NEW ZEALAND DATA SHEET

1 PROMOZIO 250/100 film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains the active ingredients atovaquone 250 mg and proguanil hydrochloride 100 mg.

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

3 PHARMACEUTICAL FORM

Pinkish brown to brown coloured, circular, biconvex, bevelled-edged, film-coated tablets with '404' debossed on one side and 'G' debossed on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Promozio 250/10 is a fixed dose combination of atovaquone and proguanil hydrochloride which acts as a blood schizonticide and also has activity against the hepatic forms of *Plasmodium falciparum.*

It is indicated for:

- Prophylaxis of *Plasmodium falciparum* malaria in adults
- Treatment of *Plasmodium falciparum* malaria in adults.

Because Promozio 250/100 is effective against drug sensitive and drug resistant *P. falciparum* it is especially recommended for prophylaxis and treatment of *P. falciparum* malaria in areas where the pathogen may be resistant to other antimalarials.

Official guidelines and local information on the prevalence of resistance to antimalarial drugs should be taken into consideration. Official guidelines will normally include WHO and public health authorities guidelines.

4.2 Dose and method of administration

The daily dose should be taken with food or a milky drink at the same time each day.

In the event of vomiting, within 1 hour of dosing, a repeat dose should be taken.

Promozio (250/100) should be swallowed whole.

Prophylaxis

Prophylaxis should start 1 to 2 days before entering a malaria-endemic area, and be continued daily until seven days after leaving the area.

If patients are unable to tolerate food, Promozio 250/100 tablets should be administered, but systemic exposure of atovaquone will be reduced.

Dosage in Adults:

One Promozio 250/100 tablet daily.

Treatment

Dosage in Adults:

Four tablets (total daily dose 1 g atovaquone/400 mg proguanil hydrochloride) as a single dose for three consecutive days.

Dosage in the Elderly (Prophylaxis and Treatment):

A pharmacokinetic study indicates that no dosage adjustments are needed in the elderly (see Section 5.2 Pharmacokinetic properties - Pharmacokinetics in the elderly).

Dosage in Hepatic Impairment (Prophylaxis and Treatment):

A pharmacokinetic study indicates that no dosage adjustments are needed in patients with mild to moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment. (see Section 5.2 Pharmacokinetic properties - Pharmacokinetics in hepatic impairment).

Dosage in Renal Impairment (Prophylaxis and Treatment):

Pharmacokinetic studies indicate that no dosage adjustments are needed in patients with mild to moderate renal impairment. In patients with severe renal impairment (creatinine clearance < 30 mL/min) alternatives to Promozio 250/100 should be recommended for the treatment of acute *P. falciparum* malaria whenever possible (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties - Pharmacokinetics in renal impairment). For prophylaxis of *P. falciparum* malaria in patients with severe renal impairment see Section 4.3 Contraindications.

4.3 Contraindications

Promozio 250/100 is contraindicated in individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or to any component of the formulation.

Promozio 250/100 is contraindicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance < 30 mL/min).

4.4 Special warnings and precautions for use

Promozio 250/100 has not been evaluated for the treatment of cerebral malaria or other severe manifestations of complicated malaria including hyperparasitaemia, pulmonary oedema or renal failure.

Safety and efficacy of atovaquone/proguanil hydrochloride combination tablet (250/100) for the treatment and prophylaxis of malaria in paediatric patients who weigh less than 11 kg have not been established.

In the event of recrudescent infections due to *P. falciparum* or failure of chemoprophylaxis, patients should be treated with a different blood schizonticide.

Parasite relapse occurred commonly when *P. vivax* malaria was treated with atovaquone/proguanil hydrochloride combination tablet (250/100) alone. Travellers with intense exposure to *P. vivax* or *P. ovale*, and those who develop malaria caused by either of these parasites, will require additional treatment with a drug such as primaquine that is active against hypnozoites.

