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/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[MA208 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 7.5mg primaquine (phosphate)

Excipients with potential clinical effect

Each dispersible tablet contains 18.65mg of lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablets.

[MA208 trade name] is a mottled orange to light orange, round, dispersible tablets. They are biconvex (rounded on top and bottom) with 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 [MA208 trade name] into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[MA208 trade name] is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* and *Plasmodium ovale* malaria.

Primaquine is used in conjunction with an effective blood schizonticide: either artemisinin-based combination therapy (ACT) or chloroquine for *P. vivax* or *P. ovale* malaria.

Testing for glucose-6-phosphate-dehydrogenase (G6PD) deficiency is needed beforehand to guide appropriate treatment.

[MA208 trade name] is also used in combination with an ACT to reduce the transmissibility of *Plasmodium falciparum* infections in low-transmission areas.

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

Posology

The recommended dose of [MA208 trade name] is based on the weight and G6PD status of the patient.

Radical cure of P. vivax or P. ovale malaria

Patients with normal G6PD function (see also section 4.4)

The recommended dose of primaquine is 1 mg/kg body weight, taken once daily for 7 days.
Typical doses of [MA208 trade name] to be taken per day are shown in the table below:

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

Patient bodyweight	Dose	Number of tablets
6 to less than 12 kg	7.5 mg	1
12 to less than 21 kg	15 mg	2
21 to less than 26 kg	22.5 mg	3
26 to less than 36 kg	30 mg	4
36 kg and over	*A formulation containing more primaquine should be used to supply the correct dose*	

Patients with intermediate G6PD deficiency (see also section 4.4)

The recommended dose is 0.5 mg/kg body weight, taken once daily for 14 days.

Typical doses of [MA208 trade name] to be taken per day is shown in the table below:

Patient bodyweight	Dose	Number of tablets
6 to less than 12 kg	3.75 mg	0.5
12 to less than 21 kg	7.5 mg	1
21 to less than 26 kg	11.25 mg	1.5
26 to less than 36 kg	15 mg	2
36 to less than 51 kg	22.5 mg	3
36 kg and over	*A formulation containing more primaquine should be used to supply the correct dose*	

Patients with severe G6PD deficiency (see also section 4.4)

The recommended dose of primaquine is 0.75 mg/kg body weight, taken once every week for 8 weeks.

Typical doses of [MA208 trade name] to be taken per week is shown in the table below:

Patient bodyweight	Dose	Number of tablets
6 to less than 12 kg	7.5 mg	1
12 to less than 21 kg	15 mg	2
21 to less than 36 kg	22.5 mg	3
51 kg and over	*A formulation containing more primaquine should be used to supply the correct dose*	

Reduction of transmission of P. falciparum malaria

In low-transmission areas, a single dose of 0.25 mg/kg bodyweight primaquine should be given with the first dose of artemisinin-based combination therapy (ACT) to patients with *P. falciparum malaria* unless contraindicated (see Section 4.3). G6PD testing is not required.

Patient bodyweight	Single dose
Less than 25 kg	*
25 to less than 50 kg	1 tablet
50 to 100 kg	2 tablets

* For these patients, other formulations containing less primaquine should be used.

Special populations

Children

Population pharmacokinetics analysis performed in a limited paediatric population indicate that in children over 15 kg, no major age or body weight effect was evidenced in primaquine pharmacokinetics parameters when doses were adjusted to body weight.

Hepatic insufficiency

No data are available in patients with hepatic impairment. It is not known whether in patients with hepatic impairment, accumulation of primaquine and its metabolites could occur or if there could be an impact on generation of metabolites contributing to pharmacological activity.

Renal insufficiency

Single dose pharmacokinetics studies performed in patients with stages IV and V chronic kidney disease indicate higher primaquine C_{max} (up to 1.7-fold higher as compared to healthy subjects) but no evidence of major difference in AUC or $t_{1/2}$. It is not known whether after repeated dosing there could be an accumulation of metabolites that are mainly excreted by renal route.

Genetic polymorphism:

- G6PD deficiency: The pharmacokinetic parameters in G6PD-deficient patients were not different from non-deficient patients.
- CYP2D6 polymorphism: Based on experiments in mice, primaquine activity probably depends on the formation of CYP2D6 metabolite(s). CYP2D6 polymorphism may be associated with variability in clinical response to primaquine.

