PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]PRIMAQUINE®

Primaquine phosphate tablets, USP

26.3 mg primaquine phosphate (equivalent to 15 mg primaquine base)

Antimalarial

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RECENT MAJOR LABEL CHANGES

Indications (1) 05/2020
Contraindications (2) 05/2020
Dosage and Administration, Recommended Dose and Dosage Adjustment (3.2) 05/2020
Dosage and Administration, Missed Dose (3.4) 05/2020
Warnings and Precautions (6) 05/2020
Warnings and Precautions, Special Populations (6.1) 05/2020

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PRIMAQUINE (primaquine phosphate) is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* and *Plasmodium ovale* malaria.

Consideration should be given to official guidance on the appropriate use of antimalarial medicinal products.

1.1 Pediatrics

Pediatric patients <u>without</u> G6PD deficiency (≥ 30 kg body weight **and** able to swallow tablets): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of primaquine in pediatric patients **<u>without</u>** G6PD deficiency, weighing **30 kg** or above **and** able to swallow tablets has been established; therefore, Health Canada has authorized an indication for pediatric use (see DOSAGE AND ADMINISTRATION).

Pediatric patients <u>with mild-to-moderate</u> G6PD deficiency (≥ 20 kg body weight **and** able to swallow tablets): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of primaquine in pediatric patients **<u>with mild-to-moderate</u>** G6PD deficiency, weighing **20 kg** or above **and** able to swallow tablets has been established; therefore, Health Canada has authorized an indication for pediatric use (see DOSAGE AND ADMINISTRATION).

1.2 Geriatrics

Geriatrics (> 65 years of age): Efficacy and safety of primaquine have not been assessed in elderly patients with *P. vivax* and *P. ovale* malaria. Due to the greater frequency of decreased renal, hepatic or cardiac function, and of concomitant disease or other drug therapy in the elderly, monitoring of efficacy and adverse reactions is needed (see WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

PRIMAQUINE is contraindicated:

- In patients who are hypersensitive to primaquine or to any ingredient in the formulation or components of the container. For a complete listing of the excipients, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section.
- In acutely ill patients suffering from systemic disease manifested by tendency to granulocytopenia, such as rheumatoid arthritis and lupus erythematosus since primaquine may cause leukopenia in those patients.
- In patients receiving concurrently other potentially hemolytic drugs or depressants of myeloid elements of the bone marrow.
- Quinacrine appears to potentiate the toxicity of antimalarial compounds which are structurally related to primaquine; therefore, the use of quinacrine in patients receiving

primaquine is contraindicated. Similarly, primaquine should not be administered to patients who have received quinacrine recently, as toxicity is increased.
- In patients with severe glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- In pregnant women.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

Primaquine is recommended only for the radical cure of *P. vivax* and *P. ovale* malaria (the prevention of relapse in *P. vivax* and *P. ovale* malaria), or following the termination of chloroquine phosphate suppressive therapy in an area where *P. vivax* or *P. ovale* malaria are endemic.

Patients suffering from an attack of *P. vivax* or *P. ovale* malaria or having parasitized red blood cells should initially receive a course of a blood schizontocide, which quickly destroys the erythrocytic parasites and terminates the paroxysm. Primaquine phosphate should then be administered in order to eradicate the exo-erythrocytic parasites.

When primaquine is used for the prevention of delayed primary attacks and relapse of *P. vivax* or *P. ovale* malaria in individuals who have returned home from areas where these plasmodial species are endemic, primaquine is generally initiated during the last 2 weeks of, or immediately following, therapy with chloroquine or another suitable antimalarial agent.

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.

3.2 Recommended Dose and Dosage Adjustment

Adults

Adult patients without G6PD deficiency:

For patients weighing up to 70 kg:
- For temperate strains: 1 tablet of 15 mg (primaquine base) daily for 14 days.
- For tropical, frequently relapsing strains: 2 tablets of 15 mg (primaquine base), i.e. 30 mg daily for 14 days.

For patients weighing > 70 kg:
- A dose of at least 30 mg daily is to be used, whatever the strain, to reach a total dose of 3.5 to 7 mg/kg (primaquine base) over 14 days (see CLINICAL TRIALS, Clinical Efficacy/Clinical Studies).

