SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Isoniazid and Rifapentine Coated Tablets (300mg+ 300mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Isoniazid BP……. 300mg

Rifapentine…… 300mg

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL form

Tablet (scored)

4. Clinical Particulars

4.1 Therapeutic indications

Isoniazid / Rifapentine Tablets are indicated for the treatment of latent tuberculosis, caused by *Mycobacterium tuberculosis.*

4.2 Posology and method of administration

Weekly Rifapentine + Isoniazid for 3 months (12 doses)

Doses as per body weight

Adults and Children

Isoniazid: 15 mg/kg

Rifapentine (by body weight):

10.0–14.0 kg = 300 mg

14.1–25.0 kg = 450 mg

25.1–32.0 kg = 600 mg

32.1–49.9 kg = 750 mg

≥50.0 kg = 900 mg

The maximum dose of Isoniazid and Rifapentine is 900 mg

4.3 Contraindications

Isoniazid is contraindicated in patients with

- hypersensitivity to the active substance or to any of the excipients
- acute liver disease of any etiology
- drug induced hepatic disease
- previous isoniazid-associated hepatic injury or
- previous severe adverse reactions to isoniazid such as drug fever, chills or arthritis.

Rifapentine is contraindicated in patients with a history of hypersensitivity to rifamycins.

4.4 Special warnings and precautions for use

Rifapentine

Hepatotoxicity

Elevations of liver transaminases may occur in patients receiving Rifapentine. Patients on Rifapentine should be monitored for symptoms of liver injury. Patients with abnormal liver tests and/or liver disease or patients initiating treatment for active pulmonary tuberculosis should only be given Rifapentine in cases of necessity and under strict medical supervision. In such patients, obtain serum transaminase levels prior to therapy and every 2-4 weeks while on therapy. Discontinue Rifapentine if evidence of liver injury occurs.

Hypersensitivity And Related Reactions

Hypersensitivity reactions may occur in patients receiving Rifapentine. Signs and symptoms of these reactions may include hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia or flu-like syndrome (weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, chills, aches, rash, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations). There have been reports of anaphylaxis.

Monitor patients receiving Rifapentine therapy for signs and/or symptoms of hypersensitivity reactions. If these symptoms occur, administer supportive measures and discontinue Rifapentine.

Relapse In The Treatment Of Active Pulmonary Tuberculosis

Rifapentine has not been evaluated as part of the initial phase treatment regimen in HIV-infected patients with active pulmonary TB.

Do not use Rifapentine as a once-weekly continuation phase regimen in HIV-infected patients with active pulmonary tuberculosis because of a higher rate of failure and/or relapse with rifampinresistant organisms.

Higher relapse rates may occur in patients with cavitary pulmonary lesions and/or positive sputum cultures after the initial phase of active tuberculosis treatment and in patients with evidence of bilateral pulmonary disease. Monitor for signs and symptoms of TB relapse in these patients.

Poor adherence to therapy is associated with high relapse rate. Emphasize the importance of compliance with therapy.

Drug Interactions

Rifapentine is an inducer of CYP450 enzymes. Concomitant use of rifapentine with other drugs metabolized by these enzymes, such as protease inhibitors, certain reverse transcriptase inhibitors, and hormonal contraception may cause a significant decrease in plasma concentrations and loss of therapeutic effect.

Discoloration Of Body Fluids

Rifapentine may produce a red-orange discoloration of body tissues and/or fluids (e.g., skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid). Contact lenses or dentures may become permanently stained.

Clostridium difficile-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of nearly all systemic antibacterial agents, including Rifapentine, with severity ranging from mild diarrhea to fatal colitis. Treatment with antibacterial agents can alter the normal flora of the colon and may permit overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, discontinue antibacterial use not directed against C. difficile if possible. Institute appropriate measures such as fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation as clinically indicated.

Porphyria

Porphyria has been reported in patients receiving rifampin, attributed to induction of delta amino levulinic acid synthetase. Because Rifapentine may have similar enzyme induction properties, avoid the use of Rifapentine in patients with porphyria.

Isoniazid

Severe and sometimes fatal hepatitis associated with isoniazid therapy has been reported. The majority of cases occurs within the first three months of therapy, but hepatotoxicity may also develop after a longer duration of treatment. Therefore, patients should be carefully monitored and interviewed at monthly intervals.

Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesias of the hands and feet, persistent fatigue, weakness of greater than 3 days duration and/or abdominal tenderness, especially of the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage.

Patient groups especially at risk for developing hepatitis include

- age > 35 years
- daily users of alcohol
- patients with active chronic liver disease and
- injection drug users.

In addition to monthly symptom reviews hepatic enzymes (specifically AST and ALT) should be measured in these patients prior to starting isoniazid therapy and periodically throughout treatment.

Furthermore, the following patients should be carefully monitored:

- patients with concurrent use of any chronically administered medication
- existence of peripheral neuropathy or conditions predisposing to neuropathy
- pregnant patients and
- HIV infected patients.

The concentration of liver enzymes is commonly raised during therapy with Isoniazid Tablets BP 300 mg. These effects on liver function tests are usually mild to moderate, and will most commonly normalise spontaneously within three months, even in the presence of continued therapy.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of Isoniazid Tablets should be strongly considered.

Peripheral neuropathy

It is the most common toxic effect of isoniazid. The frequency depends on the dose and on predisposing conditions such as malnutrition, impaired renal function, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine should be co-administered routinely at doses of 10 mg per day.

Cross-sensitivity: Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to this product.

Isoniazid should be used with caution in patients with pre-existing seizure disorders, a history of psychosis or hepatic impairment.

Diabetes Mellitus: Patients with diabetes should be carefully monitored, since blood glucose control may be affected by isoniazid.

Renal impairment: Patients with renal impairment, particularly those who are slow acetylators may be at increased risk for isoniazid adverse effects such as peripheral neuropathy, and should be monitored accordingly. As in other patients, adequate supplementation with pyridoxine (see above) should be given to avoid neurotoxicity.

4.5 Interaction with other medicinal products and other forms of interaction

Rifapentine

Protease Inhibitors And Reverse Transcriptase Inhibitors

Rifapentine is an inducer of CYP450 enzymes. Concomitant use of Rifapentine with other drugs metabolized by these enzymes, such as protease inhibitors and certain reverse transcriptase inhibitors, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the protease inhibitor or reverse transcriptase inhibitor.

Hormonal Contraceptives

Rifapentine may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control.

Cytochrome P450 3A4 And 2C8/9

Rifapentine is an inducer of cytochromes P4503A4 and P4502C8/9. Therefore, Rifapentine may increase the metabolism of other coadministered drugs that are metabolized by these enzymes. Induction of enzyme activities by Rifapentine occurred within 4 days after the first dose. Enzyme activities returned to baseline levels 14 days after discontinuing Rifapentine.

Rifampin has been reported to accelerate the metabolism and may reduce the activity of the following drugs; hence, Rifapentine may also increase the metabolism and decrease the activity of these drugs.

Dosage adjustments of the drugs in Table below or of other drugs metabolized by cytochrome P4503A4 or P4502C8/9 may be necessary if they are given concurrently with Rifapentine.

Table: Drug Interactions with Rifapentine: Dosage Adjustment may be Necessary

Drug class	**Examples of drugs within class**
Antiarrhythmics	Disopyramide, mexiletine, quinidine, tocainide
Antibiotics	Chloramphenicol, clarithromycin, dapsone, doxycycline, Fluoroquinolones (such as ciprofloxacin)
Oral Anticoagulants	Warfarin
Anticonvulsants	Phenytoin
Antimalarials	Quinine
Azole antifungals	Fluconazole, Itraconazole, Ketoconazole
Antipsychotics	Haloperidol
Barbiturates	Phenobarbital
Benzodiazepenes	Diazepam
Beta-Blockers	Propanolol
Calcium channel blockers	Diltiazem, nifedipine, verapimil
Cardiac Glycoside Preparations	Digoxin
Corticosteroids	Prednisone
Fibrates	Clofibrate
Oral Hypoglycemics	Sulfonylureas (e.g. glyburide, glipizide)
Hormonal contraceptives/Progestins	Ethinyl estradiol, levonorgestrel
Immunosuppresants	Cyclosporine, tacrolimus
Methylxanthines	Theophylline
Narcotic analgesics	Methadone
Phosphodiesterase-5 (PDE-5)	Sildenafil

Inhibitors	
Thyroid preparations	Levothyroxine
Tricyclic antidepressants	Amitriptyline, Nortriptyline

Other Interactions

The conversion of Rifapentine to 25-desacetyl rifapentine is mediated by an esterase enzyme. There is minimal potential for Rifapentine metabolism to be inhibited or induced by another drug, based upon the characteristics of the esterase enzymes.

