WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*] https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA762 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains isoniazid 300 mg, pyridoxine hydrochloride 25 mg, sulfamethoxazole 800 mg and trimethoprim 160 mg.
For the list of excipients, see section 6-1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Brown, film-coated, oval-shaped, biconvex, bevel edge, scored tablet, debossed with "S" and "T" on either side of score line on one side and "I" and "M" on either side of score line on the other side.
The tablet can be divided into two equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA762 trade name] is indicated for preventing certain opportunistic infections in people living with HIV. It is for use in adults, adolescents and children weighing over 14 kg to prevent tuberculosis, *Pneumocystis jiroveci* (*P. carinii*) pneumonitis, *Plasmodium falciparum* malaria, toxoplasmosis and bacterial infections sensitive to sulfamethoxazole/trimethoprim.

The decision to use [HA762 trade name] 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 issued by WHO.

Pyridoxine hydrochloride in [HA762 trade name] is intended to prevent isoniazid-induced neuropathy.

4.2 Posology and method of administration

Posology

[HA762 trade name] should be taken daily and the duration of treatment should take into account official guidelines and will depend on recovery of the patient's immunity and the prevalence of infectious disease.

Adults

1 tablet once daily.

Adolescents and children

Weight	Dose
Under 14 kg	[HA762 trade name] not suitable; use alternative product to give suitable doses of the active ingredients
14–25 kg	½ tablet once daily
Over 25 kg	1 tablet once daily

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.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

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

Hepatic impairment

Isoniazid and possibly sulfamethoxazole and trimethoprim can accumulate in patients with hepatic impairment. 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 [HA762 trade name] regularly each day to maximise protection and to reduce the risk of organisms developing resistance to 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.

Method of administration

The patient should take [HA762 trade name] at around the same time each day, preferably on an empty stomach (at least 2 hours after a meal and at least 1 hour before the next meal).

The tablet can be broken into two equal halves using the scoreline, but it should not be crushed or chewed. The tablet should be swallowed with water.

4.3 Contraindications

[HA762 trade name] is contraindicated in patients with:

- hypersensitivity to any of the active ingredients, to sulfonamide medicines or to any of the excipients (see section 6.1).
- acute liver disease including, drug-induced liver disease and marked liver parenchymal damage
- severe renal insufficiency when renal function status cannot be monitored
- 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

[HA762 trade name] must also not be used concomitantly with (see section 4.5):

- amodiaquine
- clozapine
- sulfadoxine/pyrimethamine, alone or in combination with artesunate

Sulfamethoxazole/trimethoprim should not be given to newborn babies in the first 6 weeks because of the predisposition of neonates to hyperbilirubinaemia and the associated risk of kernicterus.

4.4 Special warnings and precautions for use

Active infection

[HA762 trade name] 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, [HA762 trade name] 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). [HA762 trade name] must be stopped if these reactions occur.

Isoniazid-induced pancreatitis can occur. Patients should be advised to report any signs and symptoms of pancreatitis. [HA762 trade name] 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 [HA762 trade name].

Liver damage

Liver function should be assessed before starting treatment with [HA762 trade name] and regularly monitored during treatment because patients with HIV are at high risk of hepatitis with isoniazid. 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.

[HA762 trade name] should be stopped if the patient has symptoms of liver damage.

Most cases of isoniazid-associated hepatitis occur within the first 3 months of therapy, but hepatotoxicity may also develop after a longer duration of treatment. 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 serious blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia) induced by sulfamethoxazole/trimethoprim. [HA762 trade name] must be stopped if serious blood disorders occur.

[HA762 trade name] 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 [HA762 trade name] may induce haemolysis.

Diabetes mellitus

Patients with diabetes should be monitored carefully because isoniazid in [HA762 trade name] 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 [HA762 trade name] should be monitored closely if metabolic acidosis is suspected.

CNS and psychiatric effects

Isoniazid should be use with care in patients with seizure disorders or a history of psychiatric disorders.

Peripheral neuropathy

Patients with peripheral neuropathy or conditions predisposing to neuropathy should be carefully monitored. Although pyridoxine in [HA762 trade name] 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 from 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 *Clostridioides difficile*, which causes potentially serious antibacterial-associated colitis. [HA762 trade name] 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 [HA762 trade name], particularly because of the possibility of impaired kidney and liver function and concomitant use of other medicines.

