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 fromstringent regulatory authorities.[*]

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

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

1. NAME OF THE MEDICINAL PRODUCT

[HA735 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg sulfamethoxazole and 80 mg trimethoprim.

Excipients with potential clinical effect

Each tablet also contains 0.3 mg sodium benzoate. For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

White to off-white, round, biconvex, uncoated tablet with break line on one side and plain on the other side.

The tablet can be divided into two equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA735 trade name] is indicated for **preventing***Pneumocystis jirovecii*pneumonia,toxoplasmosis, malaria and some severe bacterial infections in:

- adults (including pregnant women) and children aged over 5 years with severe or advanced HIV disease
- infants and children aged under 5 years with HIV of any severity
- HIV patients in settings where malaria or severe bacterial infections are highly prevalent
- HIV patients who also have active tuberculosis

Sulfamethoxazole/trimethoprim prophylaxis is recommended for infants, children and adolescents with HIV, regardless of clinical and immune conditions. Priority should be given to all children younger than five years old regardless of CD4 cell count or clinical stage and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 cell count ≤350 cells/$mm^{3.}$

[HA735 trade name] is also indicated for **treating** HIV-related opportunistic *Pneumocystis jirovecii* pneumonia and toxoplasmosis.

Regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines, including official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Therapy should be prescribed by a health care provider experienced in the management of HIV infection.

Prophylaxis in people living with HIV

Dosage depends on body weight, as follows:

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

Body Weight	Dose	
	As tablets	**In mg**
6 to less than 14 kg	½ tablet daily*	sulfamethoxazole 200 mg/trimethoprim 40 mg daily
14 to less than 25 kg	1 tablet daily	sulfamethoxazole 400 mg/trimethoprim 80 mg daily
25 kg and over	2 tablets daily†	sulfamethoxazole 800 mg/trimethoprim 160 mg daily
*For children weighing <6 kg who are not able to swallow (half) tablets, availability of other strengths and formulations should be checked. †Other formulations containing higher quantities of sulfamethoxazole and trimethoprim may be available to reduce the number of tablets taken		

Treatment of opportunistic infections in people living with HIV

[HA735 trade name] is not suitable for doses below 200 mg/40 mg. When lower doses are needed or when patients are not able to swallow tablets, availability of other strengths and formulations should be checked.

P. jiroveci pneumonitis

75–100 mg/kg sulfamethoxazole and 15–20 mg/kg trimethoprim per 24 hours given in 3 to 4 doses for 14 to 21 days.

Toxoplasmosis encephalitis

25 mg/kg sulfamethoxazole and 5 mg/kg trimethoprim, two times daily.

Renal impairment

Creatinine clearance (mL/minute)	Recommended dosage
> 30	No dose adjustment required
15 to 30	Half the dose
<15	Not recommended

No data are available relating to dosage in children younger than 12 years with impaired renal function.

Hepatic impairment

No data are available on dosage in patients with impaired hepatic function.

Elderly

See section 4.4. Unless otherwise specified, standard dosage applies.

Missed dose and vomiting after a dose

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [HA735 trade name] and reduce its efficacy.

When advising patients on missed doses, the health care provider should take into account the prescribed dosage interval.

- For doses taken *3 or more times daily*, the patient can omit the missed dose and take the next dose when it is due.

- For doses taken *once or twice daily*, the patient should take the missed dose if it is less than 6 hours from when it was due. If it is more than 6 hours since the dose was due, the patient should omit the missed dose and take the next dose at the usual time.

Patients should be advised not to take a double dose to make up for a missed dose.

If the patient vomits *within 1 hour* of taking a dose, the patient should take an extra dose. If vomiting occurs *more than an hour* after taking the dose, the patient does not need to take an extra dose and can take the next dose as usual when it is due.

Method of administration

[HA735 trade name] should preferably be swallowed whole but may be halved if necessary for dosing. It should not be chewed or crushed.

Taking the tablets with some food or drink may minimise the possibility of gastrointestinal disturbances.

