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

[MA145 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated dispersible tablet contains 25 mg pyrimethamine and 500 mg sulfadoxine.

Excipients with known effect

Each uncoated dispersible tablet contains 51 mg of isomalt.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablets.

White to off-white, circular, flat bevelled edged, uncoated tablets debossed with '525' on one side and break line on the other side.

The tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[MA145 trade name] is indicated for intermittent preventive treatment of malaria as part of antenatal care for women in pregnancy in malaria-endemic areas.

[MA145 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

[MA145 trade name] should ideally be administered as directly observed therapy (DOT).

Intermittent preventive treatment of malaria in pregnancy

The recommended dose is 3 tablets, supplying a total dose of 75 mg/1500 mg pyrimethamine/sulfadoxine.

Doses should be given at least 1 month apart at scheduled antenatal care visits, from the beginning of the second trimester until delivery. The objective is to ensure that at least 3 doses of [MA145 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.

The correct dosage of [MA145 trade name] depends on the weight of the child:

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

Weight	Dose (number of tablets)	Amount of active substances supplied per dose
Under 5 kg	[MA145 trade name] not suitable; an alternative formulation allowing appropriate dose adjustment should be used	Not applicable
5 kg and over	½ tablet	12.5 mg pyrimethamine/250 mg sulfadoxine

Method of administration

Dispersible tablets for oral administration.

[MA145 trade name] can be given either on an empty stomach or with food.

The tablets should be dispersed in drinking water before administration of the dose.

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

Instructions for use

For **adults**, the following procedure should be used.

- Around 30 mL of clean drinking water should be taken in a small and clean cup or glass and the tablets added.
- The container should be gently swirled until tablets disperse, and the entire mixture should be given/taken immediately.
- The container should be rinsed with an additional 10 mL of water, which should be drunk by the patient to ensure the entire dose is taken.

For use in **infants**:

- The tablet should be divided into half along the break line.
- Around 10 mL of clean drinking water should be taken in a small and clean cup or glass, and the half tablet added.
- The cup should be gently swirled until the half tablet disperses and the entire mixture should be 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.

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

4.3 Contraindications

[MA145 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 [MA145 trade name] should be discontinued. Caution is advised in repeated administration of [MA145 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 [MA145 trade name]. Folic acid at a daily dose equal or above 5 mg should not be given together with [MA145 trade name] as this counteracts its efficacy as an antimalarial.

Acute illness

[MA145 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, [MA145 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 [MA145 trade name] should be stopped if one develops a rash or urticarial reaction.

Excipients

[MA145 trade name] contains 51 mg of isomalt per tablet, which may have a mild laxative effect. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 of [MA145 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 [MA145 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 second or third trimesters of pregnancy, [MA145 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.

[MA145 trade name] can be used during breastfeeding.

Fertility

No human data on the effect of [MA145 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

photosensensitivity, 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 sulfonylurea 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, folinic 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

The absorption characteristics of [MA145 trade name] have been determined after administration of single tablets (containing 25 mg pyrimethamine and 500 mg sulfadoxine) in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**	
	Pyrimethamine	**Sulfadoxine**
Maximum concentration (C_{max})	154 ± 21 ng/mL	65.8 ± 6.0 µg/mL
Area under the curve (AUC_{0-72h}), a measure of the extent of absorption	7714 ± 824 ng·hour/mL	3760 ± 300 µg·hour/mL
Time to attain maximum concentration (t_{max})	4.55 ± 2.40 hour	4.64 ± 6.53 hour

* Arithmetic mean

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

Crospovidone
Methacrylic acid-methyl methacrylate copolymer
Polyethylene glycol
Citric acid monohydrate
Orange flavour
Sodium stearyl fumarate
Isomalt
Povidone
Sodium bicarbonate
Sucralose
Silica colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store tablets in blisters in the provided carton in order to protect from light.

6.5 Nature and contents of container

Alu-PVC/PVDC blister card of tablets in a carton.

Pack size: 1, 10, 25, or 50 blister cards per carton, each card with 3 tablets
10 blister cards per carton, each card with 10 tablets.

6.6 Special precautions for disposal and other handling

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

7. SUPPLIER

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North Wing
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Worli, Mumbai 400 018
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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

MA145

9. DATE OF PREQUALIFICATION

12 April 2021

10. DATE OF REVISION OF THE TEXT

December 2022
Section 6 was updated in June 2025

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, Oringanje C. Intermittent preventive treatment for malaria in children living in areas with seasonal transmission (Review). *The Cochrane Library* 2012, Issue 2 http://www.mmv.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.