AUSTRALIAN PRODUCT INFORMATION – PLAQUENIL (HYDROXYCHLOROQUINE SULFATE)

1 NAME OF THE MEDICINE

hydroxychloroquine sulfate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Film coated tablets containing hydroxychloroquine sulfate 200 mg (equivalent to 155 mg base).

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

3 PHARMACEUTICAL FORM

White to off-white peanut shaped tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Rheumatoid arthritis; mild systemic and discoid lupus erythematosus; the suppression and treatment of malaria.

4.2 DOSE AND METHOD OF ADMINISTRATION

Rheumatoid Arthritis

Plaquenil is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, whereas minor side effects may occur relatively early. Several months of therapy may be required before maximum effects can be obtained.

Initial dosage: In adults, a suitable initial dosage is from 400 to 600 mg daily, preferably taken at meal times. In a few patients the side effects may require temporary reduction of the initial dosage. Generally, after five to ten days the dose may be gradually increased to the optimum response level, frequently without return of side effects.

Maintenance dosage: When a good response is obtained (usually in four to twelve weeks) the dose can be reduced to 200 to 400 mg daily (but should not exceed 6 mg/kg per day) and can be continued as maintenance treatment. The minimum effective maintenance dose should be employed. The incidence of retinopathy has been reported to be higher when the maintenance dose is exceeded.

If objective improvement (such as reduced joint swelling or increased mobility) does not occur within six months the drug should be discontinued.

If a relapse occurs after medication is withdrawn, therapy may be resumed or continued on an intermittent schedule if there are no ocular contraindications.

Safe use of Plaquenil for the treatment of juvenile rheumatoid arthritis has not been established.

Use in Combination Therapy: Plaquenil may be used safely and effectively in combination with corticosteroids, salicylates, NSAIDS, and methotrexate and other second line therapeutic agents. Corticosteroids and salicylates can generally be decreased gradually in dosage or eliminated after the drug has been used for several weeks. When gradual reduction of steroid dosage is suggested, it may be done by reducing every four to five days, the dose of cortisone by no more than 5 to 15 mg; of methylprednisolone from 1 to 2 mg and dexamethasone from 0.25 to 0.5 mg. Treatment regimens using agents other than corticosteroids and NSAIDS are under development. No definitive dose combinations have been established.

Lupus Erythematosus

In mild systemic and discoid cases, the antimalarials are the drugs of choice.

The dosage of Plaquenil depends on the severity of the disease and the patient's response to treatment. For adults an initial dose of 400-800 mg daily is recommended. This level can be maintained for several weeks and then reduced to a maintenance dose of 200-400 mg daily.

Malaria

Plaquenil is active against the erythrocytic forms of *P.vivax* and *P.malariae* and most strains of *P.falciparum* (but not the gametocytes of *P.falciparum*).

Plaquenil does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exo-erythrocytic forms, nor will it prevent vivax or malariae infection when administered as a prophylactic.

It is effective as a suppressive agent in patients with vivax or malariae malaria, in terminating acute attacks and significantly lengthening the interval between treatment and relapse. In patients with falciparum malaria it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P.falciparum*.

Malaria Suppression

Adults

400 mg (310 mg base) on exactly the same day of each week.

Children

The weekly suppressive dose is 5 mg (base) per kg bodyweight but should not exceed the adult dose regardless of weight.

Suppressive therapy should begin two weeks prior to exposure. Failing this, in adults an initial loading dose of 800 mg (620 mg base), or in children 10 mg base per kg, may be taken in two divided doses, six hours apart. The suppressive therapy should be continued for eight weeks after leaving the endemic area.

Treatment of the Acute Attack

Adults

An initial dose of 800 mg followed by 400 mg in six to eight hours and 400 mg on each of two consecutive days. (Total dose of 2 g or 1.55 g base). A single dose of 800 mg (620 mg base) has also proved effective.

Children

The dosage is calculated on the basis of bodyweight. (Total dose of 25 mg base per kg).

First dose - 10 mg base per kg (not exceeding a single dose of 620 mg base).

Second dose - 5 mg base per kg (not exceeding 310 mg base), six hours after first dose.

Third dose - 5 mg base per kg eighteen hours after second dose.

Fourth dose - 5 mg base per kg twenty-four hours after third dose.

For radical cure of vivax and malariae malaria, concomitant therapy with an 8-aminoquinoline is necessary.