4.3 Contraindications

[HA735 trade name] should not be given to patients with

- a history of hypersensitivity to sulfonamides, trimethoprim, sulfamethoxazole/trimethoprim or any excipients of this medicinal product (see section 6.1)
- marked hepatic damage
- severe renal insufficiency when renal function status cannot be monitored
- a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides
- known or suspected risk of acute porphyria
- documented megaloblastic anaemia due to folate deficiency

Sulfamethoxazole/trimethoprim should not be used concomitantly with:

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

Sulfamethoxazole/trimethoprim should not be given to children within the first 6 weeks of age because of the predisposition of young infants to hyperbilirubinaemia and an associated potential risk of kernicterus.

4.4 Special warnings and precautions for use

Hypersensitivity and other fatal reactions

Fatalities associated with the use of sulfamethoxazole/trimethoprim, although very rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity reactions of the respiratory tract (see section 4.8).

Life-threatening cutaneous reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. The highest risk for SJS or TEN is within the first weeks of treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions.
Sulfamethoxazole/trimethoprim should be discontinued if symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) develop. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. If the patient has developed SJS or TEN with the use of sulfamethoxazole/trimethoprim, sulfamethoxazole/trimethoprim must not be re-started in this patient at any time.

In the event of severe acute hypersensitivity reactions (e.g. anaphylaxis, drug rash with eosinophilia and systemic symptoms (DRESS), or Henoch-Schonlein purpura), sulfamethoxazole/trimethoprim therapy should be discontinued immediately, and appropriate treatment should be urgently initiated. Clinical signs,

such as rash, sore throat, fever, arthralgia, pallor, purpura or jaundice may be early indications of serious reactions.

Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.

Thrombocytopenia

Sulfamethoxazole/trimethoprim-induced thrombocytopenia may be an immune-mediated disorder. Severe, life-threatening or fatal cases of thrombocytopenia have been reported. Thrombocytopenia usually resolves within a week of discontinuing sulfamethoxazole/trimethoprim.

Streptococcal infections and rheumatic fever

Sulfamethoxazole/trimethoprim should not be used in the treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci; these organisms may not be eradicated from the oropharynx and, consequently, sequelae such as rheumatic fever may not be prevented.

Elderly

Particular care is always advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, e.g. impaired kidney and/or liver function and/or concomitant use of other drugs.

Impaired hepatic and/or renal function

Sulfamethoxazole/trimethoprim should be used with caution in patients with impaired hepatic and/or renal function, as the absorption and biotransformation of sulfamethoxazole and trimethoprim may be changed (see section 5.2). In these patients, the dose needs to be decreased or the dose interval needs to be adjusted to prevent the potential accumulation of sulfamethoxazole/trimethoprim (see section 4.2). In patients who receive long-term treatment with sulfamethoxazole/trimethoprim, regular urine analysis and monitoring of renal function tests is recommended, in particular in patients with impaired renal function.

Crystalluria

An adequate urinary output should be maintained at all times. Evidence of crystalluria *in vivo* is rare, although sulfonamide crystals have been noted in cooled urine from treated patients. In patients suffering from malnutrition the risk may be increased.

Hyperkalaemia and hyponatraemia

Close monitoring of serum potassium and sodium is recommended in patients taking high doses of sulfamethoxazole/trimethoprim, in elderly patients, in patients with underlying disorders of potassium metabolism, in patients with renal insufficiency, or if drugs known to induce hyperkalaemia are given concomitantly, as these patients may be more susceptible to hyperkalaemia and hyponatraemia.

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. [HA735 trade name] must be stopped if serious blood disorders occur.

[HA735 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.

