

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

[MA113 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pyrimethamine 25 mg and sulfadoxine 500 mg

Excipients with known effect

Each tablet also contains 20 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

White round tablets, debossed with “SP” on both sides and a scoreline on one side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[MA113 trade name] is indicated for intermittent preventive treatment of malaria as part of antenatal care for women in pregnancy in malaria-endemic areas.

[MA113 trade name] is also indicated for perennial malaria chemoprevention of children at high risk of severe malaria in areas of moderate to high perennial malaria transmission, where sulfadoxine-pyrimethamine is effective. Moderate to high perennial malaria transmission settings are defined as areas with *P. falciparum* parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000.

Treatment regimens should take into account the most recent official treatment guidelines (e.g. those of the WHO) and local information on the prevalence of resistance to antimalarial drugs.

4.2 Posology and method of administration

[MA113 trade name] should ideally be administered as directly observed therapy (DOT)

Intermittent preventive treatment of malaria in pregnancy

The recommended dose is 3 tablets, giving the total required dosage of 75 mg/1500 mg pyrimethamine/sulfadoxine.

Doses should be given at each scheduled antenatal care (ANC) visit, from the beginning of the second trimester until delivery, provided that the doses of [MA113 trade name] are given at least one month apart. WHO recommends a schedule of at least four antenatal care visits during pregnancy. The objective is to ensure that at least three doses of [MA113 trade name] are received during pregnancy.

Perennial malaria chemoprevention of children

Treatment is given at intervals of at least one month, in infants and children up to 24 months of age. The number of doses and the interval between them should be determined on the basis of official guidelines, taking into account the local conditions.

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

The correct dosage of [MA113 trade name] depends on the weight of the child.

Children weighing 5 kg or more should be given half a tablet.

For children weighing less than 5 kg, appropriate dose adjustments cannot be made and other formulations should be used.

Method of administration

Tablets for oral administration.

[MA113 trade name] can be given either on an empty stomach or with food.

Missing a dose reduces protection but does not prevent receiving the next dose.

If the child vomits the dose within 30 minutes, they should be allowed to rest for 30 minutes and then be given a second half-tablet. If they vomit a second time, no further dose should be attempted.

4.3 Contraindications

[MA113 trade name] is contraindicated in patients with:

- hypersensitivity to any of the active ingredients, to sulfonamide drugs or to any of the excipients (see section 6.1)
- premature or newborn infants in the first 2 months of life, because of the immaturity of their enzyme systems
- documented megaloblastic anaemia due to folate deficiency.

4.4 Special warnings and precautions for use

If skin eruptions, cytopenia or a bacterial or fungal superinfection occurs, use of [MA113 trade name] should be discontinued. Caution is advised in repeated administration of [MA113 trade name] to patients with blood dyscrasias and those with renal hepatic failure, in whom the drugs accumulate.

Folic acid

A dose of 0.4 mg daily of folic acid may be safely used in conjunction with [MA113 trade name]. Folic acid at a daily dose equal or above 5 mg should not be given together with [MA113 trade name] as this counteracts its efficacy as an antimalarial.

Acute illness

[MA113 trade name] should not be given if the child has an acute illness. If the child has malaria, specific treatment should be given according to recent official guidelines.

Increased adverse effects

To avoid excessive effects, [MA113 trade name] should not be given if the patient:

- has received pyrimethamine/sulfadoxine in the past 30 days
- is HIV-positive and is receiving sulfamethoxazole/trimethoprim prophylaxis

Hypersensitivity reactions

Because of a rare risk of severe hypersensitivity reactions (see section 4.3), treatment with [MA113 trade name] should be stopped if one develops a rash or urticarial reaction.

Excipients

[MA113 trade name] contains a small amount of lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of [MA113 trade name] with trimethoprim, or sulfamethoxazole /trimethoprim, or another sulfonamide can increase haematological side effects and the risk of severe cutaneous reactions. Concomitant use should therefore be avoided.

The risk of hepatic and haematological adverse effects may increase if [MA113 trade name] is given with other drugs with hepatic or haematological toxicity.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Pyrimethamine/sulfadoxine showed reproductive toxicity in animal studies (see section 5.3).