Adult patients with mild to moderate G6PD deficiency:

- 0.75 mg/kg of primaquine base once a week for 8 weeks (see WARNINGS AND PRECAUTIONS), not exceeding a 45 mg unit dose.

Children

Pediatric patients without G6PD deficiency:

- The usual dose is 0.25 to 0.5 mg/kg/day for 14 days to reach a total dose of 3.5 to 7 mg/kg (primaquine base) (see CLINICAL TRIALS, Clinical Efficacy/Clinical Studies).
- PRIMAQUINE is not suited for children weighing less than 30 kg or not able to swallow tablets.
- In children weighing 30 to 59 kg, administer 1 tablet daily for 14 days, whatever the strain.
- In children and adolescents of 60 kg and above, use the adult dose.

Pediatric patients with mild to moderate G6PD deficiency:

- 0.75 mg/kg of primaquine base once a week for 8 weeks (see WARNINGS AND PRECAUTIONS), not exceeding a 45 mg unit dose (see table below).
- PRIMAQUINE is not suited for children weighing less than 20 kg or not able to swallow tablets.

Patient bodyweight	Once weekly dose for 8 weeks
20-39 kg	1 tablet
40-59 kg	2 tablets
≥ 60 kg	3 tablets

Elderly patients:

There are no specific studies in the elderly. Due to the greater frequency of decreased renal, hepatic or cardiac function, and of concomitant disease or other drug therapy in the elderly, monitoring of efficacy and adverse reactions is needed (see WARNINGS AND PRECAUTIONS).

Hepatic impairment:

Efficacy and safety of primaquine have not been assessed in patients with hepatic impairment. Primaquine is metabolized in the liver to generate active metabolites, and it is not known if efficacy could be affected in patients with hepatic impairment. If primaquine is administered to such patients, monitoring of efficacy and adverse reactions is needed, in particular in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Renal impairment:

Safety of primaquine after repeated dose has not been assessed in patients with renal impairment. If primaquine is administered to such patients, monitoring for adverse reactions is needed, in particular in patients with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

3.3 Administration

Taking primaquine after a meal may reduce abdominal pain or cramps associated with ingestion of the drug.

3.4 Missed Dose

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

4 OVERDOSAGE

Symptoms

Abdominal cramps, vomiting, jaundice, burning epigastric distress, CNS disturbances (including headache and insomnia), cardiovascular disturbances (including cardiac arrhythmia and QT interval prolongation), methemoglobinemia (indicated by cyanosis), moderate leukocytosis or leukopenia, granulocytopenia, and anemia. Acute hemolysis may occur, with particular severity in G6PD deficient patients.

For management of a suspected drug overdose, contact your regional poison control centre.

Management should include either activated charcoal administration or appropriate attempts to recover primaquine from the stomach by emesis or gastric lavage and provision of respiratory and cardiovascular support.

Sodium lactate i.v. may be used to counter the depressant effects of primaquine on the heart. Electrical pacing of the heart may be needed.

Ammonium chloride in doses up to 12 g daily orally may be given to enhance urinary excretion.

Symptomatic methemoglobinemia should be treated with 1 to 2 mg per kg of methylene blue.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients

Oral	Tablet, 26.3 mg primaquine phosphate (equivalent to 15 mg primaquine base)	Carnauba wax, cellulose (microcrystalline), lactose, magnesium stearate, Opacode Black ink S-1-177003 (contains shellac glaze; propylene glycol; N-butyl alcohol; black iron oxide; ethanol and methanol), Opadry white YS-1-7443 (contains hypromellose; polyethylene glycol 400; titanium dioxide; and polysorbate 80), polyethylene glycol 400, red iron oxide, starch and talc. Gluten and tartrazine-free.

Each pink, film-coated, convex round tablet imprinted in black ink with a stylized W and P97 on one side and plain on the other side contains: primaquine phosphate USP 26.3 mg (equivalent to primaquine base 15 mg).

Available in bottles of 100.

6 WARNINGS AND PRECAUTIONS

General
In all patients, the concurrent administration of hemolytic agents should be avoided (see DRUG INTERACTIONS). Patients should be warned to discontinue the use of PRIMAQUINE promptly if signs suggestive of hemolytic anemia occur (such as darkening of the urine, pale skin, shortness of breath, dizziness and fatigue) and to contact their healthcare professional immediately.