4.3 CONTRAINDICATIONS

Plaquenil is contraindicated in:

- patients with pre-existing maculopathy of the eye
- patients with known hypersensitivity to 4-aminoquinoline compounds, and
- long-term therapy in children
- children under 6 years of age.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Plaquenil is not effective against chloroquine-resistant strains of *P.falciparum*.

Patients should be warned to keep Plaquenil out of the reach of children, as small children are particularly sensitive to the 4-aminoquinolines.

Plaquenil should be used with caution or not at all in patients with severe gastrointestinal, neurological or blood disorders. If such severe disorders occur during therapy, the drug should be stopped. Periodic blood counts are advised.

When used in patients with porphyria or psoriasis, these conditions may be exacerbated. Plaquenil should not be used in these conditions unless in the judgement of the physician, the benefit to the patient outweighs the possible risk.

Chronic cardiac toxicity

Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with Plaquenil. In multiple cases, endomyocardial biopsy showed association of the cardiomyopathy with phospholipidosis in the absence of inflammation, infiltration, or necrosis (see Section 4.8 Adverse effects (Undesirable effects). Drug-induced phospholipidosis may occur in other organ systems. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Plaquenil should be discontinued if cardiomyopathy develops. Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are diagnosed. Monitor cardiac function as clinically indicated during therapy. Discontinue Plaquenil if cardiotoxicity is suspected or demonstrated by tissue biopsy.

Hepatotoxicity

Serious cases of drug-induced liver injury (DILI) including hepatocellular injury, acute hepatitis and fulminant hepatic failure (including fatal cases) have been reported during use of Plaquenil (see Section 4.8 Adverse effects (Undesirable effects). Risk factors may include pre-existing liver disease, or predisposing conditions such as uroporphyrinogen decarboxylase deficiency or, concomitant hepatotoxic medications. Prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury. For patients with significant liver function abnormalities, physicians should assess the benefits/risk of continuing the treatment.

Reactivation of infections

Caution is required in the presence of inactive infection with herpes zoster virus, tuberculosis or hepatitis B virus as it is possible that reactivation of these infections may occur in patients treated with hydroxychloroquine in combination with other immunosuppressants. Reactivation of Hepatitis B virus has been reported in such patients (see Section 4.8 Adverse effects (Undesirable effects).

Hypoglycaemia

Hydroxychloroquine has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without anti-diabetic medications. Patients treated with hydroxychloroquine should be warned about the risk of hypoglycaemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycaemia during treatment with hydroxychloroquine should have their blood glucose level checked and treatment reviewed as necessary.

QT interval prolongation

Hydroxychloroquine prolongs the QTc interval and should not be used in patients receiving drugs known to prolong the QT interval, e.g. class IA and III antiarrhythmics, tricyclic

antidepressants, antipsychotics, some anti-infectives due to increased risk of ventricular arrhythmia (see Section 4.5 Interactions with other medicines and other forms of interactions and Section 4.9 Overdose).

Hydroxychloroquine should be used with caution in patients with congenital or documented acquired QT prolongation and/or known risk factors for prolongation of the QT interval such as:

- cardiac disease, e.g., heart failure, myocardial infarction
- proarrhythmic conditions, e.g., bradycardia (< 50 bpm)
- a history of ventricular dysrhythmias
- uncorrected hypokalaemia and/or hypomagnesaemia

The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded (see Section 4.5 Interactions with other medicines and other forms of interactions and Section 4.8 Adverse effects (Undesirable effects)).

Carefully consider the benefits and risks before prescribing azithromycin or other macrolide antibiotics for any patients taking Plaquenil, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see Section 4.5 Interactions with other medicines and other forms of interactions).

Ophthalmological

Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinolone therapy for discoid and systemic lupus erythematosus, or rheumatoid arthritis. Retinopathy has been reported to be dose related. Exceeding the recommended daily dose sharply increases the risk of retinal toxicity.

If there is any indication of abnormality in the visual field, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks) which are not fully explainable by difficulties of accommodation or corneal opacities, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress after cessation of therapy. (See Section 4.8 Adverse effects (Undesirable effects))

Concomitant use of hydroxychloroquine with drugs known to induce retinal toxicity, such as tamoxifen, is not recommended.

Before starting treatment with hydroxychloroquine, all patients should have a careful complete examination of both eyes which includes slit lamp microscopy for corneal changes, fundoscopy, visual acuity, central visual field and colour vision. A complete eye examination before treatment will determine the presence of any visual abnormalities, either coincidental or due to the disease and establish a baseline for further assessment of the patient's vision. Ophthalmological testing should be conducted at 6 monthly intervals in patients receiving hydroxychloroquine at a dose of not more than 6 mg per kg body weight per day.

