PRESCRIBING INFORMATION WITH 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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THERAPEUTIC CLASSIFICATION

Antimalarial

1 PHARMACOLOGY

Primaquine is an 8-aminoquinoline anti-protozoal agent which is highly active against exo-erythrocytic stages of *Plasmodium vivax*, *Plasmodium ovale* and against the primary exo-erythrocytic stages of *Plasmodium falciparum*.

Primaquine is also highly active against gametocytes of *Plasmodia*, especially *Plasmodium falciparum*.

Primaquine is readily absorbed from the gastro-intestinal tract and extensively distributed into body tissues.

Peak plasma concentration occurs about 1 to 3 hours after a dose is taken and then rapidly diminishes with a reported elimination half-life of 3 to 6 hours.

Primaquine is rapidly metabolized in the liver, its principal metabolite being carboxyprimaquine. Little unchanged drug is excreted in the urine.

2 INDICATIONS

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

3 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 AVAILABILITY section.
- In acutely ill patients suffering from systemic disease manifested by tendency to granulocytopenia, such as rheumatoid arthritis and lupus erythematosus.
- 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

4 WARNINGS

General
Discontinue the use of PRIMAQUINE promptly if signs suggestive of hemolytic anemia occur (such as darkening of the urine or a sudden decrease in hemoglobin concentration or erythrocyte count), or if there is a sudden decrease in leukocyte count.

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).

Use in special groups
Observe particular caution in individuals with a personal or family history of favism, hemolytic anemia, or nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficiency.

Hemolytic anemia and G6PD deficiency:
Due to the risk of hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD) deficient patients, G6PD testing has to be performed before using primaquine. In case of severe anemia, the G6PD testing 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. Adequate medical support and follow-up to manage haemolytic risk should be available.

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 close hematological monitoring is required.

Pregnancy
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 during treatment and for the following period after end of treatment:

- in treated women of childbearing potential, until completion of on-going ovulatory cycle (i.e. up to next menses),
- in treated males whose partners may become pregnant, for 3 months.

Lactation
It is not known whether primaquine is excreted in breast milk.

Because of the potential of primaquine to produce serious adverse reactions in nursing infants, a decision should be made whether to interrupt breast-feeding or to delay the PRIMAQUINE treatment until end of breastfeeding.

Drug Interactions
Caution is advised if primaquine is used concomitantly with other drugs that prolong the QT interval.

5 PRECAUTIONS

Anemia, methemoglobinemia and leukopenia have been observed following administration of large doses of primaquine; therefore, the adult dosage of 1 tablet daily for 14 days should not be exceeded. It is also advisable to make routine blood examinations, particularly blood cell counts and hemoglobin determinations, during therapy.

Due to potential for QT 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 WARNINGS, ADVERSE REACTIONS, OVERDOSE).

6 ADVERSE REACTIONS

Cardio-vascular: Cardiac arrhythmia and QT prolongation, mainly with high dose (see also OVERDOSE).

Gastrointestinal: Nausea, vomiting, epigastric distress, and abdominal pain.

Hematologic: Leukopenia, hemolytic anemia especially in G-6-PD deficient individuals and methemoglobinemia especially in NADH methemoglobin reductase deficient individuals.

Nervous system disorders: Dizziness.

Skin and subcutaneous tissue disorders: Rash maculo-papular, pruritus.

7 OVERDOSE

Symptoms

Abdominal cramps, vomiting, jaundice, burning epigastric distress, CNS and cardiovascular disturbances, including cardiac arrhythmia and QT prolongation, cyanosis, methemoglobinemia, moderate leukocytosis or leukopenia, and anemia. The most striking changes are granulocytopenia and acute hemolytic anemia in G6PD deficient patients. Acute hemolysis often occurs, but complete recovery can be expected if primaquine is discontinued.

Treatment

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Management should include 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.

8 DOSAGE

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

Patients suffering from an attack of *vivax* or *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 indicated for the prevention of delayed primary attacks and relapse of *Plasmodium vivax* or *Plasmodium 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.

Adults: 1 tablet (15 mg primaquine base) daily for 14 days.

In case of mild to moderate Glucose-6-phosphate dehydrogenase (G6PD) deficiency: 0.75 mg/kg of primaquine base once a week for 8 weeks (see WARNINGS).

