▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

KOZENIS (TAFENOQUINE) TABLETS AND DISPERSIBLE TABLETS

1 NAME OF THE MEDICINE

Tafenoquine succinate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

150 mg film-coated tablets:

Each tablet contains 188.2 mg of tafenoquine succinate (equivalent to 150 mg of tafenoquine).

Each tablet also contains 162.8 mg of the excipient mannitol. For a full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

50 mg film-coated dispersible tablets:

Each dispersible tablet contains 62.74 mg of tafenoquine succinate (equivalent to 50 mg of tafenoquine).

For a full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

150 mg film-coated tablets for oral administration:

Pink, film-coated, capsule-shaped tablets, plain on one side and debossed with 'GS J11' on the other side.

50 mg film-coated dispersible tablets for oral administration:

Yellow, film-coated, round-shaped dispersible tablets, plain on one side and debossed with "GS INC" on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Tafenoquine is indicated, in combination with chloroquine, for the radical cure (prevention of relapse) of *Plasmodium vivax* (*P. vivax*) malaria (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

4.2 DOSE AND METHOD OF ADMINISTRATION

All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing tafenoquine (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Pregnancy should be excluded prior to the use of tafenoquine in females of child bearing potential (see Section 4.3 CONTRAINDICATIONS and Section 4.6 FERTILITY, PREGNANCY AND LACTATION).

Do not break or crush the 150 mg tablets or 50 mg dispersible tablets. Tafenoquine should be taken with food to increase systemic absorption (see Section 5.2 PHARMACOKINETIC PROPERTIES). In the event of vomiting within 60 minutes after dosing, a repeat dose should be given. Paediatric patients should be monitored for vomiting (or for spitting out their dose) (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Re-dosing should not be attempted more than once and is not recommended if vomiting occurs 60 minutes or longer after initial dosing.

Tafenoquine should be co-administered with chloroquine on the first or second day of the three days chloroquine administration for the treatment of acute *P.vivax* malaria.

Tafenoquine is NOT indicated for the treatment of acute *P. vivax* malaria. Consideration should be given to official guidance on the appropriate use of antimalarial medicinal products in areas where chloroquine is not recommended.

Concomitant use of tafenoquine with dihydroartemisinin-piperaquine is not recommended (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). The efficacy and safety of tafenoquine with antimalarials other than chloroquine have not been established.

There are no data regarding the subsequent re-treatment of recurrent *P. vivax* infection with tafenoquine following initial dosing.

Populations

Adults, Adolescents and children weighing greater than 35 kg

A single 300 mg dose (two 150 mg tafenoquine tablets) is recommended to be given on Day 1 or Day 2 of the 3 day course of chloroquine (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

Adolescents and children (≥2 years of age) weighing >10 kg and ≤35 kg

The recommended dose of tafenoquine dispersible tablets is determined according to weight and is presented in Table 1.

Table 1. Dispersible tablet dose recommendations for patients ≥2 years of age and weighing >10 kg to ≤ 35 kg

Body Weight (kg)	Total Dose*	Number of Tablets
> 10 to ≤ 20	100 mg	Two 50 mg dispersible tablets
> 20 to ≤ 35	200 mg	Four 50 mg dispersible tablets

*Single dose to be taken on Day 1 or Day 2 of the 3-day course of chloroquine

The 50 mg dispersible tablet(s) should be fully dissolved before swallowing. Only water should be used for dissolution. The amount of water for dissolution will depend on the number of tablets prescribed (See the Instructions for Use leaflet in the 50 mg dispersible tablet packaging for complete administration instructions with illustrations). Read the Instructions for Use before starting the therapy.

The dose recommendations in Table 1 above are based on pharmacokinetic modelling. The doses across the body-weight bands were selected to achieve plasma drug levels comparable to those in adults & adolescents at the approved clinical dose (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Children less than 2 years of age

The use of tafenoquine in children < 2 years of age is not recommended as the safety and efficacy of tafenoquine have not been established in this age group.

Elderly (65 years or older)

There are limited data available on the use of tafenoquine in patients aged 65 years and older. However, there is no evidence that elderly patients require a different dose than younger adult patients (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Renal Impairment

Tafenoquine has not been studied in patients with renal impairment. Dose adjustments in patients with renal impairment are unlikely to be required as tafenoquine is administered as a single one-time dose.

Hepatic Impairment

Tafenoquine has not been studied in patients with hepatic impairment. Dose adjustments in patients with hepatic impairment are unlikely to be required as tafenoquine is administered as a single one-time dose.

4.3 CONTRAINDICATIONS

Tafenoquine is contraindicated in the following:

- G6PD deficiency or unknown G6PD status due to the risk of haemolytic anaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION).