Treatment of and prophylaxis for* Pneumocystis jiroveci *pneumonitis in patients with acquired immunodeficiency syndrome (AIDS)

The incidence of side effects in AIDS patients, particularly rash, fever, leukopenia and elevated aminotransferase (transaminase) levels, with sulfamethoxazole/trimethoprim therapy for *P. jiroveci*

pneumonitis has been reported to be increased compared with the incidence normally associated with its use in non-AIDS patients. Adverse effects are generally less severe in patients receiving sulfamethoxazole/ trimethoprim for prophylaxis. A history of mild intolerance to sulfamethoxazole/trimethoprim in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis. However, if a patient develops skin rash or any sign of adverse reaction, therapy with sulfamethoxazole/trimethoprim should be reevaluated.

Co-administration of sulfamethoxazole/trimethoprim and folinic acid should be avoided in *P. jiroveci* pneumonitis treatment.

Failure of prophylaxis

In case of failure of prophylaxis of toxoplasmosis, malaria or bacterial infections with sulfamethoxazole/trimethoprim, patients should be treated with a different drug that is active against the causative agent as such events may reflect a resistance of the micro-organism.

Sulfamethoxazole/trimethoprim prophylaxis may be continued in addition to treatment, depending on the need of prophylaxis for other infections.

Treatment with sulfadoxine-pyrimethamine (alone or with artesunate), and with artesunate-amodiaquine is contraindicated in HIV-infected patients receiving sulfamethoxazole/trimethoprim prophylaxis (see 4.3 and 4.5). This includes the use of sulfadoxine-pyrimethamine in campaigns for intermittent preventive treatment or chemoprevention.

Antibiotic-associated Colitis

Diarrhoea, particularly if severe, persistent or bloody, during or after treatment with [HA735 trade name], may be a symptom of antibiotic-associated colitis, which can be life-threatening. Therefore, if antibiotic-associated colitis is suspected or confirmed, [HA735 trade name] must be stopped immediately, and diarrhoea should be appropriately managed without delay. Products inhibiting peristalsis are contraindicated in this situation.

Metabolic acidosis

Sulfamethoxazole/trimethoprim has been associated with metabolic acidosis when other possible underlying causes have been excluded. Close monitoring is always advisable when metabolic acidosis is suspected.

Haematological effects

Sulfamethoxazole/trimethoprim has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood. However, co-administration with antifolates such as methotrexate can lead to severe myelotoxicity and hence, co-administration should only be considered with close monitoring (see section 4.5). Except under careful supervision sulfamethoxazole/ trimethoprim should not be given to patients with serious haematological disorders (see section 4.8).

Haemolysis

In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients, haemolysis may occur. This reaction is frequently dose-related.

Excipients

Each tablet also contains 0.3 mg sodium benzoate.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use with **clozapine** or **amodiaquine** may increase the risk and/or severity of bone marrow suppression. Concomitant use is contraindicated(see sections 4.3 and 4.4).

Concomitant usewith **sulfadoxine/pyrimethamine** increases the risk of severe cutaneous reactions. Concomitant use is contraindicated (see sections 4.3 and 4.4).

Potential for sulfamethoxazole/trimethoprim to affect other drugs

Trimethoprim is an inhibitor of CYP2C8 as well as OCT2 transporter. Sulfamethoxazole is an inhibitor of CYP2C9. Caution is recommended when sulfamethoxazole/trimethoprim is co-administered with drugs that are substrates of CYP2C8 and 2C9 or OCT2

- **Thiazide diuretics:** The risk of thrombocytopenia may be increased especially in the elderly.
- **Coumarins:** sulfamethoxazole/trimethoprim may increase the anticoagulant effects of coumarins such as warfarin. Close monitoring of anticoagulation effect may be required (CYP2C9 inhibition).
- **Phenytoin:** sulfamethoxazole/trimethoprim may increase the risk of phenytoin toxicity. Closer monitoring of toxicity and of serum phenytoin levels may be required (CYP2C9 inhibition).
- **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 (see section 4.4).
- **Ciclosporin:** Concomitant use of sulfamethoxazole/trimethoprim and ciclosporin may increase the risk of renal impairment and crystalluria. Close monitoring of renal function is recommended.
- **Digoxin:** Concomitant use of sulfamethoxazole/trimethoprim and digoxin may increase the risk of digoxin toxicity. Monitoring of plasma digoxin levels is recommended.
- **Hypoglycaemic drugs:** Concomitant use of sulfamethoxazole/trimethoprim with drugs for the treatment of type 2 diabetes (including sulfonylureas) may increase hypoglycaemic effect. Close monitoring of blood glucose level is recommended.
- **Lamivudine:** Sulfamethoxazole/trimethoprim increases plasma concentrations of lamivudine, but a clinically significant effect is not expected; the patient should be monitored for lamivudine toxicity in case of marked renal impairment or if high doses of sulfamethoxazole/trimethoprim are used (e.g. for *Pneumocystis jiroveci* pneumonitis treatment).