Missed dose

If a dose is missed, it should be taken as soon as possible. However, if it is time for the next dose, the regular dosing schedule should be resumed until the course is completed. A double dose should not be taken.

Method of administration

[MA208 trade name] should be taken after a meal to reduce abdominal pain and cramping associated with ingestion of the medicine.

The tablets should be dispersed in drinking water before administration of the dose. A dose of up to 2 tablets may be dispersed in 5 mL of water, while doses of 3 to 4 tablets should be dispersed in 10 mL of water.

Instructions for use

1. The required amount of drinking water should be placed in a small clean cup and the primaquine tablets added to it.

2. The cup should be gently swirled until the tablets disperse, and the patient should drink all the mixture immediately.

3. The cup should be rinsed with an additional 10 mL of water, which the patient should drink to ensure that the patient takes the full dose.

4. If the dose is not taken within 30 minutes of preparation, the mixture should be thrown away and a new dose prepared.

4.3 Contraindications

Hypersensitivity to primaquine or to any of the excipients listed in section 6.1.

[MA208 trade name] is also contraindicated in the following:

- Pregnant women.
- Women who are breastfeeding infants aged less than 1 month, or breastfeeding infants whose G6PD status is unknown.

- Infants aged less than 1 month.

Co-administration of [MA208 trade name] with certain medicines is not recommended (see section 4.5, under 'Not recommended combinations').

4.4 Special warnings and precautions for use

[MA208 trade name] is not indicated as monotherapy for the treatment of malaria. Patients suffering from an attack of *P. vivax* or *P. ovale* malaria or who have parasitised red blood cells should initially be treated with a blood schizonticide to eliminate the erythrocytic parasites. Primaquine should then be administered to eradicate the exo-erythrocytic parasites.

G6PD deficiency

Primaquine may cause haemolytic anaemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Before starting treatment, G6PD status should be assessed using a semi-quantitative near-patient test where possible. This will enable differentiation of enzyme activity thresholds relevant for selecting the appropriate treatment regimen (see section 4.2).

G6PD activity may be classified as follows:

- **Normal G6PD activity: At least 70%** of normal enzyme activity
  Patients with *normal G6PD activity* are at the lowest risk of haemolysis and may be treated with high-dose (1 mg/kg), short-course regimens.
- **Intermediate G6PD deficiency: 30% to 70%** of normal enzyme activity
  Patients with *intermediate G6PD deficiency* may be at increased risk of haemolysis, although the risk is generally lower than in patients with severe deficiency. This group includes, in particular, **heterozygous females**, in whom G6PD activity may vary and may not be reliably identified by qualitative tests.
- **Severe G6PD deficiency: Less than 30%** of normal enzyme activity
  Patients with *severe G6PD deficiency* are at high risk of haemolysis and if primaquine is given it should only be in a once-weekly regimen; appropriate monitoring and strict medical supervision for haemolysis are recommended.

If G6PD testing is not available, treatment may be considered based on a careful assessment of the benefit–risk balance and should be undertaken with caution.

Patients should be advised to discontinue treatment and seek immediate medical attention if symptoms of haemolysis occur. These may include fatigue, weakness, shortness of breath, dark urine, or jaundice.

Cardiovascular effects

Due to a potential for QT interval prolongation, [MA208 trade name] should be used with caution in:

- patients with heart disease, a history of ventricular arrhythmias, uncorrected hypokalaemia and/or hypomagnesaemia or bradycardia (< 50 bpm)
- patients receiving concomitant treatment with QT interval-prolonging agents (see section 4.5).

Haematological effects

Anaemia, methaemoglobinaemia and leukopenia have been observed following administration of large doses of primaquine (see section 4.9). The recommended dose should not be exceeded. It is advisable to carry out routine blood cell counts and haemoglobin measurements during therapy.

Methaemoglobinaemia:

Primaquine may cause a transient increase in methaemoglobin levels up to 10% in patients without risk factors (see section 4.8). Methaemoglobinaemia may be severe in patients who are deficient in nicotinamide adenine dinucleotide (NADH) methaemoglobin reductase or treated with methaemoglobinaemia-inducing drugs (such as dapsone or sulfonamide, see section 4.5). In these cases, close blood monitoring is required.

All patients should be advised to seek immediate medical attention if signs of methaemoglobinaemia occur (such as bluish lips or nails).