Children: 0.39 mg primaquine base/ kg daily for 14 days

In case of mild to moderate Glucose-6-phosphate dehydrogenase (G6PD) deficiency: 0.75 mg/kg of primaquine base once a week for 8 weeks (see WARNINGS).

NOTE: For radical cure of some strains of *Plasmodium vivax*, higher doses or longer courses may be required to overcome resistance.

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

9 AVAILABILITY

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).

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.

Bottles of 100.

10 STORAGE AND STABILITY

Store between 15-30°C.

Keep away from the reach and sight of children.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr PRIMAQUINE®

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 eliminate certain forms of malaria (specifically Plasmodium vivax and ovale malaria) and help prevent it from coming back.

How does PRIMAQUINE work?

PRIMAQUINE belongs to a group of drugs called the antimalarials. It is used to treat malaria in an infected person. PRIMAQUINE affects the parasite that causes malaria, causing it to die. This stops the infection from continuing.

What are the ingredients in PRIMAQUINE?

Medicinal ingredients: primaquine phosphate USP 26.3 mg (equivalent to primaquine base 15 mg).
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:

Pink, film coated convex round tablet.

Do not use PRIMAQUINE if:

- If you are allergic to primaquine phosphate or any of the ingredients in the product (See **What are the ingredients in PRIMAQUINE**)
- If you suffer from a medical condition such as rheumatoid arthritis or lupus erythematosus and if you are acutely ill with systemic disease
- If you are taking or have recently taken quinacrine (another antimalarial drug)
- If you are taking drugs that may damage blood cells or their formation
- If you have a disease called severe G6PD deficiency (also known as favism)
- If you are pregnant

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:

- Suffer from, or have a family history of G6PD (glucose-6-phosphate dehydrogenase) deficiency, or favism. PRIMAQUINE must not be used if you have severe G6PD deficiency.
- Suffer from nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficiency
- Suffer from hemolytic anemia, a condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over.
- Are pregnant, planning to become pregnant.You should not become pregnant while receiving treatment with Primaquine and for 1 menstrual cycle after stopping.
- Are male and planning to father a child. You should not father a child while receiving Primaquine treatment and for 3 months after stopping.
- Are breastfeeding or planning to breastfeed. Breastfeeding should be interrupted or the PRIMAQUINE treatment should be delayed until end of breastfeeding.
- Have or have had heart disease, an irregular heartbeat, low levels of magnesium or potassium in your blood, or a resting heart rate below 50 beats per minutes.

Other warnings you should know about:

Because PRIMAQUINE can cause hemolysis in persons with G6PD deficiency, a screening test must be performed prior to use to rule out such a deficiency.

Stop taking PRIMAQUINE right away and contact your doctor if you develop signs of hemolytic anemia which include darkening of the urine, dizziness, confusion, fatigue, light-headedness, or shortness of breath.

PRIMAQUINE may cause dizziness; do not drive or operate machinery until you know how the drug 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:
Do not take PRIMAQUINE if you are taking or if you have recently taken quinacrine.
PRIMAQUINE can interact with medications that have an effect on heart rhythm (prolong the QT interval)

How to take PRIMAQUINE:
Taking PRIMAQUINE after a meal may help to decrease stomach pain or cramps which are possible side effects of this medication

Usual dose:
Take PRIMAQUINE exactly as prescribed by your doctor

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 heart beat rhythm, bluish skin discoloration, fatigue, difficulty breathing, shortness of breath, confusion, light-headedness, dizziness, difficulty sleeping, and pale skin.

Missed Dose

If you miss a dose take it as soon as you remember that same day. If it is the next day and time for your next dose, resume your daily dosing schedule. Do not double dose.

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.

- Irregular heartbeat,
- Nausea,
- Vomiting,
- Heartburn,
- Stomach pain,
- Darkening of the urine,
- Blood problems such as leukopenia (decrease in white blood cells) which could increase infections, or methemoglobinemia (reduced ability of the blood to deliver oxygen) with symptoms such as shortness of breath, confusion, light-headedness, dizziness, fatigue
- Dizziness
- Rash, itching.

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

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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; 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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