SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets[1]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg isoniazid, 25 mg pyridoxine hydrochloride, 800 mg sulfamethoxazole and 160 mg trimethoprim.

Excipient with known effect: each tablet contains 0.03 mg of sodium benzoate. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim tablets are white to off-white coloured capsule-shaped, biconvex uncoated tablets scored on both the sides, which allow the tablet contents to be divided into two equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets is indicated for HIV-infected adults, adolescents and children weighing over 14 kg for the prevention of opportunistic infections particularly tuberculosis, *Pneumocystis jiroveci* (*P. carinii*) pneumonia, *Plasmodium falciparum* malaria, toxoplasmosis and bacterial infections sensitive to sulfamethoxazole/trimethoprim.

The decision on preventative treatment with Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/ Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets should take account of local prevalence of tuberculosis, malaria and relevant bacterial infections and of official guidelines on the prevention of opportunistic infections. The guidelines will normally include those from WHO:

Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (2016)

Guidelines on the management of latent tuberculosis infection (2015)

Guidelines for the treatment of malaria, 3rd edn (2015)

Pyridoxine in Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets prevents isoniazid-induced neuropathy.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

4.2 Posology and method of administration

Posology

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets should be taken once a day and the duration of treatment should take into account official guidelines and will depend on recovery of the patient's immunity.

Adults

1 tablet once a day.

Adolescents and children

Body weight	Dose
Under 14 kg	Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets is not suitable; use alternative products containing lower amounts of the active ingredients to give suitable
14–24.9 kg	½ tablet once a day
25 kg and	1 tablet once a day

Method of administration

Tablets should be taken at around the same time each day, preferably on an empty stomach (at least one hour before a meal or at least two hours after a meal).

Tablets can be broken into two equal halves, using the scorelines but they should not be crushed or chewed and they should be swallowed with water.

Renal impairment

Sulfamethoxazole can accumulate in patients with renal impairment and it may not be suitable for patients with creatinine clearance less than 30 ml/minute.

Patients with renal impairment should also be monitored for isoniazid toxicity, especially peripheral neuropathy.

Hepatic impairment

Hepatic impairment can cause accumulation of isoniazid and possibly also of sulfamethoxazole and trimethoprim. No recommendations are made on dose adjustment in hepatic impairment but the patient should be monitored for signs of toxicity.

Missed dose

It is important to take Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets regularly each day to maximise protection and to reduce the risk of organisms developing resistance to one or more of the active ingredients.

If it is less than 6 hours since the dose was due, the patient should take the missed dose at once and take the next one at the usual time. If more than 6 hours have passed since the dose was due, the patient should skip the missed dose and take the next one at the usual time. The patient should not take a double dose.

4.3 Contraindications

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets are contraindicated in patients with:

- hypersensitivity to any of the active ingredients, to sulfonamide drugs or to any of the excipients (see section 6.1)
- acute liver disease including, drug-induced liver disease and marked liver parenchymal damage
- previous severe adverse reactions to isoniazid such as drug fever, chills and arthritis
- previous isoniazid-induced liver damage
- previous severe adverse reactions to isoniazid such as drug fever, chills and arthritis
- risk of acute porphyria
- previous trimethoprim- or sulfonamide-induced immune thrombocytopenia
- megaloblastic anaemia due to folate deficiency

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets must also not be used concomitantly with clozapine because such use may increase the risk of myelosuppression and serious blood disorders.

4.4 Special warnings and precautions for use

Active infection

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets must not be given to patients with an ongoing infection such as active tuberculosis, malaria or another infection. The infection must be treated with appropriate antimicrobial regimen.

Hypersensitivity reactions

Rarely, sulfamethoxazole/trimethoprim can cause serious, life-threatening skin reactions such as toxic epidermal necrolysis or Stevens-Johnson syndrome, especially in the first few weeks of treatment. Patients should be monitored closely for skin reactions and they should be advised to report immediately signs and symptoms such as rash often with blisters, skin discoloration, mucosal lesions, sore throat, fever, arthralgia, pallor and jaundice. If a serious skin reaction is suspected, Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets must be stopped and the patient should never receive sulfamethoxazole/trimethoprim.

The patient should also be monitored for signs and symptoms of other reactions induced by sulfamethoxazole/trimethoprim such as fulminant hepatic necrosis and respiratory-tract hypersensitivity (with cough, shortness of breath and pulmonary infiltrates). Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets must be stopped if these reactions occur.