Persons taking Promozio 250/100 for prophylaxis or treatment of malaria should take a repeat dose if they vomit within 1 hour of dosing. In the event of diarrhoea, normal dosing should be continued. Absorption of atovaquone may be reduced in patients with diarrhoea or vomiting, but diarrhoea or vomiting was not associated with reduced efficacy in clinical trials of atovaquone/proguanil hydrochloride combination tablet for malaria prophylaxis. However, as with other antimalarial agents, patients with diarrhoea or vomiting should be advised to continue to comply with personal protection measures (repellents, bed nets).

In patients with acute malaria who present with diarrhoea or vomiting, alternative therapy should be considered. If Promozio 250/100 is used to treat malaria in these patients, parasitaemia should be closely monitored.

The co-administration of Promozio 250/100 with other antimalarial drugs has not been evaluated.

Parasitaemia should be closely monitored in patients receiving concurrent metoclopramide or tetracycline (see Section 4.5 Interactions with other medicines and other forms of interaction).

The concomitant administration of atovaquone/proguanil hydrochloride combination tablet and rifampicin or rifabutin is not recommended (see Section 4.5 Interactions with other medicines and other forms of interaction).

Renal Impairment

Pharmacokinetic studies indicate that no dosage adjustments are needed in patients with mild to moderate renal impairment. In patients with severe renal impairment (creatinine clearance < 30 mL/min) alternatives to Promozio 250/100 for treatment of acute *P. falciparum* malaria should be recommended whenever possible (see Section 4.2 Dose and method of administration, Section 4.3 Contraindications and Section 5.2 Pharmacokinetic properties - Pharmacokinetics in renal impairment).

Hepatic Impairment

Pharmacokinetic studies indicate that no dosage adjustments are needed in patients with mild to moderate hepatic impairment. Promozio 250/100 has not been specifically studied in patients with severe hepatic impairment.

4.5 Interaction with other medicines and other forms of interaction

Proguanil may potentiate the anticoagulant effect of warfarin and other coumarin based anticoagulants. The mechanism of this potential drug interaction has not been established. Caution is advised when initiating or withdrawing malaria prophylaxis or treatment with Promozio 250/100 in patients on continuous treatment with coumarin based anticoagulants.

Concomitant treatment with tetracycline, metoclopramide, rifampicin and rifabutin have been associated with significant decreases in plasma concentration of atovaquone (see Section 4.4 Special warnings and precautions for use). Concomitant administration of atovaquone and indinavir results in a 23% decrease in the C_{min} of indinavir in healthy individuals. Caution should be exercised when prescribing atovaquone with indinavir due to the decrease in trough levels of indinavir.

Atovaquone is highly protein bound (>99%) but does not displace other highly protein bound drugs *in vitro*, indicating significant drug interactions arising from drug displacement are unlikely.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy (Category B2)

The safety of atovaquone and proguanil hydrochloride when administered concurrently for use in human pregnancy has not been established.

Reproductive toxicity studies in animals did not indicate any teratogenic potential at dosages of atovaquone: proguanil hydrochloride of up to 50:20mg/kg/day in the rat or 100:40mg/kg/day in the rabbit. In rabbits given atovaquone alone at dosages up to 1200mg/kg/day, an increased incidence of resorptions and decreased length and weight of foetuses was noted. These effects were likely to be secondary to toxicity of atovaquone in maternal animals.

However, as animal studies are not always predictive of human response the use of Promozio 250/100 in pregnancy should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

The proguanil component of acts by inhibiting parasitic dihydrofolate reductase. There are no clinical data indicating that folate supplementation diminishes drug efficacy. For women of childbearing age receiving folate supplements to prevent neural tube birth defects, such supplements may be continued while taking Promozio 250/100.

Use in Lactation

The atovaquone concentrations in milk, in a rat study, were 30% of the concurrent atovaquone concentrations in maternal plasma. It is not known whether atovaquone is excreted in human milk.

Proguanil is excreted in human milk in small quantities.