Leukopenia

Primaquine should be used with caution in patients with established granulocytopenia, such as in rheumatoid arthritis and lupus erythematosus, as it may cause leukopenia in these patients. Concomitant administration of myelosuppressants should be avoided (see section 4.5). Primaquine therapy should be discontinued immediately if there is a sudden decrease in leukocyte counts.

CYP2D6 phenotype

Non-clinical data suggest that primaquine activity depends on the formation of CYP2D6 metabolites. CYP2D6 polymorphism may therefore be associated with variability in clinical response to [MA208 trade name].

Limited clinical data report higher treatment failure rates in patients with CYP2D6 poor or intermediate metaboliser status than in patients with normal or extensive metaboliser status.

In case of treatment failure, after checking the patient's compliance with treatment, potential concomitant use of CYP2D6 inhibitors should be checked (see section 4.5). The patient's CYP2D6 status should be assessed if feasible. For poor CYP2D6 metabolisers, alternative treatment should be considered.

Excipients

Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary. The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance 'in other patients'.

Patients who are allergic to cow's milk proteins must not be given this medicine unless strictly necessary.

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

Pharmacodynamic interactions

Combinations with the following medicines are not recommended:

- quinacrine (mepacrine) due to increased toxicity of both quinacrine and primaquine.
- medicines that can cause haemolysis (e.g. sulfonamides, methylene blue, dapsone, cotrimoxazole, quinolones).
- medicines likely to induce bone marrow aplasia in patients at risk of leukopenia (myelosuppressive drugs, antineoplastics, colchicine, penicillamine, gold salts). Primaquine may cause leukopenia in patients with established granulocytopenia. Concomitant administration of bone marrow depressants should be avoided.
- methaemoglobinaemia-inducing drugs (acetylsulfafurazol, benzocaine, dapsone, flutamide, metoclopramide, prilocaine, sodium nitroprusside, sulfadiazine, sulfadoxine, sulfafurazol, sulfaguanidine, sulfamethizol, sulfamethoxazole) due to the risk of additive methaemoglobinizing effects. If the combination cannot be avoided, close blood monitoring for signs and symptoms of methaemoglobinemia is required.

Combinations with the following medicines require precautions:

- drugs that may prolong the QT interval and/or induce torsades de pointes. Primaquine should be used with caution in patients treated with medicinal products known to prolong the QT interval, e.g. class IA and III antiarrhythmics, antipsychotics, certain antidepressants (citalopram, escitalopram), certain anti-emetics (domperidone), methadone, hydroxyzine, and certain anti-infectives (e.g. antibacterials such as certain fluoroquinolones (e.g. moxifloxacin), certain macrolides (e.g. azithromycin), certain azole antifungals (e.g. fluconazole), antiparasitic medicinal products (e.g. pentamidine, halofantrine, chloroquine, lumefantrine) and hydroxychloroquine because of the increased risk of ventricular arrhythmia.

- bradycardic drugs (class IA antiarrhythmics, beta-blockers, some class III antiarrhythmics, some calcium antagonists, digoxin, pilocarpine, anticholinesterases) due to the increased risk of ventricular rhythm disorders, especially torsades de pointes. Clinical and electrocardiographic monitoring during the combination of treatments should be performed.
- hypokalaemic drugs (hypokalaemic diuretics, alone or in combination, stimulant laxatives, glucocorticoids, tetracosactide and amphotericin B (IV route)) due to the increased risk of ventricular rhythm disorders, especially torsades de pointes. Any hypokalaemia should be corrected prior to administration of the product and clinical, electrolyte and electrocardiographic monitoring should be performed.

Pharmacokinetic interactions:

Effect of other agents on primaquine

- Potent CYP2D6 inhibitor drugs (paroxetine, fluoxetine, bupropion, quinidine, terbinafine, or cinacalcet): Caution is advised when used concomitantly with strong CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors), as they may impact the formation of active primaquine metabolites (see sections 4.4 and 5.2).
- Antimalarials: In vivo studies have shown that in the presence of antimalarials (artemether, mefloquine, quinine), the pharmacokinetic profile of primaquine is not altered. Co-administration of chloroquine, pyronaridine/artesunate, DHA/piperaquine affected the pharmacokinetic parameters of primaquine with an increase in AUC values between 15 and 30% and an increase in C_{max} between 30 and 63%.
- MAO-A inhibitors: The impact of MAO-A inhibitors on primaquine has not been evaluated. In patients without impairment of CYP2D6 activity, no clinically significant drug interactions are expected when primaquine is co-administered with MAO-A inhibitors. In patients with impaired CYP2D6 activity or an unknown CYP2D6 phenotype, caution should be exercised and administration of MAO-A inhibitors should be delayed until the end of primaquine therapy.