Isoniazid-induced pancreatitis can occur. Patients should be advised to report any signs and symptoms of pancreatitis. Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets should be stopped and the patient should never receive isoniazid if the patient develops pancreatitis.

Patients hypersensitive to ethionamide, nicotinic acid (niacin), pyrazinamide and to other chemically related medicines may also be hypersensitive to isoniazid in Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets.

Liver damage

Liver function should be assessed before starting treatment with Isoniazid/Pyridoxine hydrochloride/ Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets and the regularly during treatment because patients with HIV are at high risk of hepatitis with isoniazid. Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets should be stopped if the patient has symptoms of liver damage. Patients should be advised to report features of liver damage such as dark urine, jaundice, malaise, fatigue, abdominal tenderness (especially in the right upper quadrant), anorexia and nausea.

The risk of liver damage is increased if patients:

- are aged over 35 years
- slow acetylators (metabolism of isoniazid is slower, which can cause isoniazid accumulation)
- drink alcohol daily or excessively
- have chronic liver disease
- are malnourished
- take hepatotoxic drugs concomitantly
- abuse drugs by injecting them

Blood disorders and folate deficiency

The patient should be monitored for signs and symptoms of serious blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia) induced by sulfamethoxazole/trimethoprim. Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets must be stopped if serious blood disorders occur.

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets should not be given to patients with serious blood disorders unless that patient can be closely supervised.

Regular monitoring of blood counts is recommended in patients with folate deficiency (such as those who are elderly, malnourished or with malabsorption syndrome, abusing alcohol or receiving antiepileptic therapy). The risk of blood disorders due to sulfamethoxazole/trimethoprim is higher in those with folate deficiency.

Glucose-6-phosphate dehydrogenase deficiency

Patients with glucose-6-phosphate (G6PD) deficiency should be monitored for haemolysis because sulfamethoxazole/trimethoprim in Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/ Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets may induce haemolysis.

Diabetes Mellitus

Patients with diabetes should be monitored carefully because isoniazid in Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets may affect blood glucose control.

Hyperkalaemia and metabolic acidosis

Serum potassium should be monitored in patients at risk of hyperkalaemia and hyponatraemia who are taking sulfamethoxazole/trimethoprim.

Sulfamethoxazole/trimethoprim is associated with metabolic acidosis and patients taking Isoniazid/ Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets should be monitored closely if metabolic acidosis is suspected.

Peripheral neuropathy

Patients with peripheral neuropathy or conditions predisposing to neuropathy should be carefully monitored. Although pyridoxine in Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/ Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets reduces the risk of isoniazid-induced peripheral neuropathy, care is required in conditions such as malnutrition, renal impairment, alcoholism and diabetes.

Crystalluria

The patient should drink enough fluids to maintain adequate urine output and so avoid the small risk of crystalluria due to the precipitation of sulfonamide crystals. The risk of crystalluria is increased in malnourished patients.

Antibacterial-associated colitis

The possibility of antibacterial-associated (pseudomembranous) colitis should be considered if the patient develops diarrhoea. Rarely, long-term use of an antibacterial can lead to overgrowth of *Clostridium difficile*, which causes potentially serious antibacterial-associated colitis. Isoniazid/ Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets should be stopped if antibacterial-associated colitis is suspected and specific treatment of *C. difficile* infection should be considered. Antidiarrhoeal medicines (i.e. medicines which inhibit peristalsis) must not be given.

Elderly

Elderly patients are more susceptible to side effects of Isoniazid/Pyridoxine hydrochloride/ Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets, particularly because of the possibility of impaired kidney and liver function and concomitant use of other medicines.

4.5 Interactions with other medicinal products and other forms of interaction

Isoniazid inhibits CYP2C19 and CYP3A4, sulfamethoxazole inhibits CYP2C9, and trimethoprim inhibits CYP2C8 and OCT2 transporter. Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/ Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets should be used with care when it is co-administered with drugs that mainly use these pathways because it may increase levels of these drugs in the blood.

Diuretics

Thiazides diuretics: The risk of thrombocytopenia may be increased especially in the elderly.

