AUSTRALIAN PRODUCT INFORMATION

PRIMACIN®
Primaquine phosphate
Tablets

1 NAME OF THE MEDICINE

Primaquine phosphate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Primacin tablet contains 7.5 mg primaquine base as 13.2 mg primaquine phosphate.

Excipients with known effect: Lactose monohydrate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Primacin tablets are orange tablets, 6mm diameter, flat without breakline or logo.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Prevention of relapses (radical cure) of malaria caused by *P. vivax* and *P. ovale.*
- Adjunctive therapy in the treatment of gametocytemia due to *P. falciparum* in patients resident in areas receptive to malaria.

4.2 DOSE AND METHOD OF ADMINISTRATION

Primaquine should be taken with food.

Radical treatment

(a) 15 mg daily for 14 days.
(b) Up to 30 mg daily for 14 days in areas where resistant malaria strains occur or where treatment has failed with lower doses.
(c) The WHO advises that the treatment period of 21 days should be employed to achieve radical cure in most of South East Asia and the Pacific regions. Other antimalarial agents may be used concomitantly.
(d) For patients with G6PD deficiency: up to 45 mg once weekly for 8 weeks with monitoring for the development of haemolysis.

(e) Paediatric dose: 0.3 mg/kg/day.
(f) For the reduction of gametocytes of P. falciparum: 45 mg as a single dose for adults and 0.7 to 1.0 mg/kg for children.

4.3 CONTRAINDICATIONS

- Hypersensitivity to primaquine or other 8-aminoquinolines
- Hypersensitivity to other ingredients in Primacin tablets
- Severe glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Pregnant women
- Acutely ill patients with any serious systemic diseases characterised by a tendency to granulocytopenia, such as rheumatoid arthritis or lupus erythematosus
- Patients receiving concurrently other potentially haemolytic medicines or depressants of myeloid elements of the bone marrow

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Primaquine was first used as an anti-malarial agent in humans in the late 1940's and early 1950's. It has not been subject to the systematic long term safety testing in animals that would be expected of a drug developed more recently.

Haemolytic anaemia and G6PD deficiency
Primaquine may cause severe haemolytic anaemia in individuals with G6PD deficiency. Due to the risk of haemolytic anaemia in patients with G6PD deficiency, G6PD testing has to be performed prior to the administration of primaquine. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of haemolysis, and adequate medical support and follow-up to manage haemolytic risk should be available.

Primaquine should not be prescribed for patients with severe G6PD deficiency (see Section 4.3 Contraindications).

There is limited evidence that adults with moderately reduced G6PD deficiency may be able to tolerate 45 mg once weekly for 8 weeks. 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, baseline haematocrit and haemoglobin must be checked before treatment, and close haematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage haemolytic risk should be available.

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. Risk factors for G6PD deficiency or favism must be assessed. Baseline haematocrit and haemoglobin must be checked before treatment and close haematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage haemolytic risk should be available.

Discontinue the use of primaquine phosphate promptly if signs suggestive of haemolytic anaemia occur (darkening of the urine, marked fall of haemoglobin or erythrocyte count).

Haemolytic reactions (moderate to severe) may occur in individuals with G6PD deficiency and in individuals with a family or personal history of favism. Areas of high prevalence of G6PD deficiency are Africa, Southern Europe, Mediterranean region, Middle East, South-East Asia and Oceania. People from these regions have a greater tendency to develop haemolytic anaemia while receiving primaquine and related drugs, due to a congenital deficiency of erythrocytic G6PD.

Methaemoglobinaemia and NADH methaemoglobin reductase deficiency
Primaquine may cause methaemoglobinaemia in individuals with NADH methaemoglobin reductase deficiency. Patients should be observed carefully and treatment stopped if signs of methaemoglobinaemia are observed.

Blood monitoring
Anaemia, methaemoglobinaemia and leukopenia have been observed following administration of large doses of primaquine. Primaquine taken at daily doses of 120 mg/day, higher than recommended for Primacin tablets, has been associated with neutropenia and agranulocytosis.