Pyrimethamine/sulfadoxine should not be used during the first trimester of pregnancy unless the benefit is considered to outweigh the risks and alternative drugs are not available.

During 2nd or 3rd trimesters of pregnancy, [MA113 trade name] may be used for intermittent preventive treatment in pregnancy.

Breastfeeding

Pyrimethamine is excreted in human milk. Some sulfonamides are excreted in human milk.

Sulfonamides are avoided in premature infants and in infants with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency. Except for the preceding conditions, sulfonamides are compatible with breastfeeding.

[MA113 trade name] can be used during breastfeeding.

Fertility

No human data on the effect of [MA113 trade name] on fertility are available. Animal data showed that pyrimethamine impaired fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Side effects are not expected to affect attention or reduce co-ordination but undesirable effects such as dizziness may occur, in which case patients should not drive or use machines.

4.8 Undesirable effects

Mild adverse events associated with pyrimethamine/sulfadoxine involve the skin and mucous membranes. Serious cutaneous toxicity (Steven–Johnson syndrome) and hepatotoxicity may occur rarely.

The adverse events listed below are not based on adequately sized studies, but on literature data generally published after approval and for the use of each of these antimalarials in adults. Frequency estimates are highly variable across the studies.

Gastrointestinal reactions

glossitis, stomatitis, nausea, emesis, abdominal pain, diarrhoea, feeling of fullness

Skin and subcutaneous tissue disorders

photosensitivity, urticaria, pruritus, exfoliative dermatitis, slight hair loss, Lyell's syndrome, erythema multiforme, Stevens-Johnson syndrome, generalised skin eruptions, toxic epidermal necrolysis

General disorders

fever, chills, periarteritis nodosa and lupus erythematosus phenomenon

Nervous system disorders

headache, peripheral neuritis, convulsions, ataxia, hallucinations, insomnia, fatigue, muscle weakness, polyneuritis

Psychiatric disorders

depression, nervousness, apathy

Blood and lymphatic disorders

agranulocytosis, aplastic anaemia, megaloblastic anaemia, thrombocytopenia, leucopenia, haemolytic anaemia, purpura, hypoprothrombinaemia, methaemoglobinaemia, and eosinophilia

Cardiac disorders

allergic myocarditis/pericarditis

Ear and labyrinth disorders

tinnitus, vertigo

Endocrine disorders

Sulfadoxine, a sulfonamide, is similar to some diuretics (acetazolamide and the thiazides), and sulfonyleurea hypoglycaemics. Diuresis and hypoglycaemia have occurred rarely in patients receiving sulfonamide.

Eye disorders

periorbital oedema, conjunctival and scleral injection

Hepatobiliary disorders

hepatitis, hepatocellular necrosis, pancreatitis, transient rise of liver enzymes

Immune system disorders

hypersensitivity reactions, serum sickness, anaphylactoid reactions

Musculoskeletal and connective tissue disorders

arthralgia

Renal and urinary disorders

renal failure, interstitial nephritis, blood-urea nitrogen and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria

Respiratory disorders

pulmonary infiltrates resembling eosinophilic or allergic alveolitis

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: headache, anorexia, nausea, vomiting, agitation, convulsions, haematologic changes (megaloblastic anaemia, leucopenia, thrombocytopenia), glossitis, crystalluria.

Treatment: the patient should be urgently transferred to a specialised unit for close monitoring and supportive therapy including, where appropriate, activated charcoal and fluid administration; a parenteral

benzodiazepine, phenytoin or a barbiturate can be given for convulsions. Liver and renal function should be monitored and blood counts checked repeatedly for up to four weeks after the overdose. Should blood dyscrasia occur, folic acid (leucovorin) may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarial

Pyrimethamine combinations. ATC code P01BD51

Pyrimethamine is a diaminopyrimidine. It exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is a slow-acting blood schizontocide and is also possibly active against pre-erythrocytic forms of the malaria parasite and inhibits sporozoite development in the mosquito vector. It has in vitro activity against the four long-established human malaria parasites. There has been rapid emergence of clinical resistance.