Effect of primaquine on other agents

- CYP1A2 substrates: In vivo, primaquine has been shown to inhibit the CYP1A2 substrate antipyrine with a greater than 2-fold decrease in antipyrine clearance. Primaquine inhibits CYP1A2, potentially resulting in increased exposure to CYP1A2 substrates such as duloxetine, alosetron, theophylline, clozapine, and tizanidine. Due to limited data, the magnitude of the impact on pharmacokinetic parameters of medicinal products metabolised by CYP1A2 cannot be predicted. Caution is advised (monitoring for adverse reactions) when concomitantly administering CYP1A2 substrates.
- CYP3A4 substrates: In vitro observations suggest that primaquine may inhibit CYP3A4 at the intestinal level but not at the hepatic level. In vivo studies performed after administration of 30 or 45 mg primaquine with different CYP3A4 substrates (mefloquine, piperaquine, levonorgestrel, ethinyl estradiol) did not demonstrate an increase in exposure (AUC) for the different CYP3A4 substrates, with the exception of a 1.32-fold increase in AUC with levonorgestrel, thus indicating that the inhibitory potential of primaquine for CYP3A4 is low. However, for substances with a narrow therapeutic range (e.g. rivaroxaban, cyclosporin, ergot derivatives, tyrosine kinase inhibitors) and that are metabolised by CYP3A4, caution is advised with clinical and possibly biological monitoring during the combination.
- P-gp substrates: In vitro observations suggest that primaquine inhibits P-gp. There are no in vivo data. Caution is therefore advised (monitoring for adverse reactions) when concomitantly administering P-gp substrates with a narrow therapeutic index, such as digoxin, dabigatran, and colchicine.
- Antimalarials: In vivo studies have shown that the pharmacokinetic profile of many antimalarials (artemether, chloroquine, DHA/piperaquine, mefloquine, pyronaridine/artesunate, sulfadoxine/pyrimethamine) is not altered after administration of 30 or 45 mg primaquine.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

The safety of primaquine in human pregnancy has not been established. The use of primaquine is contraindicated during pregnancy due to the potential for G6PD deficiency in the fetus.

Preclinical data show a potential risk of genotoxicity and a potential embryo-fetal developmental toxicity. Although no clinical consequences have been identified, human data are limited.

Patients must be informed of the potential genotoxic risk. Effective contraception is recommended while on treatment and for the following period after the end of treatment:

- in treated women of childbearing potential, until completion of 2 menstrual cycles.
- in treated males whose partner may become pregnant, for 3 months.

Breast-feeding

Small amounts of primaquine are secreted into breast milk. Although the estimated infant exposure is less than 1% of a 0.5 mg/kg daily dose, there are very limited safety data in breastfed infants.

Because of the potential of primaquine or its metabolites to produce serious haematological adverse reactions in breastfed infants, especially those who may be G6PD deficient, primaquine should not be used during breastfeeding unless the breastfed infant has been tested and confirmed not to have G6PD deficiency. In addition, primaquine is contraindicated in women breastfeeding infants aged less than 1 month.

Fertility

There are no data on the effect of primaquine on fertility in humans.

4.7 Effects on ability to drive and use machines

Dizziness may occur during treatment with primaquine. This may impair the patient's ability to concentrate and react while driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

While primaquine is generally well tolerated, it may cause dose-related gastrointestinal discomfort, including abdominal pain, nausea, and vomiting. Administration with food reduces these symptoms.

The most important adverse effect is haemolysis in patients with G6PD deficiency. The degree of haemolysis is dependent on the dose, duration of exposure and extent of G6PD deficiency (see Section 4.4).

Tabulated list of adverse events

Adverse events are listed under system organ class and ranked by headings of frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. 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).

The table in this section is for adult patients only. The safety profile in children over 4 years is similar to adults with the exception of a higher frequency of gastrointestinal disorders.

Blood and lymphatic system	
Very common	Haemolysis in patients with G6PD deficiency
Uncommon	Haemolysis in patients without G6PD deficiency. Methaemoglobinaemia.

