SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rifadin 300mg Capsules
2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rifampicin Ph Eur 300 mg

For a full list of excipients, see section 6.1.
3 PHARMACEUTICAL FORM

Capsule, hard.

The gelatine capsule is composed of two red halves.
4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications for use

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

*Leprosy:* In combination with at least one other active anti-leprosy drug in the management of multibacillary and paucibacillary leprosy to effect conversion of the infectious state to a non-infectious state.

*Other Infections:* In the treatment of Brucellosis, Legionnaires Disease, and serious staphylococcal infections. To prevent emergence of resistant strains of the infecting organisms, Rifadin should be used in combination with another antibiotic appropriate for the infection.

*Prophylaxis of meningococcal meningitis:* For the treatment of asymptomatic carriers of *N. meningitidis* to eliminate meningococci from the nasopharynx.

*Haemophilus influenzae:* For the treatment of asymptomatic carriers of *H. influenzae* and as chemoprophylaxis of exposed children, 4 years of age or younger.
4.2 Posology and method of administration

Recommended Dosage

For oral administration
The daily dose of Rifadin, calculated from the patient’s body weight, should preferably be taken at least 30 minutes before a meal or 2 hours after a meal to ensure rapid and complete absorption.

Tuberculosis:

Rifadin 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 8-12 mg/kg.

**Usual Daily dose:** Patients weighing less than 50 kg - 450 mg. Patients weighing 50 kg or more – 600 mg.

**Children:** In children, oral doses of 10-20 mg/kg body weight daily are recommended, although a total daily dose should not usually exceed 600 mg.

Leprosy:

600 mg doses of rifampicin should be given once per month. Alternatively, a daily regimen may be used. The recommended single daily dose is 10 mg/kg.

**Usual daily dose:** Patients weighing less than 50 kg - 450 mg. Patients weighing 50 kg or more – 600 mg.

In the treatment of leprosy, rifampicin should always be used in conjunction with at least one other antileprosy drug.

Brucellosis, Legionnaires Disease or serious staphylococcal infections

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

Prophylaxis of meningococcal meningitis

**Adults:** 600 mg twice daily for 2 days.

**Children (1 - 12 years):** 10 mg/kg twice daily for 2 days.

**Children (3 months - 1 year):** 5 mg/kg twice daily for 2 days.

Prophylaxis of Haemophilus influenzae
Adults and children: For members of households exposed to H. influenzae B disease when the household contains a child 4 years of age or younger, it is recommended that all members (including the child) receive rifampicin 20 mg/kg once daily (maximum daily dose 600 mg) for 4 days. Index cases should be treated prior to discharge from hospital.

Neonates (1 month): 10 mg/kg daily for 4 days.

Impaired liver function:

A daily dose of 8 mg/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 terminal half-life in serum 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 impaired liver function.
4.3 Contraindications

Rifadin is contra-indicated in patients who:

- are hypersensitive to any of the rifamycins or any of the excipients (see section 6.1);
- have jaundice;
- are concurrently receiving saquinavir/ritonavir therapy (see section 4.5 Interactions).
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.

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 glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) should initially be carried out prior to therapy, weekly for two weeks, 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 Rifadin. If the patient has no evidence of pre-existing liver disease and normal pre-treatment liver function, liver function tests need only be repeated if 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 can occur in the early days of treatment. This results from competition between rifampicin and bilirubin for hepatic excretion.

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.

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).
Because of the possibility of immunological reaction including anaphylaxis (see section 4.8 Undesirable effects) occurring with intermittent therapy (less than 2 to 3 times per week) patients should be closely monitored. Patients should be cautioned against interrupting treatment.

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.
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. Coadministration of rifampicin with other drugs that are also metabolised 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 metabolised by cytochrome P-450. To maintain optimum therapeutic blood levels, dosages of drugs metabolised by these enzymes may require adjustment when starting or stopping concomitantly administered rifampicin.

Examples of drugs metabolised 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, propranolol),
- Anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, zolpicalone, 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 Rifadin therapy. Also diabetes may become more difficult to control.

**Other Interactions**

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

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 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 cord blood, the effect of rifampicin, alone or in combination with other antituberculosis drugs, on the human foetus is not known. Therefore, Rifadin 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 Rifadin 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.

Lactation
Rifampicin is excreted in breast milk, patients receiving rifampicin should not breast feed unless in the physician’s judgement 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 regimens include:

*Cutaneous reactions* which are mild and self-limiting 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. Special warnings and precautions for use).

*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 reported very rarely reported. Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

Reactions usually occurring with intermittent dosage regimens and 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 monthly 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 25 mg/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 acute interstitial nephritis.

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 colouration of the urine, sweat, sputum and tears. The patient should be forewarned of this. Soft contact lenses may be permanently stained.
4.9 Overdose

Human Experience

• 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 Pharmacodynamic properties

ATC Code: J04AB02 Antimycobacterials, antibiotics.

Rifampicin is an active bactericidal antituberculosis drug which is particularly active against the rapidly growing extracellular organisms and also has bactericidal 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

Not applicable
### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Ph Eur</th>
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<tbody>
<tr>
<td>Corn starch</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Ph Eur</td>
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</tbody>
</table>

6.2 Incompatibilities

None stated
6.3 Shelf life

4 years from date of manufacture
6.4 Special precautions for storage

Store below 25°C.
Protect from light and moisture.
6.5 **Nature and contents of container**

Amber glass bottles of 100 capsules.

Blisters packs of 100 capsules in cardboard cartons. Blisters material is aluminium foil / PVDC (Aluminium 0.025 mm; PVDC 20 gsm) and transparent PVC / PVDC foil (PVC 0.25 mm; PVDC 60 gsm).
6.6 Special precautions for disposal

No special requirements.
7 MARKETING AUTHORISATION HOLDER

Aventis Pharma Ltd
Trading as Marion Merrell or Aventis Pharma
50 Kings Hill Avenue
Kings Hill
West Malling
ME19 4AH

Or trading as
Sanofi-aventis
One Onslow Street
Guildford
Surrey
GU1 4YS
UK
8 MARKETING AUTHORISATION NUMBER(S)

PL 04425/5916R
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/04/2005
10  DATE OF REVISION OF THE TEXT

5 November 2010

Legal category

POM