Ophthalmological testing should be conducted at 3-4 monthly intervals in the following circumstances:

- Dose exceeds 6 mg per kg ideal (lean) body weight per day. Absolute body weight used as a guide to dosage, could result in an overdosage in the obese.
- Significant renal impairment
- Significant hepatic impairment
- Elderly
- Complaints of visual disturbances
- Duration of treatment exceeds 8 years.

Corneal changes often subside on reducing the dose or on interrupting therapy for a short period of time, but any suggestion of retinal change or restriction in the visual field is an indication for complete withdrawal of the drug.

The use of sunglasses in patients exposed to strong sunlight is recommended, as this may be an amplifying factor in retinopathy.

Skeletal Muscle Myopathy or Neuropathy

Muscle and nerve biopsies have shown associated phospholipidosis. Drug-induced phospholipidosis may occur in other organ systems.

Discontinue Plaquenil if muscle or nerve toxicity is suspected or demonstrated by tissue biopsy.

Aggravation of Myasthenia Gravis

Aggravation of symptoms of myasthenia gravis (Generalised weakness including shortness of breath, Dysphagia, Diplopia, etc.) have been reported in Myasthenic patients receiving hydroxychloroquine therapy.

Skin reactions

Pleomorphic skin eruptions (morbilliform, lichenoid, purpuric), itching, dryness and increased pigmentation sometimes appear after a few months of therapy. The rash is usually mild and transient. If a rash appears, Plaquenil should be withdrawn and only started again at a lower dose.

Patients with psoriasis appear to be more susceptible to severe skin reactions than other patients.

Severe cutaneous adverse reactions (SCARs)

Cases of severe cutaneous adverse drug reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported during treatment with hydroxychloroquine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. If signs and symptoms suggestive of severe skin

reactions appear, hydroxychloroquine should be withdrawn at once and alternative therapy should be considered.

Hemolytic Anaemia Associated with G6PD Deficiency

Hemolysis has been reported in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor for hemolytic anaemia as this can occur, particularly in association with other drugs that cause hemolysis.

Other monitoring on long term treatments

Patients on long-term therapy should have periodic full blood counts. If evidence of abnormalities such as, agranulocytosis, aplastic anaemia, thrombocytopenia or leukopenia becomes apparent, and cannot be attributed to the disease being treated, Plaquenil should be discontinued.

All patients on long-term therapy with this preparation should be questioned and examined periodically, including the testing of knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs discontinue the drug.

Renal Toxicity

Proteinuria with or without moderate reduction in glomerular filtration rate have been reported with the use of Plaquenil. Renal biopsy showed phospholipidosis without immune deposits, inflammation, and/or increased cellularity. Physicians should consider phospholipidosis as a possible cause of renal injury in patients with underlying connective tissue disorders who are receiving Plaquenil. Drug-induced phospholipidosis may occur in other organ systems. Discontinue Plaquenil if renal toxicity is suspected or demonstrated by tissue biopsy.

Miscellaneous

Gastrointestinal disturbances such as nausea, anorexia, abdominal cramps or rarely vomiting, occur in some patients. The symptoms usually stop on reducing the dose or temporarily stopping the drug.

Muscle weakness, vertigo, tinnitus, nerve deafness, headache and nervousness have been reported less frequently.

In the treatment of rheumatoid arthritis, if objective improvement (such as reduced joint swelling, increased mobility) does not occur within six months, the drug should be discontinued. Safe use of the drug in the treatment of juvenile rheumatoid arthritis has not been established.

Suicidal behaviour and psychiatric disorders have been reported in some patients treated with hydroxychloroquine.

Psychiatric side effects typically occur within the first month after the start of treatment with hydroxychloroquine sulfate and have been reported also in patients with no prior history of

psychiatric disorders. Patients should be advised to seek medical advice promptly if they experience psychiatric symptoms during treatment.

Extrapyramidal disorders may occur with hydroxychloroquine.

Also observe caution in patients with gastrointestinal, neurological, or blood disorders, in those with a sensitivity to quinine, and in glucose-6-phosphate dehydrogenase deficiency, porphyria and psoriasis.

Patients with porphyria cutanea tarda (PCT) are more susceptible to hepatotoxicity (see Section 4.8 Adverse effects (Undesirable effects)).

Use in hepatic impairment

Observed caution in patients with hepatic disease, as well as in those taking medicines known to affect the organ. A reduction in dosage may be necessary.