Cardiovascular
QT Interval Prolongation
Due to potential for QT interval prolongation, caution is advised in patients with cardiac disease, a history of ventricular dysrhythmias, uncorrected hypokalemia and/or hypomagnesemia, or bradycardia (<50 bpm), and during concomitant administration with QT interval prolonging agents (see ADVERSE REACTIONS and OVERDOSAGE).

Driving and Operating Machinery
Some adverse reactions (e.g. dizziness) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Hematologic
Anemia, methemoglobinemia and leukopenia have been observed following administration of large doses of primaquine (see OVERDOSAGE); therefore, the recommended dose should not be exceeded. It is also advisable to make routine blood examinations, particularly blood cell counts and hemoglobin determinations, during therapy.

Hemolytic anemia and G6PD deficiency

Due to the risk of hemolytic anemia in G6PD deficient patients, G6PD testing has to be performed before using primaquine. Before initiating treatment, it is advisable to check the patients for clinical signs of severe anemia or test hemoglobin level. In case of severe anemia, the G6PD testing and primaquine treatment should be postponed until recovery of anemia, in order to avoid false diagnosis due to reticulocytosis.

Baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Observe particular caution in individuals with a personal or family history of hemolytic anemia.

In case of mild to moderate G6PD deficiency, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine; if primaquine administration is considered, the dosage regimen should be adapted accordingly (see DOSAGE AND ADMINISTRATION) and close hematological monitoring is required.

Methemoglobinemia:
Primaquine may cause transient increase in methemoglobin levels up to 10% in patients without risk factors (see ADVERSE REACTIONS). Methemoglobinemia may be severe in patients who are deficient in nicotinamide adenine dinucleotide (NADH) methemoglobin reductase or treated with methemoglobinemia-inducing drugs (such as dapsone, or sulfonamide, see DRUG INTERACTIONS). In these cases, close blood monitoring is required.

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

Hepatic/Biliary/Pancreatic
CYP2D6 genotype:
Based on non-clinical data, primaquine activity probably depends on the formation CYP2D6 metabolite(s). Therefore, CYP2D6 polymorphism may be associated with variability in clinical response to primaquine.

Limited clinical data reported more elevated treatment failure rates in patients with CYP2D6 poor or intermediate metabolizer status than in patients with normal/extensive metabolizer status (see ACTION AND CLINICAL PHARMACOLOGY).

In case of treatment failure, after checking patient's compliance to treatment, it may be useful to reconsider potential concomitant use of CYP2D6 inhibitors (see DRUG INTERACTIONS) and to assess the patient's CYP2D6 status if feasible. For poor CYP2D6 metabolizers, alternative treatment should be considered.

Sexual Health

Fertility
There are no data in humans.

6.1 Special Populations

6.1.1 Pregnant Women

The safety of primaquine in human pregnancy has not been established. The use of primaquine is contraindicated during pregnancy (even if a pregnant woman is G6PD normal, the fetus may not be).

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. Patients have to avoid pregnancy and adequate contraception is recommended during treatment and for the following period after end of treatment:

- in treated women of childbearing potential, until completion of 2 ovulatory cycles (i.e. until 2 menses have elapsed),
- in treated males whose partners may become pregnant, for 3 months.

6.1.2 Breast-feeding

After administration of primaquine in women breastfeeding normal G6PD infants aged more than 1 month, low level of primaquine was measured both in milk and in infant plasma (estimated infant absorbed dose 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 hematological adverse reactions in breastfed infants, especially those who may be G6PD deficient, a decision should be made whether to interrupt breastfeeding or to delay maternal PRIMAQUINE treatment until end of breastfeeding.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

Blood and lymphatic system disorders:

- In patients with G6PD deficiency, hemolytic anemia occurs very commonly and may be severe or fatal in patients with severe G6PD deficiency (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).
- In patients without G6PD deficiency, hemoglobin loss and hemolytic anemia were reported with a frequency of < 0.1%.