It is not recommended that mothers receiving Promozio 250/100 breast feed their babies.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of atovaquone and proguanil hydrochloride on driving performance or the ability to operate machinery. Detrimental effect on such activities is not predicted from the pharmacology of the component drugs.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000). Very common, common and uncommon events were determined from clinical trial data. Rare and very rare events were generally derived from spontaneous data. The frequency classification "Not known" has been applied to those events where a frequency could not be estimated from the available data.

Promozio 250/100 contains atovaquone and proguanil hydrochloride, therefore, the adverse effects associated with each of these compounds may be expected with Promozio 250/100. At the doses employed for both treatment and prophylaxis of malaria, adverse events are genrally mild and of limited duration. There is no evidence of added toxicity following concurrent administration fo atovaquone and proguanil.

A summary of adverse events associated with the use of Promozio 250/100, atovaquone or proguanil hydrochloride is provided below:

Blood and Lymphatic system disorders

Common:	Anaemia[1], neutropenia[2]
Not known:	Pancytopenia in patients with severe renal impairment[4]

Immune system disorders

Not known: Angioedema[4], anaphylaxis[3], vasculitis[4]

Metabolism and nutritional disorders

Common: Hyponatraemia[2,] Anorexia[1]

Uncommon: Elevated amylase levels[2]

Psychiatric disorders

Rare: Hallucinations[1]

Nervous system disorders

Very common: Headache[1]

Common: Insomnia[1], dizziness[1]

Gastrointestinal disorders

Very common: Abdominal pain[1], nausea[2], vomiting[1], diarrhoea[1]

Uncommon: Stomatitis[1]

Not known: Gastric intolerance[4], oral ulceration[4]

Hepatobiliary disorders

Common: Elevated liver enzyme levels[2]

Not known: Hepatitis[3], Cholestasis[4]

Clinical trial data for atovaquone/proguanil hydrochloride combination tablet indicated that abnormalities in liver function tests were reversible and not associated with untoward clinical events.

Skin and subcutaneous tissue disorders

Common: Rash[1]

Uncommon: Hair loss[1], urticaria[1]

Not Known: Stevens-Johnson syndrome[3], erythema multiforme[3]

General disorders and administration site conditions

Common: Fever[1]

Respiratory, thoracic and mediastinal disorders

Common: Cough[1]

1. Frequency calculated from atovaquone-proguanil clinical trials.
2. Frequency taken from atovaquone label. Patients participating in clinical trials with atovaquone have received higher doses and have often had complications of advance Human Immunodefficiency Virus (HIV) disease. Therefore, the casual relationship between the adverse experiences and atovaquone is difficult to evaluate. These events may have been seen at a lower frequency or not at all in clinical trials with atovaquone-proguanil.
3. Observed from post-marketing spontaneous reports and the frequency is therefore Not known.
4. Observed with proguanil and the frequency is therefore Not known.

In clinical trials of atovaquone/proguanil hydrochloride combination tablet for prophylaxis of malaria, the most commonly reported adverse events, independent of attributability, were headache, abdominal pain and diarrhoea, and were reported in a similar proportion of subjects receiving atovaquone/proguanil hydrochloride combination tablet or placebo.

In clinical trials of atovaquone/proguanil hydrochloride combination tablet for treatment of malaria, the most commonly reported adverse events, independent of attributability, were abdominal pain, headache, anorexia, nausea, vomiting, diarrhoea and coughing and were generally reported in a similar proportion of patients receiving atovaquone/proguanil hydrochloride combination tablet or a comparator antimalarial medicine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

4.9 Overdose

In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mode of action

The constituents of Promozio 250/100, atovaquone and proguanil hydrochloride interfere with two different pathways in the biosynthesis of pyrimidines, required for nucleic acid replication. The mechanism of action of atovaquone against *P. falciparum* is via inhibition of mitochondrial electron transport, at the level of the cytochrome bc_1 complex, and collapse of mitochondrial membrane potential. One mechanism of action of proguanil, via its metabolite cycloguanil, is inhibition of dihydrofolate reductase, which disrupts deoxythymidylate synthesis. Proguanil also has antimalarial activity independent of its metabolism to cycloguanil, and proguanil, but not cycloguanil, is able to potentiate the ability of atovaquone to collapse mictochondrial membrane potential in malaria parasites. This latter mechanism may explain the synergy seen when atovaquone and proguanil are used in combination, as in Promozio 250/100.