It is advisable to perform routine blood examinations, particularly blood cell counts and haemoglobin determinations, during therapy.

If primaquine phosphate is prescribed for an individual who has shown a previous idiosyncratic reaction to primaquine phosphate as manifested by haemolytic anaemia, methaemoglobinaemia or leukopenia, or for an individual with a family or personal history of haemolytic anaemia or NADH methaemoglobin reductase deficiency, the person should be observed closely.

In all patients, primaquine phosphate should be discontinued immediately if marked darkening of the urine or sudden decrease in haemoglobin concentration or leukocyte count occurs.

Potential prolongation of QT interval
Due to potential for QT prolongation, monitor electrocardiogram (ECG) when using primaquine in patients with cardiac disease, long QT syndrome, a history of ventricular arrhythmias, uncorrected hypokalaemia and/or hypomagnesaemia, or bradycardia (< 50 bpm) and during concomitant administration with QT interval prolonging agents.

Lactose intolerance
Primaquine tablets contain lactose monohydrate as an excipient and should be used with caution in patients sensitive to lactose monohydrate.

Use in hepatic impairment
See Section 4.4 Special warnings and precautions for use: Use in elderly.

Use in renal impairment
See Section 4.4 Special warnings and precautions for use: Use in elderly.

Use in the elderly
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other therapy.

Paediatric use
See Section 4.2 Dose and method of administration.

Effects on laboratory tests
See Section 4.8 Adverse effects (Undesirable effects)

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Because quinacrine hydrochloride appears to potentiate the toxicity of antimalarial compounds which are structurally related to primaquine, 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.

The interaction of primaquine and proguanil has not been assessed *in vivo*. Other 8-aminoquinolines (pamaquine and pentaquine) administered with proguanil have resulted in 5 – 10 fold increases in 8-aminoquinoline concentration.

Drugs known to suppress bone marrow and drugs known to cause haemolysis should not be administered with primaquine.

Caution is advised when primaquine is used concomitantly with other medicines that prolong the QT interval.

Ketoconazole reduced metabolism of primaquine in an *in vitro* study using human liver microsomes. The effects of ketoconazole and other drugs metabolised by the cytochrome P450 system on primaquine metabolism have not been assessed *in vivo*.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
No data available.

Use in pregnancy (Category D)
Safe usage of primaquine phosphate in pregnancy has not been established. Primaquine is contraindicated in pregnant women. Even if a pregnant woman is G6PD normal, the fetus may not be.

Use in lactation
No studies have been carried out in relation to the safe use of primaquine during lactation. It is not known whether primaquine is excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse effects in nursing infants from primaquine, a decision should be made whether to discontinue nursing or discontinue primaquine, taking into account the importance of primaquine to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Gastrointestinal disorders
Common: abdominal cramps and pains, nausea, vomiting, epigastric distress. Gastrointestinal symptoms are dose related.

Blood and lymphatic system disorders
Haemolytic anaemia in individuals with G-6-PD deficiency or following administration of large doses of primaquine.

Methaemoglobinaemia in individuals with NADH methaemoglobin reductase deficiency or following administration of large doses of primaquine. Evidence of increased methaemoglobin concentration on laboratory testing may be observed more commonly.

Leukopenia has been observed following administration of large doses of primaquine. Neutropenia and agranulocytosis have been observed in subjects taking very high doses of primaquine (120 mg daily for 14 days).

Cardiac disorders
Cardiac arrhythmia, QT interval prolongation.

Nervous system disorders
Common: dizziness, headache.

Skin and subcutaneous disorders
Rash, pruritus

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms of overdosage of primaquine phosphate include abdominal cramps, vomiting, burning epigastric distress, central nervous system and cardiovascular disturbances, including cardiac arrhythmia and QT interval prolongation, cyanosis, methaemoglobinaemia, moderate leukocytosis or leukopenia, and anaemia. The most striking symptoms are granulocytopenia and acute haemolytic anaemia in sensitive persons. Acute haemolysis occurs, but patients recover completely if the dosage is discontinued.

