimate).

Baseline tests are unnecessary in children unless a complicating condition is known or clinically suspected.

Patients with impaired liver function should only be given rifampicin in cases of necessity, and then with caution and under close medical supervision. In these patients, lower doses of rifampicin are recommended and careful monitoring of liver function, especially serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) should initially be carried out prior to therapy, weekly for two weeks and then every two weeks for the next six weeks. If signs of hepatocellular damage occur, rifampicin should be withdrawn.

Rifampicin should also be withdrawn if clinically significant changes in hepatic function occur. The need for other forms of antituberculosis therapy and a different regimen should be considered. Urgent advice should be obtained from a specialist in the management of tuberculosis. If rifampicin is re-introduced after liver function has returned to normal, liver function should be monitored daily.

In patients with impaired liver function, elderly patients, malnourished patients, and possibly, children under two years of age, caution is particularly recommended when instituting therapeutic regimens in which isoniazid is to be used concurrently with rifampicin. It is rarely necessary, in the absence of clinical findings, to increase the frequency of performing routine liver function tests in patients with normal pretreatment liver unless fever, vomiting, jaundice or other deterioration in the patient’s condition occur.

Patients should be seen at least monthly during therapy and should be specifically questioned concerning symptoms associated with adverse reactions.

In some patients, hyperbilirubinaemia resulting from competition between rifampicin and bilirubin for excretory pathways of the liver at the cell level, can occur in early days of treatment. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather the decision should be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition.

Because of the possibility of immunological reaction including anaphylaxis (see section 4.8) occurring

with intermittent therapy (less than 2 to 3 times per week) patients should be closely monitored. Patients should be cautioned against interruption of dosage regimens since these reactions may occur.

Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D. Isolated reports have associated porphyria exacerbation with rifampicin administration.

Severe, systemic hypersensitivity reactions, including fatal cases such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed during treatment with anti-tuberculosis therapy (See section 4.8).

It is important to note that early manifestations of hypersensitivity such as fever, lymphadenopathy or biological abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be advised to consult immediately their physician.

Rifampicin capsules should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

Rifampicin capsules may produce a reddish coloration of the urine, sweat, sputum and tears, and the patient should be forewarned of this. Soft contact lenses have been permanently stained (see section 4.8).

All patients with abnormalities should have follow up examinations, including laboratory testing, if necessary.

Contains Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P-450 enzyme interaction

Rifampicin is a potent inducer of certain cytochrome P-450 enzymes. Co-administration of rifampicin with other drugs that are also metabolized through these cytochrome P-450 enzymes may accelerate the metabolism and reduce the activity of these other drugs. Therefore, caution should be used when prescribing rifampicin with drugs metabolized by cytochrome P-450. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered rifampicin. Examples of drugs metabolized by cytochrome P-450 enzymes are:

• Antiarrhythmics (e.g. disopyramide, mexiletine, quinidine, propafenone, tocainide)

• Antiepileptics (e.g. phenytoin)

• Hormone antagonist (antiestrogens e.g. tamoxifen, toremifene, gestinone)

• Antipsychotics (e.g. haloperidol, aripiprazole)

• Anticoagulants (e.g. coumarins)

• Antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole)

• Antivirals (e.g. saquinavir, indinavir, efavirenz, amprenavir, nelfinavir, atazanavir, lopinavir, nevirapine)

• Barbiturates

• Beta-blockers (e.g. bisoprolol, propanolol)

• Anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, zopiclone, zolpidem),

• Calcium channel blockers (e.g. diltiazem, nifedipine, verapamil, nimodipine, isradipine, nicardipine, nisoldipine)

• Antibacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin)

• Corticosteroids

• Cardiac glycosides (digitoxin, digoxin)

• Clofibrate
• Systemic hormonal contraceptives
• Oestrogen
• Antidiabetic (e.g. chlorpropamide, tolbutamide, sulfonylureas, rosiglitazone)
• Immunosuppressive agents (e.g. ciclosporin, sirolimus, tacrolimus)
• Irinotecan
• Thyroid hormone (e.g. levothyroxine)
• Losartan
• Analgesics (e.g. methadone, narcotic analgesics)
• Praziquantel
• Progestogens
• Quinine
• Riluzole
• Selective 5-HT3 receptor antagonists (e.g. ondansetron)
• Statins metabolised by CYP 3A4 (e.g. simvastatin)
• Theophylline

• Tricyclic antidepressants (e.g. amitriptyline, nortriptyline)
• Cytotoxics (e.g. imatinib)
• Diuretics (e.g. eplerenone)

Patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during rifampicin therapy. Also diabetes may become more difficult to control.

