

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Rifampicin, Isoniazid and Ethambutol Hydrochloride Tablets 150/75/275 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains ;

Rifampicin USP 150mg

Isoniazid USP 75mg

Ethambutol Hydrochloride USP 275 mg

Ingredient	Specification	Mg/ Tablets	Function
<i>Rifampin Part</i>			
Rifampin* (Non compacted) HBD	USP	153.00	Active
Microcrystalline Cellulose** (RANQ PH 101)	NF	39.58	Diluent/Disintegrant
Crospovidone (Polyplasdone)	NF	10.00	Diluent/Disintegrant
Pregelatinized starch (Starch 1500)	NF	22.42	Binder
Pregelatinized starch (Starch 1500) (For binder)	NF	10.00	Binder
Ascorbic acid	USP	3.00	Antioxidant
Purified water #	BP/LD	---	Binder Solvent
<i>Isoniazid & Ethambutol HCl Part</i>			
Isoniazid	USP	75.00	Active
Microcrystalline cellulose (RANQ PH 101)	NF	45.00	Diluent/Disintegrant
Pregelatinized starch (Starch 1500)	NF	12.00	Disintegrant
Ethambutol Hydrochloride	USP	275.00	Active
Gelatin	NF	5.00	Binder
Purified water #	BP/LD	---	Granulating Solvent
<i>Lubrication</i>			

Ingredient	Specification	Mg/ Tablets	Function
Colloidal Silicon Dioxide	NF	9.50	Flowing Agent/Disintegrant
Crospovidone	NF	42.00	Disintegrant
Microcrystalline Cellulose	NF	6.00	Disintegrant
Magnesium Stearate	NF	12.50	Lubricant
Coating			
Opadry 80W56578 Brown LD	LD	40.00	Coating Material
Purified water #	BP/LD	---	Coating Solvent

* Quantity of Rifampin mentioned is based on 100% assay. Potency of Rifampin is to be adjusted to 100% and quantity of Microcrystalline cellulose (RANQ PH 101) is to adjusted to keep total input constant. Potency calculations:

Quantity of a x 100

Rifampin (kg) = -----

% potency of Rifampin on as is basis

where a = standard quantity of Rifampin as per ORML

* Quantity inclusive of 2.0% overages

** Quantity of Microcrystalline cellulose (RANQ PH 101) (Kg) = Standard quantity of Rifampin + Standard quantity of Microcrystalline cellulose – Quantity of Rifampin dispensed, based on potency.

#Does not appear in the final product. Evaporates during drying.

USP=United States Pharmacopoeia (Current edition)

NF= National Formulary (Current edition)

BP= British Pharmacopoeia (Current edition)

LD=Laid Down (In-house Specification)

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

It is indicated for the treatment of tuberculosis, in the continuation phase, of short course chemotherapy (5 months) in Category II patients (i.e. in relapse and treatment failure cases).

4.2 Posology and method of administration

Dose can be incremented with 2 tablets for patients under 40 kgs, 3 tablets for those between 40-55 kgs and 4 tablets for those patients above 55 kg.

4.3 Contraindications

Rifampicin: Rifampicin is contraindicated in patients with a history of hypersensitivity to any of the rifamycin.

Isoniazid: Previous isoniazid-associated hepatic injury; severe adverse reactions to isoniazid, such as fever, chills, and arthritis; acute liver disease of any etiology, a history of previous hypersensitivity reaction to isoniazid, including drug induced hepatitis.

Ethambutol: Ethambutol is contraindicated in patients who are known to be hypersensitive to this drug. It is also contraindicated in patients with known optic neuritis unless clinical judgement determines that it may be used.

4.4 Special warnings and special precautions for use

Rifampicin: Rifampicin is not recommended for intermittent therapy; the patient should be cautioned against intentional or accidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases. Rifampicin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. The cause of the phenomenon is unknown. In patients receiving anticoagulants and Rifampicin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.

Urine, feces, saliva, sputum, sweat and tears may be colored red-orange by Rifampicin and its metabolites. Soft contact lenses may be permanently stained. Individuals to be treated should be made aware of these possibilities.