For all overdoses in general, the mainstay of treatment is supportive and symptomatic care.

Treatment may be conducted according to an acute oral overdose protocol, including use of activated charcoal. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.
Prompt measures should be taken to counteract depressant effects on the cardiovascular and respiratory systems.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Primaquine is an antimalarial agent. It is used as a schizontocide for the treatment of the hypnozoite stage (in the liver) of malaria. Primaquine is effective against exoerythrocytic stages of *Plasmodium vivax* and *Plasmodium ovale* and against the primary exoerythrocytic stages of *Plasmodium falciparum*. It is also effective against the sexual forms (gametocytes) of plasmodia, especially *P. falciparum*, disrupting transmission of the disease by eliminating the reservoir from which the mosquito carrier is infected. Primaquine is more active against tissue forms and gametes than asexual blood forms of plasmodia. The precise mechanism of action is not known. There is some *in vitro* evidence that some of the antiparasitic effect may be due to the binding and inhibition of entry of the parasite to the hepatoma cell.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Primaquine is rapidly absorbed (T_{max} about 2 hours) from the gastrointestinal tract and the concentration of the drug in the body is dose dependent. Oral bioavailability studies (not performed with this product) shows that primaquine is rapidly and almost completely absorbed.

Distribution
It is widely distributed and the mean apparent Vd range across studies is 260 – 300 L. It is extensively distributed in body tissues.

Metabolism
Primaquine is rapidly metabolised after an oral dose, mainly by the liver, with an elimination half-life ranging from 4.3 to 7.4 hours. The principle metabolite is carboxyprimaquine which has a longer half-life and accumulates over a 14 day course of 15 mg primaquine/day.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.

Carcinogenicity
No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Primacin tablets contain lactose monohydrate (53.6 mg), wheat starch, povidone, gelatin, glycerol, magnesium stearate and purified talc as excipients.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

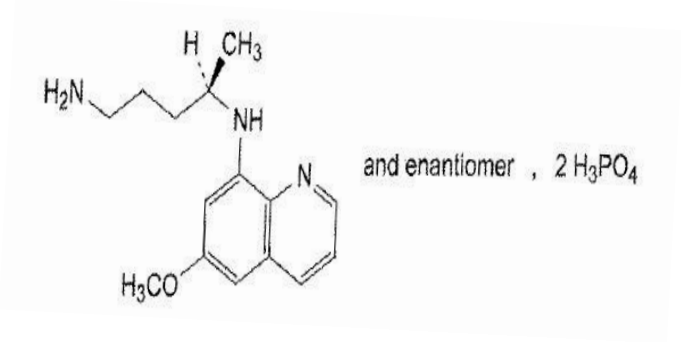
HDPE bottles with PP child-resistant closure of 28 and 56 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Molecular formula: $C_{15}H_{21}N_3O,2H_3PO_4$
Molecular weight: 455.3
Chemical name: (4RS)-N4-(6-Methoxyquinolin-8-yl)pentane-1,4-diamine bisphosphate

Primaquine phosphate is an orange crystalline powder and melts at about 200°C with decomposition. It is soluble in water and practically insoluble in ethanol.

CAS number
63-45-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Boucher & Muir Pty Ltd
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9 DATE OF FIRST APPROVAL

10 November 2014

10 DATE OF REVISION

08 May 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Updated to the revised Australian Product Information format
2, 4.5, 5.2	Rephrasing of the sentence for better clarity or to correct the grammatical errors.
3	Addition of details about tablet description
2, 4.4 and 6.1	Excipient name ‘Lactose’ updated to ‘Lactose monohydrate’ in line with the updated Australian Approved Name
6.7	Re-ordering and correction of the chemical name within the section.
8	Addition of Phone number to Sponsor details.