Use in renal impairment

Observed caution in patients with renal disease, as well as in those taking medicines known to affect the organ. A reduction in dosage may be necessary.

Use in the elderly

See Section 4.4 Special warnings and precautions for use – Ophthalmological.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacodynamic Interactions

Drugs known to prolong QT interval / with potential to induce cardiac arrhythmia:
Hydroxychloroquine should not be used in patients receiving drugs known to prolong the QT interval, e.g., Class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives due to increased risk of ventricular arrhythmia (see Section 4.4 Special precautions and warnings for use and Section 4.9 Overdose). Halofantrine should not be administered with hydroxychloroquine.

Macrolide antibiotics
Observational data have shown that co-administration of hydroxychloroquine with azithromycin in patients with rheumatoid arthritis is associated with an increased risk of

cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risks should also be undertaken before prescribing other macrolide antibiotics for any patients taking hydroxychloroquine because of the potential for a similar risk when hydroxychloroquine is co-administered with these medicines.

Antidiabetic drugs
As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

Antimalarials
Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions.

Antiepileptic drugs
The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

Others
There is a theoretical risk of inhibition of intra-cellular α-galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

Concurrent use with drugs with oculotoxic or haemotoxic potential should be avoided if possible.

It has been suggested that 4-aminoquinolines are pharmacologically incompatible with monoamine oxidase inhibitors.

Hydroxychloroquine sulphate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. These include: potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial; antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine.

Pharmacokinetic Interactions

In vivo, in humans, hydroxychloroquine is metabolised and eliminated unchanged in urine (20-25% of dose). *In vitro*, hydroxychloroquine is metabolised by CYP2C8, CYP3A4 and CYP2D6, as well as by FMO-1 and MAO-A, with no major involvement of a single CYP or enzyme (see Section 5.2 Pharmacokinetic properties). Therefore, inhibitors and inducers of CYP2C8 and CYP3A4 have the potential to interact on hydroxychloroquine. In the absence of *in vivo* drug interaction studies, caution is advised (e.g. monitoring for adverse reactions) when cimetidine or CYP2C8 and/or CYP3A4, or CYP2D6 strong inhibitors (such as gemfibrozil, clopidogrel, ritonavir, itraconazole, clarithromycin, grapefruit juice, fluoxetine, paroxetine, quinidine) are concomitantly administered.

P-glycoprotein substrates

Hydroxychloroquine inhibits P-gp *in vitro* at high concentrations. Therefore, there is a potential for increased concentrations of P-gp substrates when hydroxychloroquine is concomitantly administered. Increased digoxin serum levels were reported when digoxin and hydroxychloroquine were administered. Caution is advised (e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when P-gp substrates with narrow therapeutic index (such as digoxin, dabigatran) are concomitantly administered.

CYP2D6 substrates

Hydroxychloroquine inhibits CYP2D6 *in vitro*. In patients receiving hydroxychloroquine and a single dose of metoprolol, a CYP2D6 probe, the Cmax and AUC of metoprolol were increased by 1.7-fold, which suggests that hydroxychloroquine is a mild inhibitor of CYP2D6. Caution is advised (e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when CYP2D6 substrates with narrow therapeutic index (such as flecainide, propafenone) are concomitantly administered.

CYP3A4 substrates
Hydroxychloroquine inhibits CYP3A4 *in vitro*. In the absence of *in vivo* interaction studies with sensitive CYP3A4 substrates, caution is advised (e.g. monitoring for adverse reactions) when CYP3A4 substrates (such as ciclosporin, statins) are concomitantly administered with hydroxychloroquine.

Hydroxychloroquine has no significant potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and the main transporters BCRP, OATP1B1, OATP1B3, OAT1, and OAT3. However, hydroxychloroquine has the potential to inhibit OCT1, OCT2, MATE1 and MATE2-K transporters. Hydroxychloroquine has no significant potential to induce CYP1A2, CYP2B6 and CYP3A4.

Effects of other medicinal products on hydroxychloroquine:

Antacids and kaolin

Concomitant administration with magnesium-containing antacids or kaolin may result in reduced absorption of chloroquine. Per extrapolation, hydroxychloroquine should therefore be administered at least two hours apart from antacids or kaolin.