7.2 Less Common Clinical Trial Adverse Reactions (< 1%)

Blood and lymphatic system disorders:
- Methemoglobinemia (see WARNINGS AND PRECAUTIONS)

Cardiac disorders:
- QT interval prolongation

Gastrointestinal disorders:
- Abdominal pain
- Nausea
- Vomiting
- Epigastric distress

Skin and subcutaneous tissue disorders:
- Pruritus
- Rash maculo-papular

7.3 Clinical Trial Adverse Reactions (Pediatrics)

Pediatric population

The safety profile in children > 4 years old is similar to adults, with the exception of higher frequency of gastro-intestinal disorders.

7.4 Post-Market Adverse Reactions

Blood and lymphatic system disorders:
- Methemoglobinemia levels are usually < 10%, but methemoglobinemia may be severe in NADH methemoglobin reductase deficient individuals or in patients with other risk factors (see WARNINGS AND PRECAUTIONS and OVERDOSAGE).
- Leukopenia was observed in patients with rheumatoid arthritis or lupus erythematosus (see CONTRAINDICATIONS).

Cardiac disorders:
- Cardiac arrhythmia and QT interval prolongation, occur mainly with higher doses (see WARNINGS AND PRECAUTIONS and OVERDOSAGE).

Gastrointestinal disorders:
- Symptoms often are alleviated by taking the drug at mealtime (see DOSAGE AND ADMINISTRATION).

Nervous system disorders:
- Dizziness

8 DRUG INTERACTIONS

8.1 Drug-Drug Interactions

Pharmacodynamics interactions

Concurrent use of quinacrine (mepacrine) and primaquine is contraindicated as increased toxicity was seen when quinacrine was used with pamaquine, another 8-aminoquinoline (see CONTRAINDICATIONS).

The concurrent administration of hemolytic agents or methemoglobinemia-inducing drugs should be avoided (see WARNINGS AND PRECAUTIONS). If the association cannot be avoided, close blood monitoring is required.

Caution is advised if primaquine is used concomitantly with other drugs that prolong the QT interval such as class IA and III antiarrhythmics, some tricyclic antidepressants, some antipsychotics, some anti-infectives, some antimalarials especially halofantrine, some antiparasitics (pentamidine) (see WARNINGS AND PRECAUTIONS).

Pharmacokinetics interactions

Effect of other agents on primaquine:

Caution is advised in case of concomitant use with potent CYP2D6 inhibitors (such as SSRIs) as they might impact the formation of active metabolites of primaquine (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Primaquine exposure was slightly increased following co-administration with mild to moderate CYP2D6 inhibitors (such as chloroquine or pyronaridine artesunate) or with mild to moderate CYP3A inhibitors (such as dihydroartemisinin-piperaquine or grapefruit juice), with no evidence of clinical significance.

Primaquine pharmacokinetics were not significantly affected in the presence of mefloquine, artemether or quinine.

Effect of primaquine on other drugs:

Primaquine inhibits CYP1A2 thus potentially leading to increased exposure of CYP1A2 substrates, such as duloxetine, alosetron, theophylline and tizanidine. Since the data are limited, no predictions can be made regarding the extent of the impact on pharmacokinetics parameters of drugs metabolized by CYP1A2. Caution is advised (i.e. monitoring for adverse reactions) when CYP1A2 substrates are concomitantly administered.

The effect of primaquine on the pharmacokinetics of permeability glycoprotein (P-gp) substrates *in vivo* is unknown. However, *in vitro* observations suggest that primaquine inhibits P-gp. Therefore, there is a potential for increased concentrations of P-gp substrates. Caution is advised

(i.e. monitoring for adverse reactions) when P-gp substrates with narrow therapeutic index such as digoxin and dabigatran are concomitantly administered.

Coadministration of primaquine with antimalarials (chloroquine, mefloquine, artemether or dihydroartemisinin-piperaquine and pyronaridine-artesunate), ethinyl-estradiol/levonorgestrel or paracetamol has no relevant impact on their pharmacokinetics.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Primaquine is an 8-aminoquinoline anti-protozoal agent.

The mechanism of action has not been fully established. The major assumptions have been an inhibition of mitochondrial system of dormant parasites, and an oxidative stress generated through reactive metabolites in infected cells.

9.2 Pharmacodynamics

Primaquine was found to be active against the dormant liver form of *P. vivax* and *P. ovale*, namely the hypnozoites, as well as the primary and secondary exoerythrocytic stages of the parasites, namely the schizonts and schizogonies, respectively. In humans, primaquine activity is probably related to hydroxylated metabolites generated intrahepatically by CYP2D6, as demonstrated in mice models infected by *P. berghei*.