It has been reported that the reliability of oral contraceptives may be affected in some patients being treated for tuberculosis with Rifampicin in combination with at least one other antituberculosis drug. In such cases, alternative contraceptive measures may need to be considered.

It has also been reported that Rifampicin given in combination with other antituberculosis drugs may decrease the pharmacologic activity of methasone, oral hypoglycemics, digitoxin, quinidine, disopyramide, dapson and corticosteroids. In these cases, dosage adjustment of the interacting drugs is recommended.

Therapeutic levels of Rifampicin have been shown to inhibit standard microbiological assays for serum folate and vitamin B12. Alternative methods must be considered when determining folate and vitamin B12 concentrations in the presence of Rifampicin.

Since Rifampicin has been reported to cross the placental barrier and appear in cord blood and in maternal milk, neonates and newborns of Rifampicin-treated mothers should be carefully observed for any evidence of untoward effects.

Isoniazid: All drugs should be stopped and an evaluation of the patient should be made at the first sign of a hypersensitivity reaction.

Use of isoniazid should be carefully monitored in the following:

1. Patients who are receiving phenytoin (diphenylhydantoin) concurrently. Isoniazid may decrease the excretion of phenytoin or may enhance its effects. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant dose should be made.
2. Daily users of alcohol. Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis.
3. Patient with current chronic liver disease or severe renal dysfunction.

Periodic ophthalmoscopic examination during isoniazid therapy is recommended when visual symptoms occur.

Ethambutol:The effects of combinations of ethambutol with other antituberculous drugs on the fetus is not known. While administration of this drug to pregnant human patients has produced no detectable effect upon the fetus, the possible teratogenic potential in women capable of bearing children would be weighed carefully against the benefits of therapy. There are published reports of five women who received the drug during pregnancy without apparent adverse effect upon the fetus.

Ethambutol is not recommended for use in children under 13 years of age since safe conditions for use have not been established.

Patients with decreased renal function need the dosage reduced as determined by serum levels of ethambutol, since the main path of excretion of this drug is by the kidneys. Because this drug may have adverse effects on vision, physical examination should include ophthalmoscopy, finger perimetry, and testing of colour discrimination. In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions. In such patients expected and possible visual deterioration since evaluation of visual changes is difficult. As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

4.5 Interaction with other FPPs and other forms of interaction

Rifampicin

Being an inducer of cytochrome P-450 enzymes, Rifampicin may accelerate elimination of certain drugs using this metabolic pathway. These include phenytoin, antiarrhythmics (disopyramide, mexiletine, quinidine), anticoagulants, antifungals (fluconazole, itraconazole, ketoconazole), barbiturates, beta blockers, calcium channel blockers (diltiazem, nifedipine, verapamil), chloramphenicol, ciprofloxacin, corticosteroids, cyclosporine, cardiac glycosides, oral contraceptives, clofibrate, dapsone, diazepam, haloperidol, oral hypoglycemic agents, narcotic analgesics, progestins and theophylline. It may be necessary to adjust the dosage of

these drugs if they are given concurrently with Rifampin, Isoniazid and Ethambutol Hydrochloride Tablets 150mg/75mg/275mg.

Isoniazid

Isoniazid inhibits the metabolism of anticonvulsants, benzodiazepines, haloperidol, ketoconazole, theophylline and warfarin. It may be necessary to adjust the dosage of these drugs if they are given concurrently with Rifampin, Isoniazid and Ethambutol Hydrochloride Tablets 150mg/75mg/275mg.