Microbiology

Atovaquone is active against *Plasmodium spp* (*in vitro* IC_{50} against *P. falciparum* 0.23-1.43 ng/mL).

The antimalarial activity of proguanil is exerted via the primary metabolite cycloguanil (*in vitro* IC_{50} against various *P. falciparum* strains of 4-20 ng/mL). Some activity of proguanil and another metabolite, 4-chlorophenylbiguanide, is seen *in vitro* at 600-3000 ng/mL.

In *in vitro* studies of *P. falciparum*, the combination of atovaquone and proguanil was shown to be synergistic. This enhanced efficacy was also demonstrated in clinical studies.

5.2 Pharmacokinetic properties

There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose.

Absorption

Atovaquone is a highly lipophilic compound with low aqueous solubility and poor oral bioavailability that varies with dose and diet.

Although there are no atovaquone bioavailability data in healthy subjects, in HIV-infected patients the absolute bioavailability of a 750 mg single dose of atovaquone tablets taken with food is 21% (90% CI: 17% - 27%).

Dietary fat taken with atovaquone increases the rate and extent of absorption. When taken with a standard breakfast containing 23 g of fat, AUC was increased 2-3 times and C_{max} 5 times compared with fasting. Patients are recommended to take Promozio 250/100 tablets with food or a milky drink (see Section 4.2 Dose and method of administration).

Proguanil hydrochloride is rapidly and extensively absorbed regardless of food intake. Peak plasma concentrations occur between 2-4 hours after a single 200 mg dose. The absolute bioavailability is not known.

In a comparative bioavailability study in healthy adult volunteers, atovaquone 250 mg and proguanil 100 mg combination tablet administered as a single dose was bioequivalent to separate tablets of atovaquone 250 mg and proguanil hydrochloride 100 mg given concomitantly. In healthy adult subjects treated for 3 days, the pharmacokinetics of atovaquone, and proguanil and its metabolite cycloguanil, were not modified when atovaquone and proguanil were given alone or in combination as atovaquone 250 mg and proguanil 100 mg combination tablet.

Distribution

Apparent volume of distribution of atovaquone and proguanil is a function of body weight.

Atovaquone is highly protein bound (>99%) but does not displace other highly protein bound drugs *in vitro*, indicating significant drug interactions arising from displacement are unlikely.

Following oral administration, the volume of distribution of atovaquone in adults is approximately8.8 L/Kg.

Proguanil is 75% protein bound. Following oral administration, the volume of distribution of proguanil in adults weighing 41 to 80 kg is 42 to 27 L/Kg.

In human plasma the binding of atovquone and progunil were unaffected by the presence of the other.

Metabolism

There is no evidence that atovaquone is metabolised. Greater than 90% of atovaquone is eliminated unchanged in the faeces with negligible excretion in urine.

Proguanil hydrochloride is partially metabolised to cycloguanil and 4-chlorophenyl biguanide with less than 40% being excreted unchanged in urine. These metabolites are also excreted in the urine. Conversion of proguanil to cycloguanil is mediated in the liver by cytochrome P450 3A4 and 2C19. Conversion of proguanil to cycloguanil may be reduced in some individuals, due to genetic polymorphism of the metabolising enzyme. During administration with Promozio 250/100, at the recommended doses, proguanil metabolism status appears to have no implications for treatment or prophylaxis of malaria.