Effects of other medicinal products on [HA735 trade name]

- **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).
- **Myelosuppressive drugs:** Concomitant use of sulfamethoxazole/trimethoprim with myelosuppressive drugs such as zidovudine and ganciclovir may cause blood disorders. If concomitant treatment cannot be avoided, the patient's haematological parameters should be closely monitored.
- **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 (e.g. amiloride, triamterene and spironolactone), ACE inhibitors (e.g. enalapril and quinapril) and angiotensin-II inhibitors (see section 4.4).
- **Dapsone:** Concomitant use of trimethoprim and dapsone may increase the plasma concentration of both drugs. Monitoring for dapsone toxicity is recommended.
- **Contraceptives:** oral contraceptive failures have been reported in women taking antibacterials though not specifically with sulfamethoxazole-trimethoprim. The mechanism of any effect has not been elucidated.

Other drug interactions

When trimethoprim is administered simultaneously with drugs that form cations at physiological pH and are also partly excreted by active renal secretion (e.g. procainamide, amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the drugs.

Interaction with laboratory tests

Trimethoprim may interfere with the assay of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of serum/plasma creatinine of the order of 10%. The creatinine clearance is reduced: the renal tubular secretion of creatinine is decreased from 23% to 9% whilst the glomerular filtration remains unchanged.

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay. No interference occurs if methotrexate is measured by radioimmunoassay.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There are no or limited amount of data from the use of sulfamethoxazole/trimethoprim in pregnant women. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans. Trimethoprim is a folate antagonist and, in animal studies sulfamethoxazole/trimethoprim causes fetal abnormalities (see section 5.3).

Prophylactic treatment with sulfamethoxazole/trimethoprim is recommended in pregnant women living with HIV if they live in settings with high prevalence of malaria and/or severe bacterial infections or if they have severe or advanced HIV disease or CD4 cells counts of 350 cells/mm^3 or less. In other circumstances, use of [HA735 trade name] in pregnancy, particularly in the first trimester, will depend on whether benefits are considered to outweigh the risks. In this case, folate supplementation should be considered.

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significant maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus, when sulfamethoxazole/trimethoprim is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm and those with glucose-6-phosphate dehydrogenase deficiency.

WHO recommends that sulfamethoxazole/trimethoprim prophylaxis in infants exposed to HIV should start at 4 to 6 weeks after birth.

Breastfeeding

Trimethoprim and sulfamethoxazole are excreted in human milk. The risks of administering {DotWPProductName} in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinaemia and kernicterus should be taken into account.

Fertility

Data on the continuous treatment of adult males for one month with a sulfamethoxazole/trimethoprim combination indicated a disruption of spermatogenesis, potentially caused by folate deprivation of spermatogenic cells through the inhibitory action of trimethoprim on dihydrofolate reductase.

Sulfamethoxazole/trimethoprim did not affect the fertility of rats (see section 5.3).

4.7 Effects on ability to drive and use machines

There are no data on the effect of sulfamethoxazole/trimethoprim on the ability to drive or use machines. The clinical status and the adverse events profile of sulfamethoxazole/trimethoprim should be taken into account when considering patients' ability to drive or use machines.

4.8 Undesirable effects

The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria).