Sulfadoxine is a sulfonamide. Sulfonamides are competitive antagonists of p-aminobenzoic acid. They are competitive inhibitors of dihydropteroate synthase, the enzyme in *P. falciparum*, which is responsible for the incorporation of p-aminobenzoic acid in the synthesis of folic acid. Therefore, by acting at a different step in folate synthesis, sulfadoxine increases the effect of pyrimethamine.

P. falciparum can become resistant to the effects of pyrimethamine/sulfadoxine.

Clinical efficacy

Intermittent preventive treatment of malaria in pregnancy

Seven trials enrolling 2190 participants showed that three or more monthly doses of pyrimethamine/sulfadoxime, in comparison with two doses, increased the mean birth weight by about 56 g (95% CI, 29-83), reduced the number of low-birth-weight infants by about 20% (RR 0.80, 95% CI 0.69-0.94) and maternal parasitaemia by about 33% (RR 0.68, 95% CI 0.52-0.89). Six trials based on 1436 participants showed that three or more monthly doses compared to two doses reduced placental parasitaemia by about 50% (RR 0.51, CI 95%, 0.38-0.68)

Perennial malaria chemoprevention of children

A pooled analysis of six randomised placebo controlled studies, conducted in areas of moderate to high transmission of malaria, showed that the use of pyrimethamine/sulfadoxime in intermittent preventive treatment of malaria in infants delivered through EPI provides an overall protection in the first year of life against clinical malaria (30.3%, CI 19.8%-39.4%), anaemia (21.3%, 95% CI 8.3%-32.5%), hospital admissions associated with malaria parasitaemia (38.1%, 95% CI 12.5%-56.2%) and all-cause hospital admissions (22.9%, 95% CI 10%-34%). Pyrimethamine/sulfadoxime in intermittent preventive treatment of malaria in infants offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose.

5.2 Pharmacokinetic properties

Absorption of [MA113 trade name]

The absorption characteristics of [MA113 trade name] have been determined after administration of three (3) tablets in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Mean value (± standard deviation)	
	Pyrimethamine	Sulfadoxine
Maximum concentration (C_{max})	0.55 (0.07) µg/mL	183 (18) µg/mL
Area under the curve (AUC_{0-72h}), a measure of the extent of absorption	29.8(3.4) µg.h/mL	11037(1142) µg.h/mL
Time to attain maximum concentration (t_{max})	5.5 (1.0 – 10.0) h	5.5 (4.0 – 48.0) h

Absorption

After oral administration both sulfadoxine and pyrimethamine are well absorbed (bioavailability of >90%) in healthy adults.

Distribution

The volume of distribution for pyrimethamine and sulfadoxine is 2.3 l/kg and 0.14 l/kg, respectively. Plasma protein binding is about 90% for both pyrimethamine and sulfadoxine. Both cross the placental barrier and pass into breast milk.

Metabolism

Pyrimethamine is transformed to several unidentified metabolites. About 5% of sulfadoxine appears in the plasma as acetylated metabolite, about 2 to 3% as the glucuronide.

Elimination

The elimination half-lives are about 100 hours for pyrimethamine and about 200 hours for sulfadoxine. Both are eliminated mainly through the kidneys.

5.3 Preclinical safety data

General toxicity

Non-clinical data reveal no special hazard for humans not already covered in other sections of SmPC based on conventional studies of safety pharmacology and repeated dose toxicity.

Genotoxicity

Pyrimethamine was not found mutagenic in the Ames test. Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totalling 200–300 mg.

Carcinogenesis

Pyrimethamine was not found carcinogenic in female mice or in male and female rats.

Reproductive toxicity

Sperm motility and count were significantly decreased in pyrimethamine-treated male mice, and their fertility rate fell to zero. These adverse effects were reversible when pyrimethamine was discontinued. Testicular changes have been observed in rats treated with pyrimethamine/sulfadoxine. The pregnancy rate of female rats was not affected following treatment with 10.5 mg/kg daily, but was significantly reduced at doses of 31.5 mg/kg daily or higher. Pyrimethamine/sulfadoxine was teratogenic in rats when given in weekly doses about 12 times the normal human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: lactose monohydrate
hyprolose
sodium starch glycolate
microcrystalline cellulose
sodium lauryl sulfate
magnesium stearate
corn starch

hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store the tablets in blisters in the provided box or carton, or Store in the original container.