In addition, primaquine is active against the primary exoerythrocytic forms of *P. falciparum* and has gametocytocidal effect on all plasmodia gametocytes, in particular against *P. falciparum* gametocytes.

Relapse and resistance
Sufficiently long duration of treatment is needed to suppress *P. vivax* hypnozoites from liver, as primaquine is rapidly eliminated from the blood.

The origin of *P. vivax* relapses after primaquine treatment appears multifactorial, such as the origin of *P. vivax* strain, the discrimination between recrudescence, reinfection and relapse, the adherence to primaquine treatment and the CYP2D6 phenotype. No genetic marker of resistance has been highlighted, giving little support to an actual primaquine resistance.

The prevalence of frequent relapsing *P. vivax* strains may vary geographically and over time and local recommendations on treatments should be considered. As necessary, expert advice should be sought.

9.3 Pharmacokinetics

Absorption:
After oral dosing, primaquine is rapidly absorbed (1-3 hour t_{max}), then plasma concentration decreases with a monophasic profile. The absolute bioavailability is high (> 70%). C_{max} is about

65 ng/ml for a 15 mg single dose, 122 ng/ml for a 30 mg single dose and 174 ng/mL for a 45 mg single dose.

The effect of food on primaquine pharmacokinetics is limited, with a slight increase in mean C_{max} (not exceeding 26%) and less than a 15% increase in AUC, as compared to fasting conditions in healthy adults with a 30 mg dose.

Distribution:
Primaquine is bound to plasma proteins (mainly to alpha-1 glycoprotein). The volume of distribution is high (approximately 243 L).

After administration of primaquine in lactating women (N = 21) feeding babies > 1 month of age, low level of primaquine and carboxyprimaquine were measured both in milk and in infant plasma. As a mean, 3 mcg/kg/day of primaquine are ingested by the infant i.e. 0.6 % of the 0.5 mg/kg daily dose over 14 days.

Metabolism:
Primaquine is highly metabolized; its main circulating metabolite is carboxyprimaquine that is not expected to be active. After single dose, carboxyprimaquine exposure in plasma is approximately 30-fold higher as compared to primaquine.

In vitro, primaquine is metabolized by several enzymes: CYP1A2, 2C19, 2D6, 3A4, and Monoamine Oxidase A (MAO-A). Three major metabolism pathways have been identified:

- Oxidative deamination of the terminal amine involved in the formation of carboxyprimaquine through MAO-A. Carboxyprimaquine is further metabolized mainly into a glucuronide conjugate and into quinone imine carboxyprimaquine. *In vivo* activity and toxicity of quinone imine carboxyprimaquine is not yet fully known. Involvement of CYP2D6 in the formation of quinone imine carboxyprimaquine cannot be excluded.
- The hydroxylation of the quinoline ring leads to the formation of hydroxylated metabolites with major involvement of CYP2D6. The CYP2D6 hydroxylated metabolites are believed to play a role in efficacy and primaquine-induced hemolytic activity (see WARNINGS AND PRECAUTIONS, and ACTION AND CLINICAL PHARMACOLOGY).
- Direct conjugation of primaquine, leading to formation of glucuronide conjugates.

Metabolites other than carboxyprimaquine were not monitored in pharmacokinetic studies.

Drug interactions studies

Effect of other agents on primaquine:
In vitro, primaquine is not considered as a P-gp substrate nor as a BCRP substrate.

Effect of primaquine on other drugs:
In vitro, primaquine has no or low potential to inhibit any of the major human MAO or CYP450 isoforms (2A6, 2C8, 2C9, 2C19, 2D6, 3A4) involved in drug biotransformation except CYP1A2.

In vitro, primaquine has potential to inhibit P-gp. There are no *in vivo* data.

Elimination:
Primaquine is mainly metabolized and minimally excreted unchanged in urine (less than 4%).

The main circulating metabolite, carboxyprimaquine is subjected to further metabolism and not eliminated through urine. After administration of [^{14}C]-primaquine by oral route, 64% of the dose was recovered in urine over 143 hours (no data in feces), thus suggesting that urine is the main excretion pathway for other primaquine metabolites.

The terminal half-life is around 6 hours for primaquine and 22 hours for carboxyprimaquine.