Since Riafpentine is highly bound to albumin, drug displacement interactions may also occur

Interactions With Laboratory Tests

Therapeutic concentrations of rifampin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Similar drug-laboratory interactions should be considered for Rifapentine; thus, alternative assay methods should be considered.

Isoniazid

In vitro, isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. Thus it may increase exposure to drugs mainly eliminated through either of these pathways. The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised.

Anticonvulsants

Phenytoin, carbamazepine, valproate: Isoniazid decreases the apparent clearance of these drugs, and therefore increases drug exposure. Plasma concentrations of the anticonvulsant should be determined prior to and after initiation of isoniazid therapy; the patient should be monitored closely for signs and symptoms of toxicity and the dose of the anticonvulsant should be adjusted accordingly.

Concomitant intake of Phenytoin or Carbamazepine may increase the hepatotoxicity of Isoniazid.

Sedatives

Benzodiazepines (e.g. Diazepam, Flurazepam, Triazolam, Midazolam): Isoniazid may decrease the hepatic metabolism of benzodiazepines, leading to increased benzodiazepine plasma concentrations. Patients should be carefully monitored for signs of benzodiazepine toxicity and the dose of the benzodiazepine should be adjusted accordingly.

Phenobarbital: Concomitant use with Isoniazid may lead to increased hepatotoxicity.

Neuroleptics

Chlorpromazine: Concomitant use with Isoniazid may impair the metabolism of isoniazid. Patients should be carefully monitored for Isoniazid toxicity.

Haloperidol: Concomitant use with Isoniazid may increase plasma levels of haloperidol. Patients should be carefully monitored for haloperidol toxicity and the dose of haloperidol should be adjusted accordingly.

Anticoagulants

Coumarin- or indandione-derivates (e.g. Warfarin): concomitant use with isoniazid may inhibit the enzymatic metabolism of the anticoagulants, leading to increased plasma concentrations with an increased risk of bleeding. Therefore, INR (International Normalised Ratio) should be closely monitored.

Narcotics

Alfentanil: chronic pre-/perioperative use of Isoniazid may decrease the plasma clearance and prolong the duration of action of Alfentanil. The dose of Alfentanil may need to be adjusted accordingly.

Enflurane: Isoniazid may increase the formation of the potentially Nephrotoxic inorganic fluoride metabolite of Enflurane when used concomitantly.

Others

Theophylline: Concomitant use with isoniazid may reduce the metabolism of theophylline, thereby increasing its plasma levels. Therefore, theophylline plasma levels should be monitored.

Procainamide: Concomitant use with isoniazid may increase the plasma concentrations of isoniazid. Patients should be carefully monitored for Isoniazid toxicity.

Corticosteroids (e.g. Prednisolone): In one study, concomitant use with isoniazid decreased isoniazid exposure by 22-30%. Isoniazid dosage adjustments may be required in rapid acetylators.

Acetaminophen, paracetamol: Concurrent use with Isoniazid may increase hepatotoxicity.

Aluminium hydroxide impairs the absorption of isoniazid. During therapy with Isoniazid Tablets acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used.

Disulfiram: concurrent use with isoniazid may result in increased incidence of effects on the central nervous system. Reduced dosage or discontinuation of disulfiram may be necessary.

Hepatotoxic medications: concurrent use of isoniazid with other hepatotoxic medications may increase hepatotoxicity and should be avoided.

Neurotoxic medications: concurrent use of isoniazid with other neurotoxic medications may lead to additive neurotoxicity and should be avoided.

Interactions with food and drinks

Alcohol: concurrent daily intake of alcohol may result in an increased incidence of isoniazid induced hepatotoxicity. Patients should be monitored closely for signs of hepatotoxicity and should be strongly advised to restrict intake of alcoholic beverages.

Cheese and fish (histamine- or tyramine-rich food): concurrent ingestion with isoniazid may lead to inhibition of mono-/diamine oxidases by isoniazid, interfering with the metabolism of histamine and tyramine. Clinically, this may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or lightheadedness.

Interactions with laboratory tests

Isoniazid may cause a false positive response to copper sulfate glucose tests; enzymatic glucose tests are not affected.