Rare	Leukopenia‡
Nervous system disorders	
Uncommon	Dizziness, headache
Cardiac disorders	
Uncommon	QT interval prolongation§
Rare	Arrythmias[2]
*Gastrointestinal disorders***	
Very common	Abdominal pain
Common	Nausea, vomiting, epigastric distress
Skin and subcutaneous tissue disorders	
Uncommon	Pruritis
Rare	Maculopapular rash

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

Abdominal cramps, vomiting, jaundice, burning epigastric distress, CNS disturbances (including headache and insomnia), cardiovascular disturbances (including cardiac arrhythmia and QT interval prolongation), methemoglobinaemia (indicated by cyanosis), moderate leukocytosis or leukopenia, granulocytopenia, and anaemia. Acute haemolysis may occur and will be severe in G6PD deficient patients.

Treatment

After acute intoxication, activated charcoal may be used where practical, to limit absorption in the gut. General supportive measures include airway management and cardiac monitoring.

Symptomatic methaemoglobinaemia in patients with normal G6PD activity may be treated with 1 to 2 mg/kg of methylene blue. It is contraindicated in patients with G6PD deficiency as it requires the enzyme to be effective and it may cause additional haemolysis in these patients.

Primaquine is not significantly removed by haemodialysis.

‡ Leukopenia reported in patients with rheumatoid arthritis or SLE
§ With higher doses
** Incidence is reduced when primaquine is administered with food

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminoquinoline anti-protozoal agent.

ATC code: P01BA03.

Mechanism of action

The precise mechanism of action has not been established. The presumed mechanisms are inhibition of the mitochondrial electron transport system of the parasite and the generation of reactive oxygen species in infected calls. Primaquine may also bind to and alter the properties of protozoal DNA.

Primaquine is active against the dormant liver form (hypnozoite) of *P. vivax* and *P. ovale* and the secondary exoerythrocytic stages (schizonts and schizogonies). In humans, primaquine activity is probably related to hydroxylated metabolites generated intrahepatically by CYP2D6.

Primaquine is also active against the primary exoerythrocytic forms of *P. falciparum* and has a gametocytocidal effect on all plasmodia gametocytes, particularly *P. falciparum* gametocytes.

Clinical studies

Based on many years of clinical experience, reviewed in several meta-analyses for *P. vivax*, primaquine provides efficient radical cure for both *P. vivax* and *P. ovale* infections (cure rate of relapses > 60 to 100%) in patients receiving regimens of 15 mg or 30 mg daily for 14 days after an appropriate schizonticidal treatment. Factors affecting the efficacy are: the total dose over a sufficient treatment duration, the bodyweight of the patient, adherence to therapy and the type of *P. vivax* strain.

Dose optimisation

The recommended doses for radical cure of *P. vivax* and *P. ovale* malaria, presumptive anti-relapse therapy remain unchanged:

- 0.25 mg base/kg per day for 14 days for temperate strain infections
- 0.50 mg base/kg per day for 14 days for tropical, frequently relapsing infections

There seems to be no difference in recurrence of parasitaemia, the safety or the tolerability of a standard dose of 0.5 mg/kg/day for 7 days compared with 0.25 mg/kg/day for 14 days.

The WHO now recommends a single low-dose of 0.25 mg/kg to reduce onward transmission of *P. falciparum* in programmes to eliminate *P. falciparum* malaria and in areas threatened by resistance of *P. falciparum* to artemisinins. The lower dose is safer and considered to be as effective as 0.75 mg/kg body weight in reducing transmissibility based on limited data from assessments of direct transmission blocking in mosquito feeding studies, which is considered therapeutically more relevant than gametocyte clearance.

5.2 Pharmacokinetic properties

Absorption of [MA208 trade name]

The absorption characteristics of [MA208 trade name] have been determined after administration of two tablet of [MA208 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable'	**Mean value* (± standard deviation)**
	Primaquine (phosphate)
Maximum concentration (C_{max})	90 ± 36 ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	768 ± 332 ng.h/mL
Time to attain maximum concentration (t_{max})	1.71 ± 0.64 h