Ethambutol

No potentially hazardous interactions has been reported. Aluminium hydroxide impairs the absorption of ethambutol and an alternative antacid should be used if required

4.6 Pregnancy and lactation

Rifampicin

Pregnancy--Teratogenic Effects

Category C. Rifampicin has been shown to be teratogenic in rodents given oral doses of Rifampicin 15 to 25 times the human dose. Neonates of Rifampicin-treated mothers should be carefully observed for any evidence of adverse effects. Isolated cases of fetal malformations have been reported; however, there are no adequate and well-controlled studies in pregnant women. Rifampicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Rifampicin in oral doses of 150 to 250 mg/kg produced teratogenic effects in mice and rats. Malformations were primarily cleft palate in the mouse and spina bifida in the rat. The incidence of these anomalies was dose-dependent. When Rifampicin was given to pregnant rabbits in doses up to 20 times the usual daily human dose, imperfect osteogenesis and embryotoxicity were reported.

Pregnancy--Non-Teratogenic Effects

When administered during the last few weeks of pregnancy, Rifampicin can cause post-natal hemorrhages in the mother and infant for which treatment with vitamin K may be indicated.

Isoniazid

It has been reported that in both rats and rabbits, isoniazid may exert an embryocidal effect when administered orally during pregnancy, although no isoniazid-related congenital

anomalies have been found in reproduction studies in mammalian species. Isoniazid should be prescribed during pregnancy only when therapeutically necessary. The benefit of preventive therapy should be weighed against a possible risk to the fetus.

Ethambutol

Animal studies have shown some teratogenic effect, however an extensive review of the literature on ethambutol use during pregnancy led to the conclusion that it was second only to Isoniazid in its safety and that the rate of abnormalities reported was low with most being of a minor orthopedic nature not necessarily related to drug administration.

4.7 Effects on ability to drive and use medicines

Nil

4.8 Undesirable effects

Rifampicin

Nervous System Reactions: Headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, visual disturbances, muscular weakness, pain in extremities and generalized numbness

Gastrointestinal Disturbances: In some patients heartburn, epigastric distress, anorexia, nausea, vomiting, gas, cramps, and diarrhea.

Hepatic Reactions: Transient abnormalities in liver function tests (e.g., elevations in serum bilirubin, BSP, alkaline phosphatase, serum transaminases) have been observed. Rarely, hepatitis or a shocklike syndrome with hepatic involvement and abnormal liver function tests.

Renal Reactions: Elevations in BUN and serum uric acid have been reported. Rarely, hemolysis, hemoglobinuria, hematuria, interstitial nephritis, renal insufficiency and acute renal failure have been noted. These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intentional or accidental interruption of a daily dosage regimen, and are reversible when Rifampicin is discontinued and appropriate therapy instituted.

Hematologic Reactions: Thrombocytopenia, transient leukopenia, hemolytic anemia, eosinophilia and decreased hemoglobin have been observed. Thrombocytopenia has occurred

when Rifampicin and ethambutol were administered concomitantly according to an intermittent dose schedule twice weekly and in high doses.

Allergic And Immunological Reactions: Occasionally pruritus, urticaria, rash, pemphigoid reaction, eosinophilia, sore mouth, sore tongue, and exudative conjunctivitis. Rarely hemolysis, hemoglobinuria, hematuria, renal insufficiency or acute renal failure have been reported which are generally considered to be hypersensitivity reactions. These have usually occurred during intermittent therapy or when treatment was resumed following intentional or accidental interruption of a daily dosage regimen and were reversible when Rifampicin was discontinued and appropriate therapy instituted.

Metabolic Reactions: Elevations in BUN and serum uric acid have occurred.

Miscellaneous Reactions: Fever and menstrual disturbances have been noted.

Isoniazid

Nervous System Reactions: Peripheral neuropathy is the most common toxic effect. It is dose-related, occurs most often in the malnourished and in those predisposed to neuritis (e.g., alcoholics and diabetics), and is usually preceded by paresthesias of the feet and hands. The incidence is higher in “slow inactivators”. Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment, and toxic psychosis.

Gastrointestinal Reactions: Nausea, vomiting, and epigastric distress.