No accumulation of primaquine is observed after repeated daily dosing, while a 1.7-fold higher C_{max} and AUC_{0-24} are observed for carboxyprimaquine after 14 days of treatment as compared to single dose.

Linearity/Non-Linearity

The pharmacokinetics of primaquine and carboxyprimaquine are linear between 15 and 45 mg.

Special Populations and Conditions

Pediatrics:
Population pharmacokinetics analysis performed in a limited pediatric 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.

Geriatrics:
There are no pharmacokinetic studies in elderly.

Sex:
No gender effect has been evidenced.

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 (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics and Pharmacokinetics).

Ethnic origin:
No ethnicity effect has been evidenced.

Hepatic Insufficiency:
No data are available in patients with hepatic impairment. It is not known whether in patient 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.

10 STORAGE, STABILITY AND DISPOSAL

Store between 15-30°C.

Keep out of reach and sight of children.

11 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

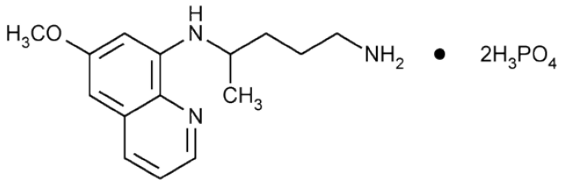
Proper name: Primaquine phosphate

Chemical name: (RS)-8-(4-Amino-1-methylbutylamino)-6-methoxyquinoline diphosphate

Molecular formula: $C_{15}H_{21}N_3O \cdot 2H_3PO_4$

Molecular mass: 455.34

Structural formula:



Physicochemical properties: Primaquine phosphate is an orange-red crystalline solid. According to the pharmacopoeial standards, it is described as “soluble” in water. Primaquine is a dibasic compound, having pKa values of 3.2 and 10.4. Primaquine phosphate possesses a chiral carbon in the diamine side chain and hence shows stereoisomerism. It exists as both R(+) and S(–) enantiomers, but only preparations containing the racemic mixture are commercially available. No polymorphism has been reported for Primaquine phosphate.

13 CLINICAL TRIALS

Clinical Efficacy/Clinical Studies

Based on extensive 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 to 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 patient, adherence to therapy and the type of *P. vivax* strain. A minimal total dose of 3.5 mg/kg bodyweight, i.e. 0.25 mg/kg/day for 14 days of treatment is needed for temperate strains. This corresponds to 15 mg of primaquine daily for 14 days for patients with average bodyweight of 60 kg.

For tropical, frequent-relapsing *P. vivax* strains prevalent in East Asia and Oceania: a minimal total dose of 7 mg/kg bodyweight, i.e. 0.5 mg/kg/day for 14 days of treatment is needed. This corresponds to 30 mg of primaquine daily for 14 days for patients with average bodyweight of 60 kg. Patients with a body weight above 70 kg may be at higher risk of therapy failure if treated with low doses; a limited number of published studies have used higher primaquine daily dosages (30 or 45 mg daily) in these patients to reach the recommended primaquine total doses.

Data in children
In pediatric randomized controlled efficacy studies with a follow up of at least 8 weeks, on over 600 patients, most children were aged > 5 years and most (> 80%) received the daily high dose of 0.50 mg/kg in various treatment regimens. In the patients receiving the 0.5 mg/kg dose for 14 days (about 140 patients), efficacy was similar to that observed in adult patients.

G6PD deficient patients
The total dose of primaquine prevails over its rhythm of administration ("total dose" effect), therefore a weekly administration (i.e. a 0.75 mg/kg weekly regimen for 8 weeks) allows to mitigate the hemolysis risk in mild to moderate/intermediate G6PD deficient patients, while maintaining primaquine efficacy.

Non-Clinical Safety Data

Repeat Dose Toxicity

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels close to the clinical exposure levels (estimated at 9 fold the human 30 mg dose exposure in cynomolgus monkeys and at 1.9 fold the human exposure in rats) and with possible relevance to clinical use were as follows: In 28 days sub-chronic toxicity studies, inflammatory and degenerative changes in the liver and kidney, elevated levels of AST and ALT (less than 10-fold), alkaline phosphatase, creatine phosphokinase and lactate dehydrogenase and lower levels fasting blood glucose levels were reported. Histopathologic findings consisting of inflammatory and degenerative changes of the striated muscle, involving the myocardium, diaphragm, tongue and skeletal muscle occurred in rats. Thymus involution, edema and gliosis in the cerebral cortex also occurred in monkeys.