4.6 Pregnancy and Lactation

Rifapentine

Pregnancy: There are no adequate and well controlled trials of Rifapentine in pregnant women. Because animal studies are not always predictive of human response, Rifapentine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Isoniazid

Pregnancy:

No adverse effects of Isoniazid on the fetus have been reported. However, isoniazid is to be used in pregnancy only when the benefits outweigh the potential risks.

Lactation

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

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. Nevertheless, the clinical status of the patient and the adverse reaction profile of this medicine, especially its potential neurotoxicity, should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Rifapentine

Blood And Lymphatics: Anemia, Lymphopenia, Neutropenia, Leukocytosis , Thrombocytosis, Thrombocytopenia, Lymphadenopathy, Nonprotein Nitrogen Increased

Eye: Conjunctivitis

*Gastrointestinal:*Dyspepsia, Vomiting, Nausea, Diarrhoea

General: Back pain, Abdominal pain, Fever, Anorexia

Hepatic & Biliary: ALT increased, AST increased

Musculoskeletal: Arthralgia

Neurologic: Headache, Dizziness

Respiratory: Hemoptysis, Coughing

Skin: Rash, Sweating increased, Pruritis, Rash Maculopapular

The following selected treatment-emergent adverse reactions were reported in less than 1% of the Rifapentine combination therapy patients during treatment and post-treatment through the first three months of followup.

Blood and Lymphatics: lymphocytosis, hematoma, purpura, thrombosis.

Cardiovascular: syncope, tachycardia, palpitation, orthostatic hypotension, pericarditis.

Metabolic & Nutritional: BUN increased, alkaline phosphatase increased.

Gastrointestinal: gastritis, esophagitis, pancreatitis, salivary gland enlargement.

General: asthenia, facial edema.

Hepatobiliary: bilirubinemia, hepatomegaly, jaundice.

Infectious Disease: infection fungal.

Musculoskeletal: myalgia, myositis.

Neurologic: somnolence, dysphonia.

Pregnancy, Puerperium and Perinatal conditions: abortion

Psychiatric: anxiety, confusion

Reproductive Disorders: vaginitis, vaginal hemorrhage, leukorrhea.

Respiratory: dyspnea, pneumonitis, pulmonary fibrosis, asthma, bronchospasm, laryngeal edema, laryngitis.

Skin: urticaria, skin discoloration,

Isoniazid

The most important adverse effects of Isoniazid are peripheral and central neurotoxic effects, and severe and sometimes fatal hepatitis.

The adverse events considered at least possibly related to treatment are listed below by body system, organ class and frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (≤1/10,000), 'not known'.

Nervous system disorders

Very common: Peripheral neuropathy, usually preceded by paraesthesias of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces this risk.

Uncommon: seizures, toxic encephalopathy

Not known: dizziness, headache, tremor, vertigo, hyperreflexia.

Psychiatric disorders

Uncommon: memory impairment, toxic psychosis

Not known: confusion, disorientation, hallucination.

Gastrointestinal disorders

Not known: nausea, vomiting, anorexia, dry mouth, flatulence, abdominal pain, constipation.

Hepatobiliary disorders:

Very common: Transient increases of serum transaminases.

Uncommon: hepatitis.

Renal and urinary disorders

Not known: urinary retention, nephrotoxicity including interstitial nephritis.

Metabolic and nutrition disorders

Not known: hyperglycaemia, metabolic acidosis, pellagra.

General disorders

Not known: allergic reactions with skin manifestation (exanthema, erythema, erythema multiforme), pruritus, fever, leucopenia, anaphylaxia, allergic pneumonitis, neutropenia, eosinophilia, Stevens-Johnson syndrome, vasculitis, lymphadenopathy, rheumatic syndrome, lupus–like syndrome.

Blood and lymphatic systems disorders

Not known: anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia (allergic), neutropenia with eosinophilia, agranulocytosis.

Respiratory, thoracic and mediastinal disorders

Not known: pneumonitis (allergic).

Musculoskeletal disorders

Not known: Arthritis.

Eye disorders:

Not known: Optic atrophy or neuritis.

4.9 Overdose

Symptoms:

Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and/or visual disturbances occur within 30 minutes to 3 hours after ingestion. With marked isoniazid overdoses (≥ 80 mg/kg body weight) respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria, and hyperglycaemia.