Potassium-sparing diuretics: The risk of hyperkalaemia is increased with concomitant use of sulfamethoxazole/trimethoprim and potassium-sparing diuretics (e.g. amiloride, triamterene and spironolactone)

Anticoagulants

Isoniazid may increase the anticoagulant effects of coumarins (e.g. warfarin) and indandiones (e.g. phenindione). Close monitoring of anticoagulant activity may be required and the anticoagulant dose adjusted if necessary.

Sulfamethoxazole/trimethoprim may also increase the anticoagulant effects of coumarins (e.g. warfarin). Close monitoring of anticoagulation effect may be required and the anticoagulant dose adjusted if necessary.

Antiepileptics

Isoniazid may increase plasma levels of phenytoin, carbamazepine, ethosuximide and valproate. The dose of the antiepileptic may need to be adjusted according to plasma concentrations of the antiepileptic and side effects.

Isoniazid used concomitantly with carbamazepine, phenytoin and primidone may increase the risk of liver damage.

Sulfamethoxazole/trimethoprim may increase the risk of phenytoin toxicity. Closer monitoring of toxicity and of serum phenytoin levels may be required.

Sedatives, analgesics and anaesthetics

Benzodiazepines: isoniazid may increase plasma levels of benzodiazepines (such as diazepam, flurazepam, midazolam and triazolam). The dose of the benzodiazepine may need to be reduced in case of excessive sedation. Further, concomitant use of isoniazid and some benzodiazepines may increase the risk of liver damage.

Alfentanil: isoniazid may prolong the duration of action of alfentanil. The dose of alfentanil may need to be adjusted.

Paracetamol: concomitant use of isoniazid and paracetamol may increase the risk of liver damage and possibly kidney damage.

General anaesthetics: isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane when used concomitantly. Further, concomitant use of isoniazid and general anaesthetics may increase the risk of liver damage.

Antipsychotics

Chlorpromazine: carbamazepine may reduce the metabolism of isoniazid. Patients should be carefully monitored for isoniazid toxicity.

Clozapine: concomitant use of sulfamethoxazole/trimethoprim with clozapine should be avoided because of the risk of serious blood disorders.

Haloperidol: isoniazid may increase plasma levels of haloperidol. Patients should be monitored for excessive effects of haloperidol and the haloperidol dose adjusted if necessary.

Drugs acting on the immune system

Methotrexate: concomitant use of sulfamethoxazole/trimethoprim and methotrexate may increase the risk of bone marrow suppression and lead to blood disorders (additive effect on folate metabolism). Sulfamethoxazole/trimethoprim should be co-administered with methotrexate only if the benefits outweigh the risk and under careful monitoring of haematological parameters

Ciclosporin: concomitant use of sulfamethoxazole/trimethoprim and ciclosporin may increase the risk of renal impairment. Close monitoring of renal function is recommended.

Corticosteroids: prednisolone may reduce plasma level of isoniazid and the dose of isoniazid may need to be increased, especially in patients who are rapid acetylators.

Drugs acting on the cardiovascular system

Digoxin: Concomitant use of sulfamethoxazole/trimethoprim and digoxin may increase the risk of digoxin toxicity. Monitoring of plasma digoxin levels is recommended.

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

Angiotensin converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists: The risk of hyperkalaemia is increased with concomitant use of sulfamethoxazole/trimethoprim and ACE inhibitors (e.g. enalapril and quinapril) and angiotensin-II receptors antagonists.

Propranolol: concomitant use of isoniazid with propranolol may increase the plasma level of isoniazid.

Anti-infective drugs

Amodiaquine: concomitant use of sulfamethoxazole/trimethoprim and amodiaquine may increase the risk of blood disorders; concomitant use is contraindicated

Sulfadoxine/pyrimethamine: concomitant use of sulfamethoxazole/trimethoprim and sulfadoxine/pyrimethamine may increase the risk of severe cutaneous reactions; concomitant use is contraindicated

Pyrimethamine: concomitant use of sulfamethoxazole/trimethoprim and pyrimethamine may increase the risk of blood disorders including pancytopenia and megaloblastic anaemia. Close monitoring of haematological parameters is recommended if concomitant administration cannot be avoided (additive effect on folate metabolism).

Itraconazole and ketoconazole: isoniazid may markedly reduce plasma levels of itraconazole and concomitant use is not recommended. Isoniazid may also reduce the plasma levels of ketoconazole.

Drugs that can raise serum potassium level

The risk of hyperkalaemia is increased with concomitant use of sulfamethoxazole/trimethoprim and drugs such as potassium-sparing diuretics, ACE inhibitors and angiotensin-II receptor antagonists.