Data from large published clinical trials were used to estimate the frequency of very common to rare adverse events. Very rare adverse events were primarily determined from post-marketing experience and therefore refer to reporting rate rather than a "true" frequency. Adverse events may vary in their incidence depending on the indication.

Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Infections and infestations	
common	*Candida* overgrowth
Blood and lymphatic system	
very rare	leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in G-6-PD deficient patients*
unknown	thrombotic thrombocytopenic purpura
Immune system disorders	
very rare	serum sickness, anaphylactic reaction, allergic myocarditis, angioedema, pyrexia, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteriitis nodosa, systemic lupus erythematosus
unknown	idiopathic thrombocytopenic purpura, drug reaction with eosinophilia and systemic symptoms (DRESS)
Metabolism and nutrition disorders	
very common	hyperkalaemia
very rare	hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis, renal tubular acidosis
Psychiatric disorders	
very rare	depression, hallucinations
unknown	apathy, nervousness
Nervous system disorders	
common	headache
very rare	aseptic meningitis*, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, dizziness
Eye disorders	
very rare	uveitis
Respiratory, thoracic and mediastinal disorders	
very rare	cough, dyspnoea, lung infiltration*
Cardiac disorders	
unknown	QT prolongation resulting in ventricular tachycardia and torsade de pointes arrhythmias
Gastrointestinal disorders	
common	nausea, diarrhoea

uncommon	vomiting
very rare	glossitis, stomatitis, *Clostridioides difficile*-associated colitis, pancreatitis
unknown	abdominal pain
Hepatobiliary disorders	
very rare	transaminases increased, blood bilirubin increased, cholestatic jaundice, hepatic necrosis[1]
Skin and subcutaneous tissue disorders	
common	rash
very rare	photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
unknown	pruritus, urticaria, acute febrile neutrophilic dermatosis (Sweet's syndrome)
Musculoskeletal and connective tissue disorders	
very rare	arthralgia, myalgia
Renal and urinary disorders	
very rare	renal impairment (sometimes reported as renal failure), tubulo-interstitial nephritis
unknown	BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria and nephrotoxicity in association with ciclosporin
General disorders	
unknown	weakness, fatigue, insomnia

* see description of selected adverse reactions

[1] Cholestatic jaundice and hepatic necrosis may be fatal.

Description of selected adverse reactions

Haematological effects

The majority of haematological changes are mild and reversible when treatment is stopped. Most of the changes cause no clinical symptoms although they may become severe in isolated cases, especially in the elderly, in those with hepatic or renal dysfunction or in those with folate deficiency. Fatalities have been recorded in at-risk patients and these patients should be observed carefully (see section 4.3).

Aseptic meningitis

Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either sulfamethoxazole/trimethoprim or to trimethoprim alone.

Pulmonary hypersensitivity reactions

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

Effects associated with Pneumocystis jiroveci *pneumonitis (PJP) management.*

Very rare: Severe hypersensitivity reactions, rash, pyrexia, neutropenia, thrombocytopenia, increased hepatic enzymes, hyperkalaemia, hyponatraemia, rhabdomyolysis.

At the high dosages used for PJP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. Severe hypersensitivity reactions have been reported in PJP patients on re-exposure to sulfamethoxazole/trimethoprim, sometimes after a dosage interval of a few days (see section 4.4).

Rhabdomyolysis has been reported in HIV positive patients receiving trimethoprim-sulfamethoxazole for prophylaxis or treatment of PJP.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Symptoms

Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and loss of consciousness. Pyrexia, haematuria and crystalluria may occur. Blood dyscrasias and jaundice are potential late manifestations of overdosage.

Nausea, vomiting, dizziness, headache, mental depression and confusion are likely signs/symptoms of overdosage of trimethoprim. Bone marrow depression has been reported in acute trimethoprim overdosage.

Treatment

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

If significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. In case of seizures, treatment with diazepam or midazolam can be initiated. Methylthioninium chloride (methylene blue) treatment can be used in the symptomatic treatment of methaemoglobinaemia.