Treatment:

Emesis, gastric lavage and activated charcoal may be of value if instituted within a few hours of ingestion. Subsequently, pyridoxine (intravenous bolus on a gram per gram basis, equal to the isoniazid dose; if latter dose is unknown an initial dose of 5 g in adults or 80 mg/kg BW in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. Further treatment should be supportive, with special attention to monitoring/support of ventilation and correction of metabolic acidosis. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

<u>Rifapentine</u>

Rifapentine, a cyclopentyl rifamycin, inhibits DNA-dependent RNA polymerase in susceptible strains of Mycobacterium tuberculosis but does not affect mammalian cells at concentrations that are active against these bacteria. At therapeutic levels, rifapentine inhibits RNA transcription by preventing the initiation of RNA chain formation. It forms a stable complex with bacterial DNA-dependent RNA polymerase, leading to repression of RNA synthesis and cell

death. Rifapentine and its 25-desacetyl metabolite accumulate in human monocyte-derived macrophages and are bactericidal to both intracellular and extracellular M. tuberculosis bacilli.

Isoniazid

Pharmacotherapeutic group: Antimycobacterial

ATC Code for isoniazid: J04AC01

Mechanism of action

Isoniazid is highly active against *Mycobacterium tuberculosis*. It is bactericidal *in vitro* and *in vivo* against actively dividing tubercle bacilli. Its primary action is to inhibit the synthesis of long chain mycolic acids, which are unique constituents of mycobacterial cell wall. Resistance to isoniazid occurs rapidly if it is used alone in the treatment of clinical disease due to mycobacteria.

5.2 Pharmacokinetic properties

Rifapentine

Absorption:

The absolute bioavailability of Rifapentine has not been determined. The relative bioavailability of Rifapentine after a single 600 mg dose to healthy adult volunteers was 70%. The maximum concentrations were achieved from 5 hours to 6 hours after administration of the 600 mg Rifapentine dose.

The administration of Rifapentine with a high fat meal increased rifapentine Cmax and AUC by 40% to 50% over that observed when Rifapentine was administered under fasting conditions.

Distribution:

In healthy volunteers, rifapentine and 25-desacetyl rifapentine were 97.7% and 93.2% bound to plasma proteins, respectively. Rifapentine was mainly bound to albumin. Similar extent of protein binding was observed in healthy volunteers, asymptomatic HIV-infected subjects and hepatically impaired subjects.

Metabolism/Excretion:

Following a single 600 mg oral dose of radiolabeled rifapentine to healthy volunteers (n=4), 87% of the total ^{14}C rifapentine was recovered in the urine (17%) and feces (70%). Greater than 80% of the total C rifapentine dose was excreted from the body within 7 days. Rifapentine was hydrolyzed by an esterase enzyme to form a microbiologically active 25-desacetyl rifapentine. Rifapentine and 25-desacetyl rifapentine accounted for 99% of the total radioactivity in plasma. Plasma AUC(0-∞) and Cmax values of the 25-desacetyl rifapentine metabolite were one-half and one-third those of the rifapentine, respectively. Based upon relative in vitro activities and AUC(0∞) values, rifapentine and 25-desacetyl rifapentine potentially contributes 62% and 38% to the clinical activities against M. tuberculosis, respectively. microbiologically active 25-desacetyl rifapentine. Rifapentine and 25-desacetyl rifapentine accounted for 99% of the total radioactivity in plasma. Plasma AUC(0-∞) and Cmax values of the 25-desacetyl rifapentine metabolite were one-half and one-third those of the rifapentine, respectively. Based upon relative in vitro activities and AUC(0∞) values,

rifapentine and 25-desacetyl rifapentine potentially contributes 62% and 38% to the clinical activities against M. tuberculosis, respectively.

Isoniazid

Absorption:

After oral administration isoniazid is rapidly absorbed with a bioavailability of ≥80%, and peak serum concentrations reached after 1-2 hours. The rate and extent of absorption are reduced when isoniazid is administered with food. Isoniazid undergoes appreciable presystemic (first pass) metabolism in the wall of small intestine and liver.

Following single dose Isoniazid 300 mg Tablets administration in healthy volunteers, the mean (± SD) isoniazid Cmax value was 7.3 µg/ml (± 1.89), and the corresponding value for AUC was 32.3 µg.h/ml (± 12.49). The mean (± SD) isoniazid tmax value was 0.7 (± 0.30) hours.

Distribution

Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57 to 0.76 l/kg. Protein binding is very low (0-10%).