Myelosuppressive drugs

Concomitant use of sulfamethoxazole/trimethoprim with myelosuppressive drugs such as amodiaquine, zidovudine and ganciclovir may cause blood disorders. If concomitant treatment cannot be avoided, the patient's haematological parameters should be closely monitored.

Hepatotoxic drugs

Concomitant use of isoniazid with hepatotoxic drugs may increase the risk of liver damage. Such drugs include antiepileptics (e.g. carbamazepine, primidone and phenytoin), general anaesthetics, benzodiazepines and disulfiram.

Neurotoxic drugs

Concomitant use of isoniazid with other neurotoxic drugs may lead to additive neurotoxicity.

Other drugs

Theophylline: isoniazid may increase plasma levels of theophylline. The dose of theophylline may need to be adjusted according to theophylline plasma levels.

Hypoglycaemic drugs: concomitant use of sulfamethoxazole/trimethoprim with drugs for the treatment of type 2 diabetes (including sulfonylureas) may increase hypoglycaemic effect.

Antacids: Antacids such as aluminium hydroxide may reduce the absorption of isoniazid. Patients should avoid concurrent use and take isoniazid at least 1 hour before taking the antacid.

Interaction with food and drinks

Alcohol: daily or excessive use of alcohol may increase the risk of isoniazid-induced liver damage. Patients should be strongly advised to restrict alcohol use and those who use alcohol excessively should be monitored for hepatotoxicity.

Cheese and fish: concurrent ingestion of isoniazid with foods rich in histamine or tyramine may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or lightheadedness

4.6 Fertility, pregnancy and lactation

Fertility

Trimethoprim in Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets can cause folate deficiency in spermatogenic cells and may disrupt spermatogenesis in men.

Pregnancy

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets should be given in pregnancy only when its benefits are considered to outweigh the risks to the fetus.

Sulfamethoxazole/trimethoprim in Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/ Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets may be associated with birth defects, particularly during the first trimester. Folate supplementation should be considered if the use of Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets is considered essential. The use of sulfamethoxazole/trimethoprim should be avoided in late pregnancy if there is a risk of precipitating hyperbilirubinaemia and kernicterus in the newborn (e.g. if born prematurely or has glucose-6-phosphate dehydrogenase deficiency).

Breastfeeding

Isoniazid in Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets enters breast milk. Therefore, consideration should be given to giving pyridoxine to the breast-feeding infant to avoid isoniazid side effects. Sulfamethoxazole/trimethoprim also enter breast milk.

4.7 Effects on ability to drive and use machines

Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets is expected to have no or negligible influence on the ability to drive and use machines. However, the patient should be sure that effects of the underlying condition or possible rare side effects of Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets do not affect their ability to perform skilled tasks.

4.8 Undesirable effects

The most common adverse effects of isoniazid are peripheral neuropathy (but less likely with Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets because of the presence of pyridoxine) and transient increase in serum transaminase; the most common adverse effect of sulfamethoxazole/trimethoprim are gastrointestinal disturbance (e.g. nausea, vomiting and anorexia), skin reactions (e.g. rash and urticarial) and hyperkalaemia.

Adverse events reported with isoniazid and sulfamethoxazole/trimethoprim are listed below. Where they can be estimated, frequencies are defined as *very common* (≥ 1/10), *common* (1/100–1/10), *uncommon* (1/1000–1/100), *rare* (1/10 000–1/1000) or *very rare* (≤ 1/10 000) including isolated reports, or *not known* (frequency cannot be estimated from the available data).

Gastrointestinal disorders

Common: nausea,

diarrhoea *Uncommon:*

vomiting

Very rare: glossitis, stomatitis, antibacterial-associated (pseudomembranous) colitis, decreased appetite

Not known: flatulence, anorexia, dry mouth, abdominal pain, pancreatitis, constipation

Hepatobiliary disorders

Very common: transient increases of serum transaminases

Uncommon: hepatitis.