In addition, mild reduction in platelets numbers was observed in rats at exposure lower than human exposure.

Genotoxicity

Primaquine is reported in the literature to be a weak genotoxic agent which elicits both gene mutations and chromosomal/DNA breaks. The publications reported positive results in the *in vitro* reverse gene mutation assays using bacteria (Ames test) and in 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). The genotoxicity data obtained *in vitro* or in rodent models are suggestive of a potential human risk.

Carcinogenicity

No carcinogenicity studies have been conducted with primaquine.

Reproductive and Developmental Toxicity

Literature data on reproductive toxicology identified potential embryo-fetal development toxicity. In studies in rats, adverse effects on fetus (visceral anomaly, skeletal variation, etc.) were observed at dose levels toxic to the dams.

No fertility studies have been conducted with primaquine; nevertheless no effects on gonads were observed in the repeated dose studies.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrPRIMAQUINE®

Primaquine phosphate tablets USP

Read this carefully before you start taking **PRIMAQUINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PRIMAQUINE**.

What is PRIMAQUINE used for?
PRIMAQUINE is used to:
- treat certain forms of malaria, and
- help prevent it from coming back.

How does PRIMAQUINE work?
PRIMAQUINE is a type of drug called an antimalarial.
- It is used to treat malaria by killing the parasite in the liver that causes malaria.
- This stops the infection from continuing.

What are the ingredients in PRIMAQUINE?
Medicinal ingredients: primaquine phosphate

Non-medicinal ingredients: carnauba wax, cellulose (microcrystalline), lactose, magnesium stearate, Opacode Black ink S-1-177003 (contains shellac glaze; propylene glycol; N-butyl alcohol; black iron oxide; ethanol and methanol), Opadry white YS-1-7443 (contains hypromellose; polyethylene glycol 400; titanium dioxide; and polysorbate 80), polyethylene glycol 400, red iron oxide, starch and talc. *Gluten and tartrazine-free*.

PRIMAQUINE comes in the following dosage forms:
Tablets: 26.3 mg primaquine phosphate (equivalent to 15 mg primaquine base)

Do not use PRIMAQUINE if:
- You are allergic to:
  - primaquine phosphate, or
  - any of the ingredients in the product (see **What are the ingredients in PRIMAQUINE**).
- You have a disease where you lack white blood cells. Examples include rheumatoid arthritis or lupus erythematosus. You should not take PRIMAQUINE if you are very sick with a systemic disease.
- You are taking or have recently taken quinacrine. Quinacrine is another medicine used to treat malaria.
- You are taking medicines that can:

  - damage your blood cells, or
  - impair the formation of new blood cells.
- You have a disease called severe G6PD (glucose-6-phosphate dehydrogenase) deficiency. This is a hereditary red blood cell disease, also known as favism.
- You are pregnant, could be pregnant, or are planning to become pregnant. You must NOT become pregnant while taking PRIMAQUINE or for **2 menstrual cycles** after stopping.
  - You must use reliable birth control to make sure you don't get pregnant while you are taking PRIMAQUINE and for 2 menstrual cycles after stopping.
- You are male and planning to father a child. You must NOT father a child while taking PRIMAQUINE or for **3 months** after stopping.
  - You must use reliable birth control to make sure you don't father a child while you are taking PRIMAQUINE and for 3 months after stopping.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PRIMAQUINE. Talk about any health conditions or problems you may have, including if you:

- Have, or have a family history of, G6PD deficiency (also known as favism). PRIMAQUINE must not be used if you have severe G6PD deficiency.
- Have a rare blood disease called nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficiency.
- Have anemia. This is a lower than normal level of red blood cells.
- Have hemolytic anemia. This is a condition where your red blood cells are destroyed before their normal lifespan is over.
- Have a liver or kidney disease.
- Are above 65 years old.
- Are breastfeeding or planning to breastfeed. Breastfeeding should be stopped while you are taking PRIMAQUINE, or treatment with PRIMAQUINE should be delayed until the end of breastfeeding. You should NOT breastfeed while taking PRIMAQUINE.
- Have or have had:
  - heart disease
  - an irregular heartbeat
  - low levels of magnesium or potassium in your blood
  - a resting heart rate below 50 beats per minutes

Other warnings you should know about:

Before your start taking PRIMAQUINE, your healthcare professional will do a blood test to see if you have G6PD deficiency. This is because PRIMAQUINE can cause the destruction of red blood cells (hemolysis) in people with G6PD deficiency. Based on the results of this test, your healthcare professional may need to change your treatment.