If appropriate, activated charcoal can be administered to 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 active sulfamethoxazole are moderately dialysable by haemodialysis, but peritoneal dialysis is not effective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Combinations of sulfonamides and trimethoprim, incl. derivatives

ATC-Code: J01EE01

Mechanism of action:

Sulfamethoxazole inhibits microbial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA). Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, sulfamethoxazole and trimethoprim block two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many microorganisms.

Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Depending on the conditions the effect may be bactericidal. Trimethoprim binds to plasmodial DHFR but less tightly than to the bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme.

Mechanism of resistance

In vitro studies have shown that bacterial resistance develops more slowly with both sulfamethoxazole and trimethoprim in combination than with either sulfamethoxazole or trimethoprim alone.

Resistance to sulfamethoxazole may occur by bacterial mutations causing an increase of the concentration of PABA, whichthereby outcompetes sulfamethoxazole resulting in a reduction of the 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 wildtype enzyme.

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

Antibacterial Spectrum

The prevalence of resistance may vary geographically and with time and local information on resistance is desirable, particularly when treating severe infections. Expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. The table below gives only an approximate guidance on probabilities whether microorganisms will be susceptible to sulfamethoxazole/trimethoprim or not.

Commonly susceptible species

Gram-positive aerobes

Staphylococcus aureus

Staphylococcus saprophyticus
Staphylococcus pyogenes

Gram-negative aerobes

Enterobacter cloacae

Haemophilus influenza

Klebsiella oxytoca

Moraxella catarrhalis
Salmonella spp.

Stenotrophomonas maltophilia

Yersinia spp.

Other organisms

Plasmodium falciparum

Pneumocystis jiroveci Toxoplasma gondii

Species for which acquired resistance may be a problem

Gram-positive aerobes

Enterococcus faecalis

Enterococcus faecium

Nocardia spp.

Staphylococcusepidermidis
Streptococcus pneumoniae

Gram-negative aerobes *Brucella spp.*

Citrobacter spp.

Enterobacter aerogenes

Escherichia coli

Klebsiella pneumoniae

Klebsiella pneumonia

Proteus mirabilis

Proteus vulgaris

Providencia spp.

Serratia marcesans

Inherently resistant organisms

Gram-negative aerobes

Pseudomonas aeruginosa

Shigella spp.

Vibrio cholera

5.2 Pharmacokinetic properties

Absorption of [HA735 trade name]

The absorption characteristics of [HA735 trade name] have been determined after administration of the equivalent to 2 tablets of [HA735 trade name] in healthy volunteers in the fasting state as follows:

	Arithmetic mean (± standard deviation)	
	sulfamethoxazole	**trimethoprim**
Maximum concentration (C_{max})	51.5 ± 6.4 µg/mL	1.7 ± 0.3 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	679 ± 87 µg·hour/mL	23.3 ± 5.9 µg·hour/mL
Time to attain maximum concentration (t_{max})	2.26 ± 0.7 hour	1.6 ± 1.1 hour

Pharmacokinetics of Sulfamethoxazole and Trimethoprim

	Sulfamethoxazole	**Trimethoprim**
General		
Absorption		
Absolute bioavailability	NA	NA
Oral Bioavailability	Near complete oral absorption	Near complete oral absorption
Food effect	No significant effect	No significant effect
Distribution		
Volume of distribution (mean)	NA	NA