Very rare: blood bilirubin increased, cholestatic jaundice, hepatic necrosis

Metabolic and nutrition disorders

Very common: hyperkalaemia

Very rare: hypoglycaemia, hyponatraemia, metabolic acidosis, renal tubular acidosis

Not known: hyperglycaemia, pellagra

Cardiac disorders

Not known: QT prolongation resulting in ventricular tachycardia and torsade de pointes arrhythmias

Blood and lymphatic system (see also, below, under 'Description of selected adverse reactions')

Very rare: leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in glucose-6-phosphate dehydrogenase deficiency

Not known: sideroblastic anaemia, neutropenia with eosinophilia

Nervous system disorders

Very common: peripheral neuropathy but the inclusion of pyridoxine in {Product name} largely reduces this risk

Common: headache

Uncommon: seizures, toxic encephalopathy

Very rare: aseptic meningitis (see also, below, under 'Description of selected adverse reactions'), peripheral neuritis, ataxia, vertigo, tinnitus, dizziness

Not known: tremor, hyperreflexia

Psychiatric disorders

Uncommon: memory impairment, toxic psychosis

Very rare: depression, hallucinations

Not known: confusion, disorientation, hallucination, apathy, nervousness, insomnia

Immune system disorders

Very rare: serum sickness, anaphylactic reaction, allergic myocarditis, angioedema, pyrexia, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteriitis nodosa, systemic lupus erythematosus

Not known: anaphylaxis, idiopathic thrombocytopenic purpura

Respiratory, thoracic and mediastinal disorders

Very rare: cough, dyspnoea, lung infiltration (see also, below, under 'Description of selected adverse reactions')

Not known: pneumonitis (allergic)

Infections and infestations

Common: Candida overgrowth

Renal and urinary disorders

Very rare: renal impairment (sometimes reported as renal failure), tubulo-interstitial nephritis

Not known: urinary retention, raised blood-urea nitrogen and serum creatinine, toxic nephrosis with oliguria and anuria, crystalluria, nephrotoxicity in association with ciclosporin

Musculoskeletal and connective tissue disorders

Very rare: arthralgia, myalgia

Not known: arthritis; rhabdomyolysis has been reported in patients with HIV infection receiving sulfamethoxazole/trimethoprim for treating or preventing *P. jirvoci* pneumonitis

Eye disorders

Very rare: uveitis

Not known: optic atrophy or neuritis

Skin and subcutaneous tissue disorders

Common: rash

Very rare: photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see also, below, under 'Description of selected adverse reactions')

Not known: drug reaction with eosinophilia and systemic symptoms (DRESS), pruritus, urticaria

General disorders

Not known: eosinophilia, vasculitis, lymphadenopathy, rheumatic syndrome, weakness, fatigue

Description of selected adverse reactions

Haematological effects

Most haematological effects are mild and they are reversible on stopping treatment. However, rarely, the effects may be severe, especially in the elderly, in those with hepatic or renal dysfunction or in those with folate deficiencies. Fatalities have occurred in at-risk patients and these patients should be monitored carefully.

Aseptic meningitis

Aseptic meningitis is rapidly reversible on withdrawal of the drug, but may recur in some cases on re- treatment with either sulfamethoxazole/trimethoprim or trimethoprim alone.

Pulmonary hypersensitivity reactions

Cough, dyspnoea and lung infiltration may be early indicators of respiratory hypersensitivity which, while very rare can be fatal.

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. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Symptoms

Isoniazid

Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and 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 may occur. Typical laboratory findings are severe metabolic acidosis, acetonuria, and hyperglycaemia.

Sulfamethoxazole/trimethoprim

Features of overdosage with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and loss of consciousness. Pyrexia, haematuria and crystalluria may also occur. Blood disorders and jaundice are potential late effects of overdosage.

Nausea, vomiting, dizziness, headache, mental depression and confusion are features of overdosage with trimethroprim. Bone marrow depression has been reported in acute trimethoprim overdosage.

Treatment

Isoniazid

Activated charcoal may be of value if instituted within a few hours of ingestion. Pyridoxine counteracts some of isoniazid's toxic effects and it is already included in the product. Intravenous diazepam can be used to treat seizures not responding to pyridoxine and haemodialysis may be of value. Further treatment should be supportive, with special attention to monitoring and support of ventilation and correction of metabolic acidosis.

Sulfamethoxazole/trimethoprim

No specific antidote is available for overdose with sulfamethoxazole/trimethoprim. Treatment is symptomatic and supportive, including general measures such as monitoring of vital signs, as well as observation of the clinical status of the patient. Monitoring of blood counts and blood chemistry, including electrolytes is advisable.

Activated charcoal by mouth can increase elimination of unabsorbed active substance. Diuresis can be used if renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim.