Before and during your treatment, your healthcare professional may ask for blood tests to make sure there is no trouble with your red blood cells.

Stop taking PRIMAQUINE right away and contact your healthcare professional if you have: darkening of the urine, pale skin, dizziness, confusion, fatigue, light-headedness, shortness of breath. These are signs of hemolytic anemia.

Contact your healthcare professional right away if you have bluish lips or nails. These are signs of damage to your red blood cells (methemoglobinemia).

Driving or Using Machines: PRIMAQUINE may cause dizziness. Do not drive or operate machinery until you know how PRIMAQUINE affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PRIMAQUINE:

- quinacrine. PRIMAQUINE must not be used together with quinacrine.
- medicines that can destroy or damage red blood cells or impair formation of red or white blood cells such as: some anti-infectives (sulfamides, dapsone, cotrimoxazole, quinolones), medicines used to treat cancer, colchicine, methylene blue, penicillamine, gold salts. PRIMAQUINE should not be used together with these medicines.
- medicines known to affect the way your heart beats:
  - this includes medicines used for abnormal heart rhythm:
    - antiarrhythmics such as:
      - quinidine
      - hydroquinidine
      - disopyramide
      - sotalol
      - dofetilide
      - ibutilide
      - amiodarone
  - medicines used to treat depression:
    - tricyclic antidepressants such as:
      - amitriptyline
      - imipramine
  - medicines used to treat mental health problems: antipsychotics
  - medicines used to treat bacterial infections:
    - macrolide antibiotics such as:
      - erythromycin
    - fluoroquinolone antibiotics such as:
      - moxifloxacin
  - medicines used to treat malaria (in particular halofantrine),
  - medicines used to treat other infections: pentamidine.
- medicines used to treat depression, known as selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine or paroxetine.
- digoxin (for heart disease), dabigatran (to prevent blood clots), theophylline (for respiratory disorders), alosetron (for vomiting) and tizanidine (for nerve disorders).

How to take PRIMAQUINE:
Taking PRIMAQUINE after a meal may help to decrease stomach pain or cramps.

Usual dose:
Take PRIMAQUINE exactly as prescribed by your healthcare professional. You should check with your healthcare professional if you are not sure. To make sure your treatment works, you should take your medicine for as long as your healthcare professional tells you to.

Overdose:

If you think you have taken too much PRIMAQUINE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Symptoms that you have taken too much PRIMAQUINE include: stomach cramps, vomiting, yellowing of the skin and the whites of the eyes, heartburn, heart problems, including problems with your heartbeat rhythm, bluish skin discoloration, fatigue, difficulty breathing, shortness of breath, confusion, light-headedness, dizziness, difficulty sleeping, pale skin.

Missed Dose:
If you miss a dose of PRIMAQUINE, take it as soon as possible. However, if it is time for your next dose, do not take a double dose. Just carry on with your regular schedule, until you are finished taking all your pills.

What are possible side effects from using PRIMAQUINE?
These are not all the possible side effects you may feel when taking PRIMAQUINE. If you experience any side effects not listed here, contact your healthcare professional. Please also see **Other warnings you should know about** section**.**

Side effects may include: nausea, vomiting, itching, stomach cramps, anemia (low red blood cells), heartburn, rash, dizziness, low white blood cells.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Hemolytic anemia (low red blood cells due to their destruction): darkening of the urine, pale skin, shortness of breath, dizziness and fatigue			x
Methemoglobinemia (damage of red blood cells): bluish lips or nails		x	
Abnormal heartbeat rhythm: irregular heartbeat		x	

If you have a troublesome symptom or side effect that is not listed here, or one that becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 15-30°C.

Keep out of reach and sight of children.

If you want more information about PRIMAQUINE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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