CYP inhibitors or inducers

Physiologically Based PK (PBPK) predictions show that strong CYP2C8 or CYP3A4 inhibitors would increase hydroxychloroquine exposure by less than 1.5-fold. In the absence of *in vivo* drug interaction studies, caution is advised (e.g. monitoring for adverse reactions) when CYP2C8 and/or CYP3A4 strong inhibitors (such as gemfibrozil, clopidogrel, ritonavir, itraconazole, clarithromycin, grapefruit juice) are concomitantly administered.

PBPK predictions show that strong CYP2C8 and/or CYP3A4 inducers would decrease by 2-fold hydroxychloroquine exposure. Lack of efficacy of hydroxychloroquine was reported when rifampicin, a CYP2C8 and/or CYP3A4 strong inducer, was concomitantly administered. Caution is advised (e.g. monitoring for efficacy) when CYP2C8 and CYP3A4 strong inducers (such as rifampicin, St John's Wort, carbamazepine, phenobarbital) are concomitantly administered.

Effects of hydroxychloroquine on other medicinal products:

CYP3A4 substrates

Hydroxychloroquine inhibits CYP3A4 *in vitro* and PBPK predictions show that hydroxychloroquine is a moderate CYP3A4 inhibitor *in vivo*. Hydroxychloroquine would increase the exposures of drugs highly metabolised by CYP3A4 such as midazolam and simvastatin by 2.1- and 4.2-fold, respectively. An increased plasma level of ciclosporin (a CYP3A4 and p-gp substrate) was reported when ciclosporin and hydroxychloroquine were coadministered. Caution is advised (e.g. monitoring for adverse reactions) when CYP3A4 substrates (such as ciclosporin, statins) are concomitantly administered.

CYP2D6 substrates

Hydroxychloroquine inhibits CYP2D6 *in vitro.* In patients receiving hydroxychloroquine and a single dose of metoprolol, a CYP2D6 probe, the Cmax and AUC of metoprolol were increased by 1.7-fold, which suggests that hydroxychloroquine is a mild inhibitor of CYP2D6. However, given that metoprolol is a moderate sensitive substrate, the maximum increase in exposure could result in levels considered consistent with a moderate or strong inhibitor when co-administered with a sensitive substrate. Caution is advised (e.g. monitoring of adverse reactions or for plasma concentrations as appropriate) when CYP2D6 substrates with narrow therapeutic index (such as flecainide, propafenone) are concomitantly administered.

P-glycoprotein substrates

Hydroxychloroquine inhibits P-gp *in vitro* at high concentrations. Therefore, there is a potential for increased concentrations of P-gp substrates when hydroxychloroquine is concomitantly administered.

Increased digoxin serum levels were reported when digoxin and hydroxychloroquine were coadministered. Caution is advised (e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when P-gp substrates with narrow therapeutic index (such as digoxin, dabigatran) are concomitantly administered.

Praziquantel

In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel. It is not known if there is a similar effect when hydroxychloroquine and praziquantel are co-administered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no animal data on hydroxychloroquine action on fertility.

Only limited reproductive toxicity data are available for hydroxychloroquine, therefore chloroquine data are considered due to the similarity of structure and pharmacological properties between the 2 products.

A study in male rats showed a decrease in testosterone levels, weight of testes, epididymis, seminal vesicles and prostate after 30 days of oral treatment with chloroquine at 5 mg/day. In another rat study with chloroquine the male fertility rate was decreased after 14 days of intraperitoneal treatment at 10 mg/kg/day.

There are no data in humans.

Use in pregnancy

Category D.

Hydroxychloroquine crosses the placenta. It should be noted 4-aminoquinolines in therapeutic doses have been associated with central nervous system damage, including ototoxicity (auditory and vestibular toxicity, congenital deafness), retinal haemorrhages and abnormal retinal pigmentation. Literature review of observational data and meta-analyses, on the use of hydroxychloroquine in women with autoimmune disease during pregnancy excluded a large risk of congenital malformations (RR>3). However, the statistical power to detect modest risks was limited and various limitations of observational data do not allow robust exclusion of causality.

Due to lack of studies, no conclusions can be made from the epidemiologic literature about paternal exposure to Hydroxychloroquine affecting fertility or birth outcomes.

In animal studies on chloroquine, embryo-fetal developmental toxicity was shown at very high, supratherapeutic doses (ranging from 250 to 1500 mg/kg bodyweight).