Dialysis may be considered. Both trimethoprim and sulfamethoxazole are moderately dialysable by haemodialysis, but peritoneal dialysis is not effective.

If significant blood disorders or jaundice occur, specific therapy, including folinic acid, should be started for these complications. In case of seizures, treatment with diazepam or midazolam can be initiated. Methylthioninium chloride (methylene blue) treatment can be used for the treatment of methaemoglobinaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Isoniazid (Pharmacotherapeutic group: antimycobacterial) ATC code: J04AC01

Pyridoxine (Pharmacotherapeutic group: other plain vitamin preparations) ATC code: A11HA02

Sulfamethoxazole/trimethoprim (Pharmacotherapeutic group: combinations of sulphonamides and trimethoprim, including derivatives) ATC code: J01EE01

Mechanism of action

Isoniazid

Isoniazid is highly active against *Mycobacterium tuberculosis*. It is bactericidal against actively dividing tubercle bacilli. It inhibits 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 for the treatment of clinical disease due to mycobacteria.

Pyridoxine

Pyridoxine, converted to pyridoxal phosphate, is a co-enzyme for transamination and is involved in many metabolic processes. Because isoniazid metabolites attach to pyridoxine and inactivate it, pyridoxine supplementation helps to overcome isoniazid-induced pyridoxine inactivation.

Sulfamethoxazole/trimethoprim

Sulfamethoxazole inhibits microbial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA). Trimethoprim blocks dihydrofolate reductase (DHFR), the enzyme responsible for converting dihydrofolic acid to tetrahydrofolic acid. Depending on the conditions, this effect may be bactericidal. Trimethoprim's affinity for mammalian DHFR is some 50 000 times less than for the corresponding bacterial enzyme.

Thus, sulfamethoxazole and trimethoprim block two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many microorganisms.

Antimicrobial activity

Isoniazid

Isoniazid is highly active against *Mycobacterium tuberculosis* and it may be active against some other mycobacteria strains.

Isoniazid is bactericidal against actively dividing *M. tuberculosis* but it may only be bacteriostatic against semi-dormant bacilli.

M. tuberculosis quickly develops resistance to isoniazid if it is used alone in the treatment of active tuberculosis. Resistance is prevented or delayed by combining isoniazid with other antibacterials that are active against mycobacteria. The development of resistance is much less common when isoniazid is used alone in prophylaxis, probably because the bacillus load is low.

Sulfamethoxazole/trimethoprim

Organisms that are commonly susceptible to sulfamethoxazole/trimethoprim include some Gram-postive organisms (*Staphylococcus aureus, Staph. saprophyticus* and *Staph. pyogenes*), some Gram- negative organisms (*Enterobacter cloacae, Haemophilus influenzae, Klebsiella oxytoca, Moraxella catarrhalis, Salmonella* spp. and *Yersinia* spp.) and some protozoans (*Plasmodium falciparum, Pneumocystis jiroveci* and *Toxoplasma gondii*).

In vitro studies have shown that bacterial resistance develops more slowly when sulfamethoxazole and trimethoprim are given in combination than when either sulfamethoxazole or trimethoprim is used alone.

Resistance to sulfamethoxazole may occur by bacterial mutations which increase the concentration of para-aminobenzoic acid and thereby overcome the effects of sulfamethoxazole resulting reduced inhibitory effect on dihydropteroate synthetase enzyme. Another resistance mechanism is plasmid-mediated and results from production of an altered dihydropteroate synthetase enzyme, with reduced affinity for sulfamethoxazole compared to the wild-type enzyme.

Resistance to trimethoprim occurs through a plasmid-mediated mutation which results in production of an altered dihydrofolate reductase enzyme with reduced affinity for trimethoprim compared to the wild-type enzyme.

5.2 Pharmacokinetic properties

Isoniazid

Absorption

After oral administration isoniazid is rapidly absorbed with a bioavailability of at least 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 marked first-pass metabolism in the wall of small intestine and liver.

Following single-dose administration of Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/ Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets in healthy volunteers, the mean (± SD) isoniazid C_{max} value was 6.2 ± 2.2 µg/ml and the corresponding value for AUC_{0-t} was 26.7 ± 17.9 µg·hour/ml. The median (± SD) isoniazid t_{max} value was 0.84 ± 0.5 hours.