Hepatic Reactions: Elevated serum transaminases (SGOT; SGPT), bilirubinemia, bilirubinuria, jaundice, and occasionally severe and sometimes fatal hepatitis. The common prodromal symptoms are anorexia, nausea, vomiting, fatigue, malaise, and weaknesses. Mild and transient elevations of serum transaminase levels occurs in 10 to 2 % of persons taking isoniazid. The abnormality usually occurs in the first 4 to 6 months of treatment but can occur at any time during therapy. In most instances, enzyme levels return to normal with no necessity to discontinue medication. In occasional instances, progressive liver damage occurs, with accompanying symptoms. In these cases, the drug should be discontinued immediately. The frequency of progressive liver damage increases with age. It is rare in persons under 20, but occurs in up to 2.3 % of those over 50 years of age.

Hematologic Reactions: Agranulocytosis, hemolytic sideroblastic or aplastic anemia, thrombocytopenia and eosinophilia.

Hypersensitivity Reactions: Fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy and vasculitis.

Metabolic And Endocrine Reactions: Pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, and gynecomastia.

Miscellaneous Reactions: Rheumatic syndrome and systemic lupus erythematosus-like syndrome.

Ethambutol

Ethambutol may produce decreases in visual acuity which appear to be due to optic neuritis and to be related to dose and duration of treatment. The effects are generally reversible when administration of the drug is discontinued promptly. In rare cases recovery may be delayed for up to 1 year or more and the effect may possibly be irreversible in these cases.

The change in visual acuity may be unilateral or bilateral and hence each eye must be tested separately and both eyes tested together. Testing of visual acuity should be performed before beginning ethambutol therapy and periodically during drug administration, except that it should be done monthly when a patient is on a dosage of more than 15 mg/kg per day. If careful evaluation confirms the magnitude of visual change and fails to reveal another cause, Ethambutol should be discontinued and the patient reevaluated at frequent intervals. Progressive decreases in visual acuity during therapy must be considered to be due to ethambutol.

Ethambutol may show subjective visual symptoms before, or simultaneously with, the demonstration of decreases in visual acuity, and all patients receiving ethambutol should be questioned periodically about blurred vision and other subjective eye symptoms.

Other adverse reactions reported include: anaphylactoid reactions, dermatitis pruritus and joint pain; anorexia, nausea, vomiting, gastrointestinal upset, abdominal pain; fever, malaise, headache, and dizziness; mental confusion, disorientation and possible hallucinations. Numbness and tingling of the extremities due to peripheral neuritis have been reported infrequently.

Elevated serum uric acid levels occurs and precipitation of acute gout has been reported. Transient impairment of liver function as indicated by abnormal liver function tests is not an

unusual finding. Since ethambutol is recommended for therapy in conjunction with one or more other antituberculous drugs, these changes may be related to the concurrent therapy.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacokinetic properties:

Rifampicin: The oral administration of Rifampicin produces peak concentrations in plasma in 2 to 4 hours. The half-life of Rifampicin varies from 1.5 to 5 hours and is increased in the presence of hepatic dysfunction; it may be decreased in patients receiving isoniazid concurrently who are slow inactivators of this drug. Up to 30% of a dose of Rifampicin is excreted in the urine; less than half of this may be unaltered antibiotic. Adjustment of dosage is not necessary in patients with impaired renal function.

Isoniazid: Peak plasma concentrations of 3 to 5 mcg/ml develop 1 to 2 hours after oral ingestion of usual doses. From 75 to 95% of a dose of isoniazid is excreted in the urine within 24 hours, as metabolites. The main excretory products in man are the result of enzymatic acetylation (acetylisoniazid) and enzymatic hydrolysis (isonicotinic acid). The rate of acetylation significantly alters the concentrations of the drug that are achieved in plasma and its half-life in the circulation. The half-life of the drug may be prolonged in the presence of hepatic insufficiency.

Ethambutol: After oral administration, 75 to 80% of ethambutol is absorbed from the gastrointestinal tract. A single dose of 15 mg/kg produces a plasma concentration of about 5mcg/ml at 2 to 4 hours. The drug has a half life of 3 to 4 hours. Within 24 hours, two thirds of an ingested dose of ethambutol is excreted unchanged in the urine; upto 15% is excreted in the form of two metabolites, an aldehyde and a dicarboxylic acid derivative. Renal clearance of ethambutol is approximately $7 \text{ ml. min}^{-1} \cdot \text{kg}^{-1}$, and the drug is excreted by tubular secretion in addition to glomerular filtration.

