SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rimactane® 150 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is 3-(4-Methyl-1-piperazinyliminomethyl) rifamycin SV.

One capsule contains 150 mg rifampicin Ph. Eur.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules.

Opaque, two-piece, hard gelatine capsules, reddish- brown in colour, marked with 'NG 150'.

4 CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Rifampicin is a major drug in the management of tuberculosis (all forms) and certain opportunistic mycobacterial infections. It is effective in cases resistant to other anti-tuberculosis agents and shows no cross-resistance outside the rifampycin group of drugs. In the treatment of tuberculosis

Rifampicin must always be combined with other anti-tuberculosis agents. It is effective in combination with isoniazid, streptomycin, pyrazinamide, ethambutol and the majority of second line drugs.

Prophylaxis of meningococcal meningitis in close contact adult and paediatric patients

4.2 Posology and method of administration

For the management of tuberculosis and certain opportunistic mycobacterial infections:

Rifampicin must always be given in association with other anti-tuberculosis drugs, to prevent emergence of resistant strains.

Use in Adults: 450-600mg daily as a single dose (based on approximately 10mg per kg body weight). (Those patients 50kg (8 stone) and over should take 600mg rifampicin daily, whilst patients under 50kg should take 450mg).

The following chemotherapeutic agents are employed today as combined therapy for tuberculosis: rifampicin (Rimactane) (RMP), isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB), streptomycin (STM).

The dosages recommended by the Centres for Disease Control and Prevention are as follows:

Drug	Daily			Twice a week			3 times a week		
	mg/kg		max. mg	mg/kg		max. mg	mg/kg		max. mg
	Children	Adults		Children	Adults		Children	Adults	
RMP	**10-20**	**10**	**600**	**10-20**	**10**	**600**	**10-20**	**10**	**600**
INH	**10-15**	**5**	**300**	**20-40**	**15**	**900**	**20-40**	**15**	**900**
PZA	**30-40**	**15-30**	**2,000**	**50-70**	**50-70**	**4,000**	**50-70**	**50-70**	**3,000**
EMB	**15-25**	**5-25**	**2,500**	**50**	**50**	**2,500**	**25-30**	**25-30**	**2,500**
STM	**20-30**	**15**	**1,000**	**25-30**	**25-30**	**1,500**	**25-30**	**25-30**	**1,000**

For the treatment of sputum-positive pulmonary tuberculosis, preference is given to the following regimens: (For dosage information please refer to the text above for Rifampicin and to the table for other components of the treatment).

Continuous therapy
Daily for a total of 9 months
Initial phase for 2 months: RMP + INH + PZA + EMB or STM
Continuation phase for 7 months: RMP + INH

A total duration of 9 months is recommended for tuberculosis with HIV infection and for tuberculous meningitis, disseminated tuberculosis, or spinal involvement with neurological complications.

Daily for a total of 6 months:
Initial phase for 2 months: RMP + INH + PZA + EMB or STM
Continuation phase for 4 months: RMP + INH

Partially intermittent therapy
Total duration 6 months:
Initial phase for 2 months: RMP + INH + PZA + EMB or STM daily
Continuation phase for 4 months: RMP + INH twice or 3 times a week

Fully intermittent therapy

Total duration 6 months:	RMP + INH + PZA + EMB or STM 3 times a week

DOTS strategy (directly observed treatment, short-course, i.e. administration of the antituberculous agents under supervision) should be considered for all patients, irrespective of the treatment regimen they are receiving.

Use 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.

Use in Elderly: No special dosage regime is necessary but concurrent hepatic insufficiency should be taken into account (see Pharmacokinetics).

For the chemoprophylaxis of meningococcal meningitis:

Note: Rifampicin should not be used to treat overt meningococcal meningitis.

Use in Adults: 600mg twice daily (12 hourly) for 2 days.

Use in Children:
Children over 1 month: 10 mg per kg every 12 hours for 2 days
Children under 1 month: 5 mg per kg every 12 hours for 2 days
The maximum dose is 600 mg

*Use in the Elderl*y: There is no evidence to suggest that dose adjustments are necessary.

This prophylactic administration should be started as soon as possible. It is recommended that Rifampicin is only given for 2 days in this indication since resistance to this class of antibacterial agent may develop.