Elimination

The elimination half-life of atovaquone is about 2-3 days in adults.

Oral clearance of atovaquone and progunil is a function of body weight.

Following oral administration, the clearance of atovaquone in adults weighing 41 to 80 kg is approximately 0.16 to 0.05 L/h/kg.

Following oral administration, the clearance of proguanil in adults weighing 41 to 80 kg is 1.6 to 0.85 L/h/kg.

In adults the elimination half life for proguanil or cycloguanil is about 12-15 hours.

Pharmacokinetics in the elderly

There is no clinically significant change in the average rate or extent of absorption of atovaquone or proguanil between elderly and young patients. Systemic availability of cyloguanil is higher in the elderly compared with young patients, but there is no clinically significant change in its elimination half-life (see Section 4.2 Dose and method of administration).

Pharmacokinetics in renal impairment

In patients with mild to moderate renal impairment, oral clearance and/or AUC data for atovaquone, proguanil and cycloguanil are within the range of values observed in patients with normal renal function. Atovaquone C_{max} and AUC are reduced in patients with severe renal impairment. The elimination half lives for proguanil and cycloguanil are prolonged in patients with severe renal impairment with corresponding increases in AUC, resulting in the potential of drug accumulation with repeated dosing (see Section 4.2 Dose and method of administration, Section 4.3 Contraindications, and Section 4.4 Special warnings and precautions for use).

Pharmacokinetics in hepatic impairment

In patients with mild to moderate hepatic impairment, there is no clinically significant change in exposure to atovaquone compared with healthy patients. In patients with mild to moderate hepatic impairment there is an increase in proguanil AUC with no change in its elimination half life and there is a decrease in C_{max} and AUC for cycloguanil. No data are available in patients with severe hepatic impairment. (See Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use).

5.3 Preclinical safety data

Repeat dose toxicity:

Findings in repeat dose studies with the atovaquone:proguanil hydrochloride combination were entirely proguanil related. As proguanil has been used extensively and safely in the treatment and prophylaxis of malaria at doses similar to those used in Promozio 250/100, these findings are considered of little relevance in the clinical situation.

Mutagenicity:

A wide range of mutagenicity tests have shown no evidence that atovaquone or proguanil have mutagenic activity as single agents.

Mutagenicity studies have not been performed with atovaquone in combination with proguanil.

Cycloguanil, the active metabolite of proguanil, was also negative in the Ames test, but was positive in the Mouse Lymphoma assay and the Mouse Micronucleus assay. These positive effects with cycloguanil (a dihydrofolate antagonist) were significantly reduced or abolished with folinic acid supplementation.

Carcinogenicity:

Oncogenicity studies of atovaquone alone in mice showed an increased incidence of hepatocellular adenomas and carcinomas. No such findings were observed in rats and mutagenicity tests were negative. These findings appear to be due to the inherent susceptibility of mice to atovaquone and are considered of no relevance in the clinical situation.

Oncogenicity studies on proguanil alone showed no evidence of carcinogenicity in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Hyprolose

Sodium starch glycollate type A

Poloxamer

Povidone

Colloidal anhydrous silica

Magnesium stearate

Opadry complete film coating system 03C86943 BROWN.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store tablets below 25°C.

6.5 Nature and contents of container

Promozio 250/100 tablets are provided in PVC-PVDC/Al blister packs of 12 or 24 tablets.

Not all pack sizes are marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Australia

sanofi-aventis australia pty ltd

Building D, 12-24 Talavera Road

Macquarie Park NSW 2113

Australia

Tel: 1800 818 806

New Zealand

sanofi-aventis new zealand pty ltd

Level 8

56 Cawley St

Ellerslie

Auckland

New Zealand

Tel: 0800 727 838

9 DATE OF FIRST APPROVAL

20 July 2017

10 DATE OF REVISION OF THE TEXT

07 April 2020

Summary table of changes:

Section changed	Summary of new information
All	Editorial
4.8	Standard statement added