5.2 Pharmacodynamic properties: Rifampicin

The mode of action of Rifampicin is by inhibition of DNA-dependent RNA polymerase. This occurs in bacteria in low concentrations, much higher ones being required to inhibit mammalian RNA synthesis. In tuberculosis, Rifampicin is bactericidal for both intracellular and extracellular microorganisms. Microbial resistance to Rifampicin can develop, although certain Rifampicin-resistant bacteria have decreased virulence. It is unusual to encounter initial resistance.

Rifampicin has been shown to inhibit certain DNA viruses such as herpes, adenovirus and pox virus, but at concentrations 500 - 1000 times higher than those required to inhibit the growth of bacteria.

Bacterial Resistance : Against acute organisms resistance develops more readily and therefore it is usual to give Rifampicin in combination with other agents, as in tuberculosis and leprosy. Bacterial resistance may develop rapidly to Rifampicin and occurs as a one - step process. One of every 10⁷ - 10⁸ tubercle bacilli is resistant to Rifampicin; so the drug should not be used on its own. Rifampicin is generally administered in a dose of 450 - 600 mg on an empty stomach.

Antibacterial Activity

Rifampicin is bactericidal against a wide range of organisms, including mycobacteria. Despite this broad spectrum of activity, the antibiotic has been principally used in the management of tuberculous infections at all sites and in leprosy.

Rifampicin inhibits the growth of most Gram-positive and many Gram-negative organisms such as *E. coli*, *Proteus* spp. and *Pseudomonas*. The drug is highly active against *Neisseria meningitidis* and *N. gonorrhoea*. Rifampicin is very active against *Legionella* species in cell cultures.

Rifampicin inhibits growth of *Mycobacterium tuberculosis* and has some activity against atypical mycobacteria such as *M. kansasii*, *M. scrofulaceum* and *M. intracellulare* with MIC values of under 4mg/l. Rifampicin increases the in vitro activity of streptomycin and isoniazid.

Ethambutol

Ethambutol is bacteriostatic. It is effective against *Mycobacterium tuberculosis* and *M. bovis* with a MIC of 0.5 to 8 µg per ml but possesses little sterilizing activity. It is effective against tubercle bacilli resistant to other anti-tubercular agents. It is proposed that Ethambutol inhibits cell wall synthesis by preventing the incorporation of mycolic acids. Another study suggests that its activity against *Mycobacterium* spp. but not other bacteria may be due to inhibition of spermidine synthesis specifically in mycobacteria.

Ethambutol is active against virtually all strains of *Mycobacterium tuberculosis* and *M. bovis* and is also active against other mycobacteria such as *M. Kansasii*. Ethambutol has no effect on other microorganisms. Ethambutol usually suppresses the growth of isoniazid and streptomycin-resistant mycobacteria. Resistance to ethambutol develops very slowly and with difficulty in vitro, but in clinical practice some 50% of patients develop acquired resistance to ethambutol when the drug is given as monotherapy for 6 months.

Isoniazid

INH is bactericidal in vitro and in vivo against actively dividing tubercle bacilli; it is less active against non-dividing tubercle bacilli. Its primary action is to inhibit the synthesis of long chain mycolic acids which are unique constituents of mycobacterial cell walls. Isoniazid in low concentrations may prevent elongation of the very long chain fatty acid precursor of the mycolic acids. Since mycolic acids are unique to mycobacteria this explains the high degree of selectivity of isoniazid for these bacteria. Isoniazid may also have effects of nucleic acid biosynthesis and glycolysis.

INH concentrations of 600 mg/l or greater are required to inhibit Gram-positive and Gram-negative bacteria, but the minimum inhibitory concentration for *Mycobacterium tuberculosis* is 0.05 - 0.025 mg/l.