When rifampacin is give concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of rifampacin with saquinavir/ritonavir is contraindicated (see section 4.3).

When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

Concurrent use of ketoconazole and rifampicin has resulted in decreased serum concentrations of both drugs.

Concurrent use of rifampicin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition.

Concomitant antacid administration may reduce the absorption of rifampicin. Daily doses of rifampicin should be given at least 1 hour before the ingestion of antacids.

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.

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.

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

At very high doses in animals rifampicin has been shown to have teratogenic effects. There are no well controlled studies with rifampicin in pregnant women. 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 foetus is not known. Therefore, rifampicin should be used in pregnant women or in women of child bearing potential only if the potential benefit justifies the potential risk to the foetus. When rifampicin is administered during the last few weeks of pregnancy it may cause post-natal haemorrhages in the mother and infant for which treatment with vitamin K1 may be indicated.

Breast-feeding

Rifampicin is excreted in breast milk, infants should not be breast fed by a patient receiving rifampicin unless in the physician's judgment the potential benefit to the patient outweighs the potential risk to the infant.

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

Reactions occurring with either daily or intermittent dosage regiments include:

Skin and subcutaneous tissue disorders

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 disorders

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

Hepatobiliary disorders

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

Nervous system disorders

Central Nervous system: Psychoses have been rarely reported.

Vascular disorders

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.

Blood and lymphatic system disorders

Eosinophilia, leucopenia, oedema have been reported to occur in a small percentage of patients treated with rifampicin.

Agranulocytosis has been very rarely reported.

Endocrine disorders

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

Musculoskeletal and connective tissue disorders

Muscle weakness and myopathy have been reported to occur in a small percentage of patients treated with rifampicin.

Immune system disorders

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 haemolytic anaemia

- Acute renal failure usually due to acute tubular necrosis or to acute interstitial nephritis.

General disorders and administration site conditions

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

Occasional disturbances of the menstrual cycle have been reported in women receiving long term anti-tuberculosis 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 professionals are asked to report any suspected adverse reactions via the internet at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Signs and Symptoms

Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy will probably occur within a short time after acute ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Brownish-red or orange colouration of the skin, urine, sweat, saliva, tears and faeces will occur, and its intensity is proportional to the amount ingested. Facial or periorbital oedema has also been reported in paediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.

The minimum acute lethal or toxic dose is not well established. However, nonfatal acute overdoses in adults have been reported with doses ranging from 9 to 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14-60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports.

Nonfatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses have been reported.

Management

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 Pharmacodynamics properties

Pharmacotherapeutic group: Antimycobacterials, antibiotics, ATC code: J04AB02

Rifampicin is an active bactericidial antituberculosis drug which is particularly active against the rapidly growing extracellular organisms and also has bactericidial activity intracellularly. Rifampicin has activity against slow and intermittently-growing M Tuberculosis.

Rifampicin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. Cross-resistance to rifampicin has only been shown with other rifamycins.

5.2 Pharmacokinetic properties

Rifampicin is readily absorbed from the gastrointestinal tract. Peak serum concentrations of the order of 10 µg/ml occur about 2 to 4 hours after a dose of 10 mg/kg body weight on an empty stomach.

Absorption of rifampicin is reduced when the drug is ingested with food.

The pharmacokinetics (oral and intravenous) in children are similar to adults.

In normal subjects the biological half-life of rifampicin in serum averages about 3 hours after a 600 mg dose and increases to 5.1 hours after a 900 mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2-3 hours. At a dose of up to 600 mg/day, it does not differ in patients with renal failure and consequently, no dosage adjustment is required.

Rifampicin is rapidly eliminated in the bile and an enterophepatic circulation ensues. During this process, rifampicin undergoes progressive deacetylation, so that nearly all the drug in the bile is in this form in about 6 hours. This metabolite retains essentially complete antibacterial activity. Intestinal reabsorption is reduced by deacetylation and elimination is facilitated. Up to 30 % of a dose is excreted in the urine, with about half of this being unchanged drug.

Rifampicin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampicin is about 80 % protein bound. Most of the unbound fraction is not ionized and therefore is diffused freely in tissues.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber which are additional to those already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Starch

Talcum powder

Magnesium Stearate

Size 0 hard gelatine capsules

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30^0C, in a dry place. Protect from light.

6.5 Nature and contents of container

PVC - Aluminium Blister Pack

A Carton of 10 blisters of 10 capsule each.

6.6 Special precautions for disposal

Not applicable

7. Applicant of Manufacturer

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