* arithmetic mean

Pharmacokinetics of primaquine

Absorption	
Absorption	t_{max} 1-3 hours
Absolute bioavailability	96%
Oral bioavailability	At least 96%
Food effect	C_{max} ↑ 26%, AUC ↑ 15%
Distribution	
Volume of distribution (mean)	2.9-7.9 L/kg
Plasma protein binding *in vitro*	75% (mainly alpha-1 glycoprotein)
Tissue distribution	Extensive, with high erythrocyte concentrations. Crosses the placenta and passes into breast milk in small amounts.
Elimination	
Mean systemic clearance (Cl/F)	0.31-1.19 L/h/kg
% of dose excreted in urine	< 4% unchanged excreted in urine. 64% of dose recovered over 143 hours
% of dose excreted in faeces	Biliary excretion. Appears in faeces within 24 hours of administration.
Pharmacokinetic linearity	Dose proportional between 15 and 45 mg
Drug interactions *(in vitro)*	
Transporters	Not a substrate of P-gp or BCRP Inhibitor of P-gp
Metabolising enzymes	Primaquine is metabolized by MAO-A into the main inactive metabolite carboxyprimaquine. Hydroxylation by CYP2D6 generates the reactive species responsible for the antimalarial effects and haemolytic toxicity. CYP1A2, 2C19, 3A4 and direct conjugation of primaquine play a smaller role in metabolism.
	Low potential to inhibit any of the major MAO or CYP450 isoforms, except CYP1A2.

PQN: primaquine; BCRP: breast cancer resistance protein; P-gp: permeability glycoprotein

Special populations

Hepatic insufficiency:

No data are available in patients with hepatic impairment. It is not known whether in patients with hepatic impairment accumulation of primaquine and its metabolites could occur or if there could be an impact on generation of metabolites contributing to pharmacological activity.

Renal insufficiency:

Single dose pharmacokinetics studies performed in patients with stages IV and V chronic kidney disease indicate higher primaquine C_{max} (up to 1.7-fold higher as compared to healthy subjects) but no evidence of

major difference in AUC or $t_{1/2}$. It is not known whether after repeated dosing there could be an accumulation of metabolites that are mainly excreted by renal route.

Paediatrics:

Population pharmacokinetics analysis performed in a limited paediatric population indicate that in children > 15 kg, no major age or body weight effect was evidenced in primaquine pharmacokinetics parameters when doses were adjusted to body weight.

Genetic polymorphism:

- G6PD deficiency: The pharmacokinetic parameters in G6PD-deficient patients were not different from non-deficient patients.
- CYP2D6 polymorphism: Based on experiments in mice, primaquine activity probably depends on the formation CYP2D6 metabolite(s). CYP2D6 polymorphism may be associated with variability in clinical response to primaquine.

5.3 Preclinical safety data

Primaquine is a weak genotoxic agent which elicits both gene mutations and chromosomal/DNA breaks. The *in vitro* reverse gene mutation assays using bacteria (Ames test) and the *in vivo* studies using rodents (mouse bone marrow cell sister chromatid exchange, mouse bone marrow cell chromosome abnormality, and rat DNA strand-breaks in multiple organs) gave positive results.

In studies in rats, adverse effects on the fetus (visceral anomaly, skeletal variation, etc.) were observed at dose levels toxic to the dams.

No fertility studies have been conducted with primaquine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Microcrystalline cellulose

Pregelatinized starch

Sodium starch glycolate

Purified talc

Sucralose

Trusil tonovin SPL

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

Do not store above 30°C.

6.5 Nature and contents of container

Aluminium blister

[MA208 trade name] is provided in aluminium foil on aluminium foil blister cards, each containing 7 tablets. Available in cartons of 2×7 or 24×7 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused 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)

MA208

9. DATE OF PREQUALIFICATION

23 September 2026

10. DATE OF REVISION OF THE TEXT

September 2026

References

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WHO policy brief: Testing for G6PD deficiency for safe use of primaquine in radical cure of *P. vivax* and *P. ovale* 2016 (http://apps.who.int/iris/bitstream/handle/10665/250297/WHO-HTM-GMP-2016.9-eng.pdf;jsessionid=514237439B564F5A88C54908FCA01C66?sequence=1)

PRIMAQUINE SANOFI 15 mg, film-coated tablet - Summary of product characteristics (https://rec-bdm.ansm.integra.fr/affichageDoc.php?specid=62907143&typedoc) accessed 21 September 2026

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Treatment of Malaria: CDC Guidelines for Clinicians (United States) Last reviewed May 11, 2020 https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Guidelines.pdf

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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