Plasma protein binding *in vitro*	66%	50%
Tissue distribution	Concentration of active sulfamethoxazole in amniotic fluid, aqueous humour, bile, CSF, middle ear fluid, sputum, synovial fluid and interstitial fluid is approximately 20 to 50% of plasma concentration.	Tissue levels are generally higher than plasma levels. Concentrations in bile, prostatic fluid, saliva, sputum and vaginal secretions exceed those in plasma. Concentrations in aqueous humour, breast milk, CSF, middle ear fluid, synovial fluid and interstitial fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues to approximately maternal serum concentrations.
Metabolism	Via acetylation, oxidation and glucuronidation	Via oxidation and hydroxylation.
Elimination		
Elimination half-life	9 – 11h	9 – 17h
Mean systemic clearance (Cl/F)		
% of dose excreted in urine	15-30% as intact drug and 55-70% N4-acetylated metabolite (total 85%)	At least 67% as intact drug and at least 10 – 15% as metabolites.
% of dose excreted in faeces	NA	NA
Pharmacokinetic linearity	NA	NA
Drug interactions *(in vitro)*		
Transporters		inhibitor of OCT2
Metabolising enzymes	inhibitor of CYP2C9	inhibitor of CYP2C8

Special populations

Renal impairment:

Sulfamethoxazole: No change in half-life of intact sulfamethoxazole with renal impairment. Increased half-life of acetylated metabolite when creatinine clearance < 25 mL/min.

Trimethoprim: Elimination half-life increased by 1.5 to 3.0-fold when creatinine clearance < 10 mL/min.

Hepatic impairment:

Possible changes in absorption and biotransformation of both components in case of severe hepatic impairment.

Elderly patients:

Sulfamethoxazole: Slight reduction in renal clearance.

Trimethoprim: No change.

Paediatric population:

See special dosage regimens (see section 4.2).

5.3 Preclinical safety data

Genotoxicity
While a range of in vitro and in vivo tests did not indicate a potential risk of chromosomal abnormalities with treatment of sulfamethoxazole/trimethoprim, some tests resulted in positive findings.

Toxicity to reproduction
Fertility and reproduction studies in rats have shown 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 therapeutic dose, sulfamethoxazole and trimethoprim have been reported to cause cleft palate and other foetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses.

General toxicity
No other toxicological findings considered to be of relevance to the dose level recommended for patient treatment have been reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised starch
Docusate sodium (mixed with sodium benzoate)
Sodium starch glycolate
Magnesium stearate
This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

HDPE Bottle

Do not store above 30ºC. Store in a dry place protected from light. Avoid exposure to temperatures above 30ºC.

Blister pack

Do not store above 30ºC. Store in a dry place protected from light. Avoid exposure to temperatures above 30ºC.

Store the tablets in the blisters in the original carton.

6.5 Nature and contents of container

HDPE Bottle

Round HDPE bottle with 1 sachet of 3 g silica gel and a white polypropylene screw cap, with pulp and white printed heat seal liner.
Pack size: 500 tablets.

Blister pack

Clear PVC/PVdC-Aluminium blister. Each blister card contains 7 tablets. Such 10 blister cards are packed in a carton along with a patient information leaflet.
Pack size: 10 × 7 tablets.

Clear PVC/PVdC-Aluminium blister. Each blister card contains 10 tablets. Such 10 blister cards are packed in a carton along with a patient information leaflet.
Pack size: 10 × 10 tablets.

6.6 Special precautions for disposal and other handling

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

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA735

9. DATE OF PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

January 2024

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FDA label, Bactrim, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/017377s074lbl.pdf

UK SmPC, Co-trimoxazole 80/400 mg tablets, available at http://www.medicines.org.uk/emc/medicine/30695

Dutch SmPC, Bactrimel 48/ml, suspensie voor oraal gebruik, available at http://db.cbg-meb.nl/IBteksten/h06214.pdf

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Manyando C, Njunju EM, D'Alessandro U, Van Geertruyden JP. Safety and efficacy of co-trimoxazole for treatment and prevention of Plasmodium falciparum malaria: a systematic review. PLoS ONE 8: e56916, 2013.

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Further references relevant to sections of the SmPC include:

Section 4.5

University of Liverpool, HIV Drug interactions, available at: http://www.hiv-druginteractions.org/

University of Liverpool, HEP Drug interactions, available at: http://www.hep-druginteractions.org/**Section 4.6**

Murdia A et al. Sulpha-trimethoprim combinations and male fertility. Lancet 2:375-6, 1978.

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