Distribution

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

Metabolism

Isoniazid is extensively metabolised in the mucosal cells of the small intestine and in the liver. First, isoniazid is inactivated through acetylation. Then acetylisoniazid is hydrolysed. The rate and extent of isoniazid acetylation is genetically determined and individuals are identified either as fast or slow acetylators (reflecting genetic polymorphism in the enzyme N-acetyl transferase). Ethnic groups have differing proportions of these acetylator phenotypes. Acetylator status is the main determinant of plasma concentration of isoniazid at a given dose. At recommended doses, the concentration in fast acetylators is about half that in slow acetylators.

Elimination

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.

Sulfamethoxazole/trimethoprim

Absorption

Sulfamethoxazole and trimethoprim are rapidly and nearly completely absorbed after oral administration. The presence of food does not appear to delay absorption. Steady-state levels in adults are reached after dosing for 2–3 days.

Following single-dose administration of Isoniazid/Pyridoxine hydrochloride/Sulfamethoxazole/ Trimethoprim 300 mg/25 mg/800 mg/160 mg Tablets in healthy volunteers, the mean (± SD) C_{max} value for sulfamethoxazole was 54 ± 11 µg/ml, and the corresponding value for AUC_{0-t} was 791 ± 147 µg·hour/ml. The mean (± SD) sulfamethoxazole t_{max} value was 2.1 ± 1.0 hours.

The mean (± SD) trimethoprim C_{max} value was 1.68 ± 0.47 µg/ml, and the corresponding value for AUC was 26.7 ± 8.0 µg·hour/ml. The mean (± SD) trimethoprim t_{max} value was 5.5 hours (range 1–10 hours).

Distribution

About 66% of sulfamethoxazole in the plasma is protein-bound. The concentration of sulfamethoxazole in amniotic fluid, aqueous humour, bile, cerebrospinal fluid, middle-ear fluid, sputum, synovial fluid and tissue (interstitial) fluids is about 20 to 50% of the plasma concentration.

About 50% of trimethoprim in the plasma is protein-bound. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, with especially high concentrations in the lungs and kidneys. Trimethoprim concentrations exceed those in plasma in bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Levels in the aqueous humour, breast milk, cerebrospinal fluid, middle-ear fluid, synovial fluid and tissue (intestinal) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and fetal tissues reaching concentrations approximating those of maternal serum.

Metabolism

Sulfamethoxazole is conjugated to the inactive N_4-acetyl derivative, which accounts for about 15% of the total amount of sulfamethoxazole in the blood. The extent of metabolism is higher in renal impairment and lower in hepatic impairment. Elimination in the urine is dependent on pH.

Around 10 to 20% of the trimethoprim dose is metabolised in the liver and a small proportion appears in the faeces through the bile.

Elimination

The half-life of sulfamethoxazole is about 9 to 11 hours but it can be longer in renal impairment. About 80 to 100% of a dose is excreted in the urine, with up to about 60% as the acetyl derivative and the remainder as unchanged drug and glucuronide conjugate. Elimination in the urine is dependent on pH.

The half-life of trimethoprim is about 8 to 10 hours in adults (a little longer in children). The larger portion of the drug (40 to 60%) is excreted within 24 hours in the urine, mainly as unchanged drug. Urinary concentrations of trimethoprim vary widely.

5.3 Preclinical safety data

Isoniazid

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

Sulfamethoxazole/trimethoprim

Many *in vitro* and *in vivo* tests have not indicated a potential for chromosomal abnormalities with sulfamethoxazole/trimethoprim but some tests were positive.

Fertility and reproduction studies in rats revealed no adverse effects on fertility or general reproductive performance with oral doses exceeding the recommended human daily dose.

At doses in excess of recommended human dose, sulfamethoxazole and trimethoprim have been reported to cause cleft palate and other fetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by dietary folate. In rabbits, fetal loss occurred at doses of trimethoprim in excess of human therapeutic doses.

No other toxicological findings considered to be of relevance to the doses recommended for patient treatment have been reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Maize starch
Sodium starch glycolate
Povidone
Docusate sodium benzoate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

White 65 cc HDPE bottle with white 45 mm HDPE cap with induction sealing and rayon sanicoil, containing 30 tablets.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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HA639

9. DATE OF FIRST PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT:

May 2017.
Section 6 updated in December 2017

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/

Reference list

General

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Section 4.5

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Section 4.9

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