4.5 Interaction with other medicinal products and other forms of interaction

As [HA762 trade name] contains isoniazid, pyridoxine, sulfamethoxazole and trimethoprim, any interactions of each of these may occur with the combination.

Isoniazid inhibits CYP2C19 and CYP3A4, sulfamethoxazole inhibits CYP2C9, and trimethoprim inhibits CYP2C8 and OCT2 transporter. [HA762 trade name] 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.

In addition to the medicines listed in the table below, some types of medicines that can increase the risk of certain side effects of [HA762 trade name] are:

Myelosuppressive drugs

Concomitant use of sulfamethoxazole/trimethoprim with myelosuppressive drugs may cause blood disorders. Such drugs include amodiaquine, ganciclovir and zidovudine. For this reason, amodiaquine must not be given with [HA762 trade name]; if concomitant use of other myelosuppressive drugs cannot be avoided, the patient's blood counts 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.

The following table includes of medicines which may interact with [HA762 trade name].

Drugs	**Interaction**	**Recommendation concerning co-administration**
Diuretics		
Thiazides diuretics	Concomitant use of sulfamethoxazole/trimethoprim with thiazide diuretics may increase the risk of thrombocytopenia	The risk of thrombocytopenia may be increased especially in the elderly.
Potassium-sparing diuretics (e.g. amiloride, triamterene and spironolactone)	Concomitant use of sulfamethoxazole/trimethoprim with potassium-sparing diuretics may increase the risk of hyperkalaemia	
Anticoagulants		
Coumarins (e.g. warfarin) and indandiones (e.g. phenindione)	Isoniazid may increase the anticoagulant effects; sulfamethoxazole/trimethoprim may also increase the anticoagulant effects of coumarins	Close monitoring of anticoagulant activity may be required and the anticoagulant dose adjusted if necessary
Antiepileptics		
Carbamazepine, ethosuximide, phenytoin and valproate	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
Carbamazepine, phenytoin and primidone	Isoniazid used concomitantly with carbamazepine, phenytoin and primidone may increase the risk of liver damage	
Phenytoin	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) Concomitant use of isoniazid and some benzodiazepines may increase the risk of liver damage	The dose of the benzodiazepine may need to be reduced in case of excessive sedation
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	

Drugs	Interaction	Recommendation concerning co-administration
General anaesthetics	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane when used concomitantly. Concomitant use of isoniazid and general anaesthetics may increase the risk of liver damage.	
Antipsychotics		
Chlorpromazine	Chlorpromazine may reduce the metabolism of isoniazid	Patients should be carefully monitored for isoniazid toxicity
Clozapine	Concomitant use of sulfamethoxazole/trimethoprim with clozapine increases the risk of serious blood disorders	Avoid concomitant use of [HA762 trade name] and clozapine
Haloperidol	Isoniazid may increase plasma levels of haloperidol	Patients should be monitored for excessive effects of haloperidol and 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)	[HA762 trade name] should be co-administered with methotrexate only if the benefits outweigh the risk and under careful monitoring of blood counts
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	Isoniazid dose 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	

Drugs	Interaction	Recommendation concerning co-administration
Anti-infectives		
Amodiaquine	Concomitant use of sulfamethoxazole/trimethoprim and amodiaquine may increase the risk of blood disorders	Concomitant use of [HA762 trade name] and amodiaquine is contraindicated
Sulfadoxine/pyrimethamine	Concomitant use of sulfamethoxazole/trimethoprim and sulfadoxine/pyrimethamine may increase the risk of severe cutaneous reactions	Concomitant use of [HA762 trade name] and sulfadoxine/pyrimethamine is contraindicated
Pyrimethamine	Concomitant use of sulfamethoxazole/trimethoprim and pyrimethamine may increase the risk of blood disorders including pancytopenia and megaloblastic anaemia (additive effect on folate metabolism)	Close monitoring of blood counts is recommended if concomitant administration cannot be avoided
Itraconazole and ketoconazole	Isoniazid may markedly reduce plasma levels of itraconazole and may reduce plasma levels of ketoconazole	Concomitant use of [HA762 trade name] and itraconazole or ketoconazole is not recommended
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

Food and drinks

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.