Data from a population-based cohort study (Huybrechts et al-2021) including 2045 hydroxychloroquine exposed pregnancies suggests a small increase in the relative risk (RR) of major congenital malformations associated with hydroxychloroquine exposure in the first trimester (n = 112 events). For a daily dose of ≥ 400 mg the RR was 1.33 (95% CI, 1.08 – 1.65). For a daily dose of < 400 mg the RR was 0.95 (95% CI, 0.60 – 1.50). At higher doses ≥ 400 mg, caution should be exercised, and hydroxychloroquine should be avoided in pregnancy except when, in the judgement of the physician, the potential benefits outweigh the potential hazards. Close monitoring of pregnancy is recommended for early detection of congenital malformations.

The use of this drug in the treatment of malaria or suppression of malaria in high risk situations may be justified if the treating physician considers the risk to the fetus is outweighed by the benefits to the mother and fetus.

Use in lactation

Hydroxychloroquine is excreted in breast milk and it is known that infants are extremely sensitive to the toxic effects of 4-amonioquinones. In one study, the daily HCQ exposures to infant from breast milk were estimated to be less than 2% of the maternal dose (after bodyweight correction).

Although hydroxychloroquine is excreted in breast milk, the amount is insufficient to confer any protection against malaria to the infant. Separate chemoprophylaxis for the infant is required.

There are very limited data on the safety in the breastfed infant during long-term hydroxychloroquine treatment; the prescriber should assess the potential risks and benefits of use during breastfeeding, according to indication and duration of treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be warned about driving and operating machinery since hydroxychloroquine can impair visual accommodation and cause blurring of vision. If the condition is not self-limiting, the dosage may need to be temporarily reduced.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Note	*very common*	≥ 1/10 (≥ 10%)
	common	≥ 1/100 and < 1/10 (≥ 1% and <10%)
	uncommon	≥1/1000 and < 1/100 (≥ 0.1% and <1.0%)
	rare	≥1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
	very rare	< 1/10,000 (< 0.01%)
	not known	frequency cannot be estimated from available data

Blood and Lymphatic System Disorders

Rare: bone marrow depression, anaemia, aplastic anaemia, leucopenia, thrombocytopenia

Very rare: agranulocytosis

Immune System Disorders

Not known: urticaria, angioedema, bronchospasm

Metabolism and nutrition disorders

Common: anorexia

Not known: hypoglycaemia

Hydroxychloroquine may exacerbate porphyria

Psychiatric Disorders

Common: affect lability

Very rare: psychosis, suicidal behaviour, nightmares, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders

Renal and urinary disorders

Not known: Renal Phospholipids leading to renal injury

Nervous System Disorders

Common: headache

Uncommon: dizziness, nerve deafness, nervousness

Rare: convulsions, neuromyopathy

Very rare: nystagmus, ataxia

Not known: extrapyramidal disorders such as dystonia, dyskinesia, tremor

Eye Disorders

Common: blurring of vision

Uncommon: corneal changes, retinal changes, retinopathy with changes in pigmentation and visual field defects. In its early form, it appears reversible on discontinuation of Plaquenil. If allowed to develop, there may be a risk of progression even after treatment withdrawal.

Patients with retinal changes may be asymptomatic initially, or may even have scotomatous vision with paracentral, pericentral ring types, temporal scotomas and abnormal colour visions.

Corneal changes including oedema and opacities have occurred from three weeks (infrequently) to some years after the beginning of therapy. They are either symptomless or may cause disturbances such as halos, blurring of vision, or photophobia. They may be transient or are reversible on stopping treatment. Should these types of corneal changes occur with Plaquenil, it should be either stopped or temporarily withdrawn.

Not known: Cases of maculopathies and macular degeneration have been reported and may be irreversible.

Reversible extra-ocular muscle palsies and temporary blurring of vision due to interference with accommodation have also been noted.

Retinal changes such as abnormal macular pigmentation and depigmentation (sometimes described as a "bull's eye"), pallor of the optic disc, optic atrophy and narrowing of the retinal arterioles have been reported.

Originally, the condition was thought to be progressive and irreversible but more recent evidence suggests that routine ophthalmological examinations may detect retinal changes,

especially pigmentation, at an early and reversible stage when there is no apparent visual disturbance.

Much evidence suggests that there is a threshold of dosage above which retinopathy appears. These results seem to correlate more with daily dosage than with a cumulative dose, although the risk increases with increased duration of treatment.

Before starting treatment with hydroxychloroquine, all patients should have a careful complete examination of both eyes which includes slit lamp microscopy for corneal changes, fundoscopy, visual acuity, central visual field and colour vision, repeated at six month intervals during therapy (see Section 4.4 Special warnings and precautions for use – Opthalmological).