4.3 Contraindications

Rifampicin is contraindicated in patients who:

- are hypersensitive to any of the rifamycins or to any of the excipients listed in section 6.1;
- have jaundice;
- are concurrently receiving saquinavir/ritonavir therapy (see section 4.5 Interactions with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

In the treatment of tuberculosis 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 pretreatment measurement 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, then every two weeks for the next six weeks. If signs of hepatocellular damage occur, rifampicin should be withdrawn.

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

In patients with or likely to have liver function abnormalities including those with chronic liver disease, chronic alcoholism, elderly patients, malnourished patients, and possibly, children under two years of age, the benefit of combined treatment with rifampicin must be weighed against the possible risks. This applies particularly to combination of isoniazid and/or pyrazinamide with rifampicin. In the presence of severely impaired liver function or jaundice the dosage may have to be reduced. If a patient has no evidence of pre-existing liver disease and normal pretreatment liver function, liver function tests need only be repeated if fever, vomiting, jaundice or other deterioration in the patient's condition occurs.

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

As rifampicin is excreted principally by the biliary tract, caution should be exercised in treating patients with hepatic disorders.

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.

Patients receiving Rifampicin for the chemoprophylaxis of meningococcal meningitis should be kept under close surveillance. Special attention should be paid to signs of overt infection.

Rifampicin should not be used to treat an overt meningococcal infection.

To prevent the emergence of resistant bacteria, Rifampicin must always be combined with other antibiotics/chemotherapeutic agents when used to treat infections.

Intermittent therapy
The "flu syndrome" (see section 4.8 Undesirable effects) is chiefly encountered during intermittent therapy and may be a prelude to serious complications such as thrombocytopenia, purpura, haemolytic anaemia, dyspnoea and asthma-like attacks, shock and renal failure. In the event of its onset, therefore, one should consider the possibility of switching to daily medication. Such a switch must always be made where the "flu syndrome" assumes a relatively severe form and if the aforementioned serious complications occur, the medication must be withdrawn at once and never reinstituted.

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.

When changing over from intermittent to daily therapy, an incremental dosage must be employed, starting with approx. 75-150 mg on the first day. The desired therapeutic dose should be reached within 3-4 days. During this time the patient's renal function should be closely monitored. Corticosteroids may prove useful in attenuating possible immunopathological reactions.

Resumption of therapy after its interruption: Since severe reactions such as shock and renal failure may occur in rare cases upon resumption of therapy, incremental dosing under close surveillance is mandatory (see "intermittent therapy").

Owing to its enzyme-inducing effect, rifampicin must be employed with extreme caution in patients with porphyria, because activation of delta-aminolaevulinic acid synthetase may lead to an acute manifestation of the porphyria. Rifampicin can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D.

To preclude all possibility of pregnancy during treatment with Rifampicin, non-hormonal means of contraception must be employed (see section 4.5 Interaction with other medicinal products and other forms of interactions).

Patients should abstain from alcohol while receiving treatment with Rifampicin.

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.

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

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.

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 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:

- analgesics (e.g. methadone, narcotic analgesics)
- antiarrhythmic agents (disopyramide, quinidine, mexiletine, tocainide, propafenone)
- antibacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin, trimethoprim)
- anticoagulants (e.g. courmarins)
- antidiabetic (e.g. chlorpropamide, tolbutamide, sulfonylureas, rosiglitazone)
- antiepileptics (cabamazepine, lamotrigine, phenytoin)
- antifungal agents (ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole)
- antimalarials (mefloquine, atovaquone)
- antimuscarinics (e.g. fesoterodine)
- antipsychotics (haloperidol, aripiprazole, clozapine)
- antivirals (e.g. saquinavir, indinavir, efavirenz, amprenavir, nelfinavir, atazanavir, lopinavir, nevirapine)
- anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, zolpicolone, zolpidem)
- barbiturates (e.g. hexobarbital)