Concurrent ingestion of isoniazid with foods rich in histamine or tyramine, such as cheese and fish, 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 breastfeeding

Fertility

[HA762 trade name] can cause folate deficiency in spermatogenic cells and may disrupt spermatogenesis in men.

Pregnancy

[HA762 trade name] can be given in pregnancy according to official guidelines including those from the WHO.

Sulfamethoxazole/trimethoprim in [HA762 trade name] may be associated with birth defects, particularly when it is used during the first trimester. For this reason, folate supplementation should be considered if [HA762 trade name] is given during pregnancy. 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

[HA762 trade name] 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 and breast-feeding should be avoided if the newborn infant is at particular risk of hyperbilirubinaemia and kernicterus.

4.7 Effects on ability to drive and use machines

[HA762 trade name] is not expected to reduce the ability to drive and use machines. However, the patient should be sure that the underlying condition or possible rare side effects of [HA762 trade name] 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 because [HA762 trade name] contains 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, pancreatitis
Not known	flatulence, anorexia, dry mouth, abdominal pain, 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 [HA762 trade 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, 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	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

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 *Pneumocystis jiroveci* pneumonitis

Eye disorders

Very rare	uveitis
Not known	optic atrophy or neuritis

Skin and subcutaneous tissue disorders

Common	rash
Rare	toxic epidermal necrolysis
Very rare	photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome
Not known	drug reaction with eosinophilia and systemic symptoms (DRESS), pruritus, urticaria

General disorders

Not known	vasculitis, 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 with folate deficiencies. Fatalities have occurred in at-risk patients and they should be monitored carefully.

Aseptic meningitis

Aseptic meningitis is rapidly reversible on withdrawal of the medicine, but it may recur 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 providers 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), 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 sulphonamides 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 used within a few hours of isoniazid ingestion. Pyridoxine in the product counteracts some of isoniazid's toxic effects. Intravenous diazepam can be used to treat seizures that have not responded 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 and observation of the patient's clinical status. 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) can be used for treating 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 mycobacterial infection.

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-positive 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 in reduced inhibition of 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

Absorption of [HA762 trade name]

The absorption characteristics of [HA762 trade name] have been determined after administration of one tablet in healthy volunteers, in the fasted state, as follows:

Pharmacokinetic variable	**Mean value* (±standard deviation)**		
	Isoniazid	**Sulfamethoxazole**	**Trimethoprim**
Maximum concentration (C_{max})	9466 ± 3231 ng/mL	55.8 ± 6.5 µg/mL	1434 ± 259 ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	33846 ± 14751 ng·h/mL	722 ± 105 µg·h/mL	19901 ± 3898 ng·h/mL
Time to attain maximum concentration (T_{max})	0.67 h	2.00 h	2.00 h

*arithmetic mean

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.

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.

Pyridoxine hydrochloride

Pyridoxine hydrochloride is absorbed from the gastrointestinal tract and is converted to the active forms pyridoxal phosphate and pyridoxamine phosphate. It crosses the placental barrier and appears in breast milk. It is excreted in the urine as 4-pyridoxic 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.

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 (interstitial) 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 N4-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

Core tablet:

Microcrystalline cellulose
Hydroxypropyl cellulose
Sodium starch glycolate
Colloidal silicon dioxide
Stearic acid
Partially pregelatinized maize starch
Docusate sodium
Low-substituted hydroxypropyl cellulose
Magnesium stearate

Film coat:

Hypromellose
Titanium dioxide
Macrogol/PEG
Talc
Iron oxide yellow
Iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30ºC. Store in the original container.

6.5 Nature and contents of container

HDPE Bottle

White, round, HDPE bottle and closed with a white, opaque polypropylene screwcap with liner, without a desiccant. Pack size: 30 tablets.

Blister pack

Cold form Alu-OPA/PVC/Alu blister card. Each blister card contains 10 tablets. Pack size: 1 x 10's tablets.

6.6 Special precautions for disposal and other handling

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

7. SUPPLIER

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9. DATE OF PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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Section 4.4

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Section 4.9

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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines