

## 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.*

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\*[https://extranet.who.int/prequal/sites/default/files/document\\_files/75%20SRA%20clarification\\_Feb2017\\_newtempl.pdf](https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf)

## 1. NAME OF THE MEDICINAL PRODUCT

[MA191 trade name]†

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains 12.5 mg pyrimethamine and 250 mg sulfadoxine.

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Dispersible tablet

White to off-white, round, uncoated tablets. They are flat on the top and bottom with a bevelled edge. The tablets have a break line on one side and are plain on the other side.

The break line can be used to divide [MA191 trade name] into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

[MA191 trade name] is 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 cases per 1000 population.

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

[MA191 trade name] should ideally be administered as directly observed therapy (DOT).

#### *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 [MA191 trade name] depends on the weight of the child:

Weight	Dose (number of tablets)	Amount of active substances supplied per dose
Under 5 kg	½ tablet	6.25 mg pyrimethamine/125 mg sulfadoxine
5 kg or more	1 tablet	12.5 mg pyrimethamine/250 mg sulfadoxine

#### *Method of administration*

Dispersible tablets for oral administration.

[MA191 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.

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

### *Instructions for use*

The following procedure should be used.

- The tablet should be divided into half along the break line if necessary.
- Around 10 mL of clean drinking water should be taken in a small and clean cup or glass, and the appropriate dose added.
- The cup should be gently swirled until the tablet disperses and the entire mixture should be given to the child to drink immediately.
- The cup 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**

[MA191 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
- patients with 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 [MA191 trade name] should be discontinued. Caution is advised in repeated administration of [MA191 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 [MA191 trade name]. Folic acid at a daily dose equal or above 5 mg should not be given together with [MA191 trade name] as this counteracts its efficacy as an antimalarial.

#### *Acute illness*

[MA191 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, [MA191 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 [MA191 trade name] should be stopped if one develops a rash or urticarial reaction.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Concomitant use of [MA191 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 [MA191 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 2<sup>nd</sup> or 3<sup>rd</sup> trimesters of pregnancy, [MA191 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.

[MA191 trade name] can be used during breastfeeding.

##### *Fertility*

No human data on the effect of [MA191 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 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 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

No pharmacokinetic data are available for [MA191 trade name]. A bioequivalence study was conducted with [MA192 trade name] containing 25 mg pyrimethamine and 500 mg sulfadoxine that is essentially the same as [MA191 trade name] in qualitative terms and with respect to the ratio of the active substance and other ingredients.

The absorption characteristics of [MA192 trade name] have been determined after administration of tablets of [MA192 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Mean value ± standard deviation	
	arithmetic mean ± SD	
	Pyrimethamine	Sulfadoxine
Maximum concentration (C <sub>max</sub> )	203 ± 19 ng/mL	85.5 ± 7.6 µg/mL
Area under the curve (AUC <sub>0-72h</sub> ), a measure of the extent of absorption	9605 ± 1269 ng.hour/mL	4794 ± 419 µg.hour/mL
Time to attain maximum concentration (t <sub>max</sub> )	3.04 ± 1.29 hour	3.60 ± 2.02 hour

### *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**

microcrystalline cellulose

pregelatinised starch

crospovidone

colloidal silicon dioxide

povidone

sucralose

magnesium stearate

## **6.2 Incompatibilities**

Not applicable

## **6.3 Shelf life**

24 months

## **6.4 Special precautions for storage**

Do not store above 30°C. Protect from light. Store the tablets in blisters in the provided box or carton.

## **6.5 Nature and contents of container**

Clear colourless plastic (PVC) on aluminium foil blister cards, each containing three (3) tablets. Available in cartons of 10 x 3, 50 x 3, or 100 x 3 tablets.

## **6.6 Special precautions for disposal and other handling**

No special requirements

## **7. SUPPLIER**

Ipca Laboratories Limited  
48, Kandivli Industrial Estate  
Kandivli (W), Mumbai 400 067  
India

## **8. WHO REFERENCE NUMBER (WHO Prequalification Programme)**

MA191

## **9. DATE OF PREQUALIFICATION**

25 April 2024

## **10. DATE OF REVISION OF THE TEXT**

May 2024

### ***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)  
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*Section 4.6*

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*Section 5.2*

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*Section 5.3*

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*Detailed information on this medicine is available on the World Health Organization (WHO) website:*  
<https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products>