- beta-blockers (e.g. bisoprolol, propanolol, carvedilol)
- bosentan
- calcium-channel blockers (e.g. diltiazem, nimodipine, isradipine, nicardipine, nisoldipine, nifedipine, amlodipine, verapamil)
- cardiac glycosides (digitoxin, digoxin)
- corticosteroids (Addison patients may develop a crisis; exacerbation of pemphigus may occur)
- cytotoxics (mycophenolate, dasatinib, imatinib, lapatinib, temsirolimus)
- diuretics (e.g. eplerenone)
- hormone antagonist (antiestrogens e.g. tamoxifen, toremifene, gestinone, exemastane)
- selective 5-HT3 receptor antagonists (e.g. ondansetron)
- statins metabolised by CYP 3A4 (e.g. fluvastatin, simvastatin)
- female sex hormones (oestrogens, progestogens, tibolone)
- immunosuppressive agents (e.g. ciclosporin, sirlimus, tacrolimus)
- tadalafil
- theophylline;
- thyroid hormones (e.g. levothyroxine)
- tricyclic antidepressants (e.g. amitriptyline, nortriptyline)
- ulcer-healing drugs (e.g. cimetidine)
- clofibrate
- systemic hormonal contraceptives
- irinotecan
- losartan
- praziquantel
- quinine
- riluzole.

Patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during Rifampicin therapy.

Diabetes may become more difficult to control. Treatment for corticoid-dependent asthma, patients may become more difficult or impossible

Other interactions
When rifampicin is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of Rifampicin with saquinvir/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.

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

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 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.

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 or use machines

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

4.8 Undesirable effects

Frequency estimates:	Common:	> 1/100
	Uncommon:	≥ 1/1,000 to ≤ 1/100
	Rare:	≥ 1/10,000 to ≤ 1/1,000
	Very rare:	< 1/10,000
	Unknown	Cannot be estimated from available data

Reactions occurring with either daily or intermittent dosage regimens include:

System Organ Class	Common	Uncommon	Unknown
Infections and infestations			Pseudomembranous colitis, influenza consisting of episodes of pyrexia, chills, headache, dizziness
Blood and lymphatic system disorders	Thrombocytopenia with or without purpura, usually associated with intermittent therapy, but is reversible if drug is discontinued as soon as purpura occurs.	leukopenia	Disseminated intravascular coagulation,eosinophilia, agranulocytosis, haemolytic anaemia
Immune system disorders			anaphylactic reaction
Endocrine disorders			adrenal insufficiency in patients with compromised adrenal function have been observed.
Metabolism and nutritional disorders			decreased appetite
Psychiatric disorders			Psychotic disorder

System Organ Class	Common	Uncommon	Unknown
Nervous system disorders			Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.
Eye disorders			Tear discoloration
Vascular disorders			Shock, flushing, vasculitis
Respiratory, thoracic and mediastinal disorders			Dyspnoea, wheezing, sputum discoloured
Gastrointestinal disorders	Nausea, vomiting	Diarrhoea	Gastrointestinal disorder, abdominal discomfort
Hepatobiliary disorders			Hepatitis, hyperbilirubinaemia
Skin and subcutaneous tissue disorders			Erythema multiforme including Stevens-Johnson syndrome and toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (See section 4.4), skin reaction, pruritus, rash pruritic, urticaria, dermatitis allergic, pemphigoid, sweat discoloration.

System Organ Class	Common	Uncommon	Unknown
Musculoskeletal and connective tissue disorders			Muscle weakness, myopathy, bone pain
Renal and urinary disorders			acute kidney injury usually due to renal tubular necrosis or tubulointerstitial nephritis, chromaturia
Pregnancy, puerperium and perinatal conditions			Post-partum haemorrhage, foetal-maternal haemorrhage
Reproductive system and breast disorders			Menstrual disorder
Congenital, familial and genetic disorders			Porphyria
General disorders and administration site conditions			Oedema
Investigations	Blood bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased		Blood pressure decreased, blood creatinine increased, hepatic enzyme increased

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.

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.

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 Yellow Card Scheme (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in Google play or Apple App store.

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

Pharmacotherapeutic group: Antimycobacterials, antibiotic.
ATC code: J04AB02.

Mechanism of action
Rifampicin exerts, both *in vitro* and *in vivo* bactericidal effects on Mycobacterium tuberculosis. It also exhibits variable activity against other atypical species of Mycobacterium.

In vivo it exerts its bactericidal effect not only on micro-organisms in the extracellular spaces but also on those located intracellularly. Rifampicin has a potent sterilising effect.

Rifampicin inhibits the DNA-dependent RNA polymerase of sensitive bacterial strains, but without affecting the corresponding mammalian enzyme.

Since relatively rapid "one-step" selection of resistant bacteria occurs with rifampicin, the drug must not be employed as monotherapy to treat overt infections. Bacteria resistant to rifampicin display no cross-resistance to other antibiotics with the exception of the rifamycins.