6.5 Nature and contents of container

3 tablets are packed in a PVC/Alu blister card.

Pack sizes:

1 blister card per box, 600 boxes per carton.

10 blister cards per box, 100 boxes per carton.

50 blister cards per box, 36 boxes per carton.

100 blister cards per box, 21 boxes per carton.

Tablets are packed in LDPE bag in HDPE bottle with polypropylene cap with induction seal containing 2g silica gel desiccant.

Pack sizes

100 tablets per bottle, 80 bottles per carton

Tablets are packed in HDPE bottle with polypropylene cap with induction seal containing 2g silica gel desiccant.

Pack sizes

1000 tablets per bottle, 20 bottles per carton

Tablets are packed in HDPE bottle with polypropylene cap with induction seal containing 1g silica gel desiccant.

Pack sizes

100 tablets per bottle, 100 bottles per carton

6.6 Special precautions for disposal and other handling

Extemporaneous oral formulation for use in **infants**:

- The tablet should be divided into half along the break line and the half tablet crushed.
- The crushed half tablet can be added to a small amount of semi-solid food and given to the child to consume immediately.
- Alternatively, around 10 mL of clean drinking water should be taken in a small and clean cup or glass, and the crushed half of the tablet added.
- The cup should be gently swirled until the half tablet disperses and the entire mixture is given to the child to drink immediately.
- The container should be rinsed with an additional 5-10 mL of water, and given to the child to drink to ensure the whole dose is taken.

7. SUPPLIER

Guilin Pharmaceutical Co. Ltd.

No. 43 Qilidian Road
Guilin, Guangxi
China, 541004
Tel. No.: +86 773 3675053
Fax No.: +86 773 3675692
Email: ra@guilinpharma.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

MA113

9. DATE OF PREQUALIFICATION

31 October 2018

10. DATE OF REVISION OF THE TEXT

December 2022

References

Consolidated WHO guidelines for malaria, June 2022. Available at: <https://www.who.int/teams/global-malaria-programme/guidelines-for-malaria>

WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) April 2013 (revised January 2014)
<https://www.who.int/malaria/publications/atoz/iptp-sp-updated-policy-brief-24jan2014.pdf>

Intermittent preventive treatment for infants using sulfadoxinepyrimethamine (SP-IPTi) for malaria control in Africa: Implementation Field Guide WHO Global Malaria Programme (GMP) and Department of Immunization, Vaccines & Biologicals (IVB) and UNICEF (2011)
http://apps.who.int/iris/bitstream/handle/10665/70736/WHO_IVB_11.07_eng.pdf;jsessionid=37F97ACFF934C9B17E95AA0BE9ADB3D6?sequence=1

Meremikwu MM, Donegan S, Sinclair D, Esu E, Oranganje C. Intermittent preventive treatment for malaria in children living in areas with seasonal transmission (Review). *The Cochrane Library* 2012, Issue 2
http://www.mmw.org/sites/default/files/uploads/docs/access/SMC_Tool_Kit/publications/Meremikww-ipt-review.pdf

Section 4.6

Transfer of drugs and other chemicals into human milk. American Academy of Pediatrics Committee on Drugs. *Pediatrics* (2001);108(3):776-89.

Section 5.2

De Kock M, Tarning J, Workman L, Nyunt MM, Adam I, Barnes KI, Denti P. Pharmacokinetics of Sulfadoxine and Pyrimethamine for Intermittent Preventive Treatment of Malaria During Pregnancy and After Delivery. *CPT Pharmacometrics Syst Pharmacol* (2017); 6(7): 430–438.

Section 5.3

Kalla NR, Saggar SK, Puri R, Mehta U: Regulation of male fertility by pyrimethamine in adult mice. *Res Exp Med Berl* (1997); 197: 45-52.

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