Any adverse changes in the ocular findings or the appearance of scotoma, night blindness or other retinal changes require immediate discontinuation of Plaquenil; these patients should not subsequently receive any pharmacologically similar drugs.

Ear and Labyrinth Disorders

Uncommon: vertigo, tinnitus

Not known: hearing loss

Cardiac Disorders

Rare: cardiomyopathy which may result in cardiac failure, and in some cases a fatal outcome (see Section 4.4 Special warnings and precautions for use)

Not known: Chronic toxicity should be considered when conduction disorders (bundle branch block / atrioventricular heart block) as well as biventricular hypertrophy are diagnosed.

Not known: QT interval prolongation in patients with specific risk factors, which may lead to arrhythmia (torsade de pointes, ventricular tachycardia) (See Section 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions and 4.9 Overdose).

Gastrointestinal Disorders

Very common: abdominal pain, nausea

Common: diarrhoea, vomiting

Hepatobiliary Disorders

Uncommon: abnormal liver function tests

Very rare: Drug-induced liver injury (DILI) including hepatocellular injury, acute hepatitis and fulminant hepatic failure

Not known: Hepatitis B reactivation

Skin and Subcutaneous Tissue Disorders

Common: skin rashes, alopecia, pruritus

Uncommon: pigmentary changes, bleaching of hair

Very rare: erythema multiforme, photosensitivity, exfoliative dermatitis, Sweet's syndrome and severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustolosis (AGEP) (see Section 4.4 Special warnings and precautions for use)

Musculoskeletal and Connective Tissue Disorders

Uncommon: sensorimotor disorders

Not known: absent or hypoactive deep tendon reflexes, muscle weakness or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups (muscle weakness may be reversible after drug discontinuation, but recovery may take many months). Depression of tendon reflexes and abnormal nerve conduction studies

Very rare: extraocular muscle palsies

Miscellaneous

Rare: exacerbation or precipitation of porphyria and attacks of psoriasis

Very rare: weight loss, lassitude

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

Overdosage with the 4-aminoquinolines is dangerous. Children are particularly sensitive to these compounds and a number of fatalities have been reported following the accidental ingestion of chloroquine, sometimes in relatively small doses (0.75 or 1 gram in one 3 year old child).

The 4-aminoquinolines are very rapidly and completely absorbed after ingestion and toxic symptoms following overdosage may occur within 30 minutes. Toxic symptoms consist of headache, drowsiness, visual disturbances, hypokalaemia, cardiovascular collapse and convulsions.

The ECG may reveal rhythm and conduction disorders including, QT prolongation, torsade de pointe, ventricular tachycardia, ventricular fibrillation, width-increased QRS complex, bradyarrhythmias (including bradycardia), nodal rhythm, atrioventricular block, followed by sudden potentially fatal respiratory and cardiac arrest. Immediate medical attention is required as these effects may appear shortly after the overdose.

Treatment

Treatment is symptomatic and must be prompt. Emesis is not recommended because of the potential for CNS depression, convulsions and cardiovascular instability. Activated charcoal should be administered. The dose of activated charcoal should be at least five times the estimated amount of hydroxychloroquine ingested.

Consideration should be given to using diazepam parenterally as there have been reports that it may decrease cardiotoxicity.

Respiratory support and management of shock should be instituted as necessary.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antimalarials, ATC code: P01BA02

Mechanism of action

Anti-malarial. Plaquenil also exerts a beneficial effect in mild systemic and discoid lupus erythematosus and rheumatoid arthritis. The precise mechanism of action is not known.

Malaria

Like chloroquine phosphate, Plaquenil is highly active against the erythrocytic forms of *P.vivax* and *P.malariae* and most strains of *P.falciparum* (but not the gametocytes of *P.falciparum*).

Plaquenil does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exo-erythrocytic forms of the parasite, nor will it prevent vivax or malariae infection when administered as a prophylactic. It is highly effective as a suppressive agent in patients with vivax or malariae malaria, in terminating acute attacks, and significantly lengthening the interval between treatment and relapse. In patients with falciparum malaria it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P.falciparum*.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, peak plasma or blood concentrations is achieved in approximately 3 to 4 hours. Mean absolute oral bioavailability is 79% (SD: 12%) in fasting conditions. Food does not modify the oral bioavailability of hydroxychloroquine.