5.2 Pharmacokinetic properties

Absorption
Rifampicin is rapidly and completely absorbed. Following a single dose taken on an empty stomach (600 mg) the peak serum concentrations (approx. 10 µg/ml) are observed after about 2 hours. Ingestion with food may adversely affect the absorption of rifampicin.

Distribution
The apparent distribution volume is 1.6 L/kg in adults and 1.1 L/kg in children. Binding to serum proteins amounts to 84%-91%.

Rifampicin penetrates rapidly into various body fluids and tissues, including bone tissue. Rifampicin crosses the blood/brain barrier in the case of inflamed meninges only, but concentrations in the cerebrospinal fluid may remain above the MIC for *Mycobacterium tuberculosis* for up to two months with continuous therapy of 600 mg/day orally.

Rifampicin crosses the human placenta and is secreted in human breast milk. However, it is estimated that a breast-fed infant would receive no more than 1% of the usual therapeutic dose.

Biotransformation
Rifampicin is metabolised in the liver, the principal metabolite being 25-O-deacetylrifampicin, which is microbiologically active and, like rifampicin, subject to enterohepatic circulation. Rifampicin induces its own metabolism.

Elimination
The plasma elimination half-life of rifampicin increases with increasing doses and amounts to 2.5h, 3-4h and about 5h after single doses of 300 mg, 600 mg and 900 mg respectively. After a few days of repeated daily administration, the bioavailability of rifampicin diminishes, and the half-life value following repeated doses of 600 mg falls to 1-2 hours.

Owing to its enzyme-inducing effect in the liver, rifampicin accelerates its own metabolism, with the result that its systemic clearance, which amounts to approx. 6 L/h after the first dose, rises to approx. 9 L/h after repeated dosing.

Although the bulk of the drug is eliminated in the bile, 80% of the quantity excreted being accounted for by the deacetylrifampicin metabolite, rifampicin also appears in the urine. In a dosage range of 150-900 mg, 4-18% of a dose is excreted dose-dependently in the urine in unchanged form.

Characteristics in patients
In elderly patients, renal clearance is reduced, but, owing to the large scale on which the drug is eliminated via the liver, the plasma concentrations are similar to those in young patients.

With impaired renal function, the elimination half-life becomes prolonged only at doses exceeding 600 mg daily. Provided that hepatic excretory function is normal, the dosage in patients with impaired renal function does not need to be reduced below 600 mg daily. Rifampicin is eliminated by peritoneal or haemodialysis. Dosage adjustment is not necessary during dialysis. Because rifampicin is dialysable it is recommended that the drug should not be administered until after the period of dialysis is complete.

In patients with severe hepatic dysfunction the dosage may have to be adjusted as plasma concentrations are raised and half-life prolonged.

5.3 Preclinical safety data

There is limited evidence as to the carcinogenic potential of rifampicin in animals. In female mice of a strain known to be susceptible to hepatomas, a significant increase in such tumours was observed after 1 year of treatment with rifampicin in quantities equivalent to 2-10 times the maximum clinical doses.

In mice of another strain treated for 1 year, and in rats treated for 2 years, no significant increase was noted in the incidence of any type of tumour. Studies with various mammalian models, as well as with bacteria, yielded no evidence that rifampicin has a mutagenic effect.

In daily doses of 150-250 mg/kg, rifampicin proved teratogenic in mice and rats, insofar as an increased occurrence of spina bifida and cleft palate was observed. In rabbits it had no teratogenic effect. In all three animal species, unspecific embryotoxic effects occurred after doses > 150 mg/kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The capsules contain
calcium stearate
lactose
titanium dioxide (E171)
iron oxide red (E172)
gelatine
shellac glaze
propylene glycol (E1520)
ammonium hydroxide (E527)
iron oxide black (E172).

6.2. Incompatibilities

None known.

6.3. Shelf life

Four years.

6.4. Special precautions for storage

Protect from light and heat (store below 30ºC).

Medicines should be kept out of reach of children.

6.5. Nature and contents of container

The capsules are opaque, two-piece, hard gelatine capsule size 1, reddish-brown in colour, marked with the monogram NG on each half and the code

300, and come in securitainers of 100 and PVC/PE/PVdC blister packs of 60.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria.

8. MARKETING AUTHORISATION NUMBER(S)

PL: 04520/0044.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1st February, 2000.

10 DATE OF REVISION OF THE TEXT

03/12/2018