Metabolism:

Isoniazid undergoes extensive metabolism that takes place in the mucosal cells of the small intestine and in the liver. First isoniazid is inactivated through acetylation. Subsequently acetyl-isoniazid is further hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, who are termed fast or slow acetylators (this is due to a genetic polymorphism in the metabolizsing enzyme N-acetyl transferase). Different ethnic groups contain differing proportions of acetylator phenotypes. Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that seen in slow acetylators.

Excretion:

Up to 95% of ingested isoniazid is excreted in the urine within 24 hours, primarily as inactive metabolites. Less than 10% of the dose is excreted in the faeces. The main excretion products in the urine are N-acetylisoniazid and isonicotinic acid.

Special populations

Renal impairment:

The documentation of the pharmacokinetics of isoniazid and its metabolites in patients with renal impairment is incomplete. However, the half-life of isoniazid is prolonged and exposure is increased, in slow acetylators. The exposure to the (inactive) metabolites of isoniazid is likely to be increased in both fast and slow acetylators.

5.3 Preclinical safety data

Rifapentine

Hepatocellular carcinomas were increased in male NMRI mice (Harlan Winklemann) which were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (0.04 times the recommended human dose based on body surface area conversions). In a two year rat

study, there was an increase in nasal cavity adenomas in Wistar rats treated orally with rifapentine at 40 mg/kg/day (0.6 times human dose based on body surface area conversions).
Rifapentine was negative in the following genotoxicity tests: in vitro gene mutation assay in bacteria (Ames test); in vitro point mutation test in Aspergillus nidulans; in vitro gene conversion assay in Saccharomyces cerevisiae; host-mediated (mouse) gene conversion assay with Saccharomyces cerevisiae; in vitro Chinese hamster ovary cell/hypoxanthineguaninephosphoribosyl transferase (CHO/HGPRT) forward mutation assay; in vitro chromosomal aberration assay utilizing rat lymphocytes; and in vivo mouse bone marrow micronucleus assay.
The 25-desacetyl metabolite of rifapentine was positive in the in vitro mammalian chromosome aberration test in V79 Chinese Hamster cells, but was negative in the in vitro gene mutation assay in bacteria (Ames test), the in vitro Chinese hamster ovary cell/hypoxanthine-guaninephosphoribosyl transferase (CHO/HGPRT) forward mutation assay, and the in vivo mouse bone marrow micronucleus assay. Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats at doses of up to 20 mg/kg/day (one-third of the human dose based on body surface area conversions).

Isoniazid

Non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. In male rats spermatogenesis impairment and abnormalities in testicular histopathology was seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose, Pregelatinised Starch, Croscarmellose Sodium, Iron Oxide Red, Povidone K-30, Microcrystalline Cellulose, Low-Substituted Hydroxypropyl Cellulose, Calcium Stearate, Sodium Starch Glycolate type A, Sodium Ascorbate, EDTA Disodium, Sodium Lauryl Sulfate, Hydroxypropyl Cellulose, Hypromellose 2910, Opadry® 03F565224 Brown IHS.

6.2 Incompatibilities

None

6.3 Shelf life

24 months from the manufacturing date.

Never use after the expiry date clearly indicated on the outer packaging.

6.4 Special precautions for storage

Do not store above 30°C. Protect from excessive heat and humidity.

6.5 Nature and contents of container<and special equipment for use, administration or implantation

Blister Pack: 3 X 12's Count

Lidding Foil: 30 micron aluminum plain foil with 6-8gsm HSL (Width – 172mm)
Forming Foil: Cold form laminate 25 micron OPA/45 micron Al foil /60 micron PVC (Width – 172mm)

Strip Pack: 3 X 12's Count

Lidding Foil: Plain 40micron aluminium foil (soft tempered) laminated with 150 gauge polyethylene film width – 209 mm (Top Foil)
Forming Foil: Plain 40micron aluminium foil (soft tempered) laminated with 150 gauge polyethylene film width – 209 mm (Bottom Foil)

6.6 Special precautions for disposal<and other handling>

None

7. APPLICANT/SUPPLIER

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8. WHO PREQUALIFICATION REFERENCE NUMBER

9. DATE OF <PREQUALIFICATION>/<RENEWAL OF PREQUALIFICATION

10. DATE OF REVISION OF THE TEXT

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3. Guidelines on the management of latent tuberculosis infection, available at http://apps.who.int/medicinedocs/documents/s21682en/s21682en.pdf