Distribution

Hydroxychloroquine has a large volume of distribution (5500 L when assessed from blood concentrations, 44 000 L when assessed from plasma concentrations), due to extensive tissue accumulation (such as eyes, kidney, liver and lungs) and has been shown to accumulate in blood cells, with a blood to plasma ratio of 7.2. Approximately 50% of hydroxychloroquine is bound to plasma proteins.

Metabolism

Hydroxychloroquine is mainly metabolised to N-desethylhydroxychloroquine, and two other metabolites in common with chloroquine, desethylchloroquine and bidesethylchloroquine. *In vitro*, hydroxychloroquine is metabolised mainly by CYP2C8, CYP3A4 and CYP2D6 as well as by FMO-1 and MAO-A, with no major involvement of a single CYP or enzyme.

Excretion

Hydroxychloroquine presents a multi-phasic elimination profile with a long terminal half-life ranging from 30 to 50 days. PBPK predictions indicate that the effective accumulation half-life of hydroxychloroquine is about 5.5 days and that 90% of steady state is achieved within 5 weeks in blood after repeated oral administration of 400 mg hydroxychloroquine sulfate once a day in patients with rheumatoid arthritis. Approximately 20-25% of the hydroxychloroquine dose is eliminated as unchanged drug in the urine. After chronic repeated oral administration of 200 mg and 400 mg hydroxychloroquine sulfate once a day in adult patients with lupus or rheumatoid arthritis, the average steady-state concentrations were around 450-490 ng/mL and 870-970 ng/mL in blood, respectively.

The pharmacokinetics of hydroxychloroquine appears to be linear in the therapeutic dose range of 200 to 500 mg/day.

Renal impairment

Renal impairment is not expected to significantly modify the pharmacokinetics of hydroxychloroquine in patients with renal impairment because hydroxychloroquine is mainly metabolised and only 20-25% of the hydroxychloroquine dose is eliminated as unchanged drug in the urine. PBPK predictions show that hydroxychloroquine exposure would increase by 17-30% in patients with severe renal impairment (see Section 4.4 Special warnings and precautions for use – Use in renal impairment).

Hepatic impairment

The effect of hepatic impairment on hydroxychloroquine pharmacokinetics has not been evaluated in a specific PK study. PBPK predictions show that hydroxychloroquine exposure

would increase by 41%-57% in patients with moderate and severe hepatic impairment (see Section 4.4 Special warnings and precautions for use – Use in hepatic impairment).

Paediatric use

The pharmacokinetics of hydroxychloroquine in children aged below 18 years of age have not been established.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Based on the standard genotoxicity studies conducted, hydroxychloroquine is not considered to present a genotoxic risk to humans.

Hydroxychloroquine is not mutagenic in the bacterial reverse mutation (Ames) test.

It showed no clastogenicity or aneugenicity in the *in vivo* micronucleus test in rats following oral administration. Hydroxychloroquine was weakly positive in human lymphocyte micronucleus assay *in vitro* in the absence of metabolic activation but was negative in the presence of metabolic activation.

Carcinogenicity

No carcinogenicity studies are available on hydroxychloroquine. A dietary carcinogenicity study in rats with the parent drug chloroquine was negative. No other carcinogenicity study was conducted in mice or other species. In the absence of sufficient human and animal data an increased risk of cancer in patients receiving long term treatment cannot be ruled out.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the inactive ingredients calcium hydrogen phosphate dihydrate, maize starch and magnesium stearate. The film coating contains hypromellose, macrogol 400, titanium dioxide, polysorbate 80 and carnauba wax.

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

Plaquenil tablets should be stored below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

HDPE bottle with a PP child resistant closure – 100 tablets.

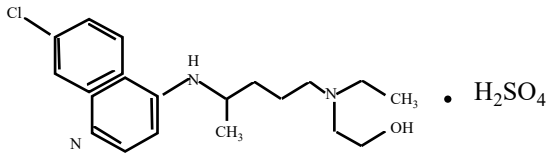
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Hydroxychloroquine sulfate is designated chemically as 2 {N (4-(7-Chloro-4-quinolylamino)pentyl)- -N-ethylamino}ethanol sulfate, and has the following chemical structure:



$C_{18}H_{26}ClN_3O$, H_2SO_4

Molecular Weight: 433.96

CAS number

747-36-4 (hydroxychloroquine sulfate)

118-42-3 (hydroxychloroquine)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

sanofi-aventis australia pty ltd

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Sydney NSW 2000

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Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

19 August 1994

10 DATE OF REVISION

22 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Minor editorial update to reporting suspected adverse reactions statement
4.9	Minor editorial update to Poisons statement
8	Update of sponsor address