INH resistance is a relatively uncommon occurrence in developed countries but is an increasing problem in developing countries. In the United States about 4.0% of *Mycobacterium tuberculosis* isolates demonstrate primary resistance to INH. Resistance mutants occur at random and spontaneously in growing tubercle bacilli at a mutation rate of $1 - 3 \times 10^{-6}$ per bacterium per generation. Although the mechanism is not well understood, such mutants

appear to take up drug less readily than sensitive cells rather than to inactivate the drug at an increased rate. Controlled prospective studies are needed to evaluate regimens for treatment of persons infected with or exposed to INH resistant bacilli as the choice between available alternatives is uncertain.

Apart from its antimycobacterial action, isoniazid has no pharmacological effect in man. Isoniazid is well absorbed from an oral dose and peak concentrations occur within 1 - 2 hours. If isoniazid is given daily, inhibitory concentrations of drug are easily achieved. However, if the drug is given less frequently, the rate of acetylation of the drug (drug inactivation) can be of clinical importance. In rapid acetylators the therapeutic efficacy of isoniazid decreases significantly to a point where relapse is more likely than in slow acetylators when the drug is administered less often than twice weekly. The therapeutic effectiveness of isoniazid is determined by the intensity and duration of exposure to the drug.

For adult patients, daily oral doses of 5 mg/kg (upto 300 mg) are recommended. A higher dose of 10 mg/kg has been used in severely ill patients but there is no clear evidence that this higher dose is more effective than the standard dose. In children and adolescents, a higher daily dose in the range of 10 - 20 mg/kg may be used.

Pyridoxine should be administered with isoniazid to minimize side effects particularly in malnourished patients and those predisposed to neuropathy (the elderly, pregnant women, diabetics, alcoholics and patients with uraemia).

5.3 Pre-clinical safety data:

Rifampicin

Acute and subacute toxicity tests in rodents show good tolerance at well above therapeutic doses. The LD50 in mouse following oral administration is approximately 1250 mg/kg in 24 hours. In rat the LD50 values are 1700 mg/kg for oral administration, 550 mg/kg for intraperitoneal administration and 330 mg/kg for intravenous administration.

Rats given 50 mg/kg and 100 mg/kg daily for 26 weeks showed no notable toxicity, but at doses over 100 mg/kg there were dose related histological changes in the liver. Rabbits also

given doses over 100 mg/kg for 4 weeks or more showed progressive hepatotoxicity, including jaundice and fatty changes at 400 mg/kg. Dose related minor histological changes were observed in the liver of monkeys given 40 - 80 mg/kg for 2 to 4 weeks.

Ethambutol

The acute toxicity of Ethambutol in mice and rats by oral, subcutaneous, intraperitoneal and intravenous administration was found to be low, the LD50s being of the order of 8000 mg/kg after intravenous dosage with 200 - 300 mg.

In sub-acute and chronic toxicity studies in dogs, cats and monkeys, dosages giving serum concentrations in excess of 50 µg/ml were associated with reversible decolorations of the tapetum lucidum of the fundus in all three species but visual impairment only in monkeys and with ECG changes and eosinophilic hyaline change and vacuolation in the myocardium.

Isoniazid

Acute and chronic toxicity studies have not been performed in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients Microcrystalline

Cellulose

Crospovidone

Pregelatinized starch (Starch 1500)

Ascorbic acid

Gelatin

Colloidal Silicon Dioxide

Magnesium Stearate

Opadry 80W56578 Brown

6.2 Incompatibilities : Not reported

6.3 Shelf life : 3 years

6.4 Special precautions for storage

ALU-PVC/PVDC blister: Store below 25°C, protected from excessive humidity. Protect from light.

ALU-ALU Blister: Store below 30°C, protected from excessive humidity. Protect from light

6.5 Nature and contents of container

Available as a blister pack of 28 tablets. Such 24 blisters are packed in carton along with Pack Insert.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORISATION HOLDER

Lupin Limited
3rd floor, Kalpataru Inspire,
Off Western Express Highway,
Santacruz (East) Mumbai-400055, India.

8. NUMBER IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