- Breastfeeding an infant who is G6PD deficient or if the G6PD status of the infant is unknown (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION).
- Patients with known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any component of the formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haemolytic anaemia and G6PD deficiency

Due to the risk of haemolytic anaemia in patients with G6PD deficiency or unknown G6PD status, quantitative G6PD testing must be performed before prescribing tafenoquine (see Section 4.3 CONTRAINDICATIONS). Withhold tafenoquine from patients with G6PD enzyme levels <70% of normal (see section 5.2 PHARMACOKINETIC PROPERTIES). Monitor patients for clinical signs or symptoms of haemolytic anaemia. Advise patients to seek medical attention if signs of haemolytic anaemia occur.

Methaemoglobinaemia

Asymptomatic elevations in methaemoglobin were observed in clinical studies (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). If signs or symptoms of methaemoglobinaemia occur, appropriate therapy should be instituted. Caution is advised in patients with nicotinamide adenine dinucleotide (NADH)-dependent methaemoglobin reductase deficiency.

Psychiatric Effects

Mild to moderate, psychiatric adverse reactions (e.g. anxiety, abnormal dreams) have been reported in clinical trials of tafenoquine (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). While there were no reports of serious psychiatric adverse reactions in clinical trials following a single 300 mg dose, cases of depression and psychosis have occurred following higher single doses (350 to 600 mg) of tafenoquine, mostly in subjects with a previous history of psychiatric disorders. Serious psychiatric disorders such as psychosis and depression have been associated with some quinoline anti-malarials. Caution is advised when administering tafenoquine to patients with a current or past history of serious psychiatric disorders. Individual patient risk-benefit should be assessed. Due to the long half-life of tafenoquine (15 days), psychiatric effects and hypersensitivity reactions may be delayed in onset and/or duration.

Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g. angioedema, urticaria) have been observed with administration of KOZENIS (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Institute appropriate therapy if hypersensitivity reactions occur. Do not re-administer KOZENIS.
Inform patients that hypersensitivity reactions have occurred with KOZENIS. Advise patients of the symptoms of hypersensitivity reactions and instruct them to seek medical advice promptly if such symptoms occur.

Long Acting Properties of Tafenoquine

Due to the long half-life of tafenoquine, the onset and/or duration of potential adverse reactions could be delayed up to three months. Advise patients to seek medical attention if delayed reactions occur.

Use in the elderly
Refer to section DOSE AND METHOD OF ADMINISTRATION, Elderly (65 years or older).

Paediatric use
Refer to section DOSE AND METHOD OF ADMINISTRATION, Children and Adolescents (up to 16 years of age).

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Tafenoquine is an inhibitor of human transporters organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE) *in vitro*, potentially resulting in increased exposure to their substrates (e.g., dofetilide) (see Section 5.2 PHARMACOKINETIC PROPERTIES). There is a small risk of lactic acidosis due to increased metformin exposure secondary to blockade of these transporters. Therefore, use with caution with metformin. Drugs with a narrow therapeutic index that are substrates of the renal transporters OCT2 and MATE should not be co-administered (e.g. phenformin, buformin, dofetilide, procainamide, and pilsicainide).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a rat fertility study, tafenoquine was given orally at 1.5, 5, and 15 mg/kg/day (up to about 0.5 times the human dose based on body surface area comparisons) to males for at least 67 days, including 29 days prior to mating, and to females from 15 days prior to mating through early pregnancy. Tafenoquine resulted in reduced number of viable foetuses, implantation sites, and corpora lutea at 15 mg/kg in the presence of maternal toxicity (mortality, piloerection, rough coat, and reduced body weight).

Use in pregnancy

(Category C)

Tafenoquine is contraindicated in pregnancy. There is a risk of haemolysis in patients with G6PD deficiency; and, even if a pregnant woman is not G6PD deficient, the foetus may be deficient in G6PD.

The effect of tafenoquine on human pregnancy is unknown. Tafenoquine resulted in dose related abortions when given orally to pregnant rabbits during organogenesis (GD 6 to 18), at doses of 7 mg/kg (about 0.4 times the clinical exposure based on body surface area comparisons) and above. Doses higher than 7 mg/kg were also associated with maternal toxicity (mortality and reduced body weight gain). In a similar study in rats, doses of 3, 10, or 30 mg/kg/day resulted in maternal toxicity (enlarged spleen, reduced body weight and reduced food intake) but no fetotoxicity, at the high-dose (equivalent to the clinical exposure based on body surface area comparisons). There was no evidence of malformations in either species. It is unknown if tafenoquine crosses the placenta. Women of child-bearing potential should have a pregnancy test prior to starting treatment with tafenoquine and avoid becoming pregnant for 3 months after taking tafenoquine.

Use in lactation

It is not known whether tafenoquine is excreted in human milk. In a pre- and postnatal development study in rats, tafenoquine administered throughout pregnancy and lactation produced maternal toxicity and a reversible decrease in offspring body weight gain and decrease in motor activity; at 18 mg/kg/day, which is equivalent to about 0.6 times the clinical dose based on body surface area comparisons.

Tafenoquine should not be used during breastfeeding when the infant has G6PD deficiency or the status is unknown as haemolytic anaemia may occur (see Section 4.3 CONTRAINDICATIONS).

Tafenoquine should only be used in a nursing mother if the expected benefit justifies the risk to an infant that is not G6PD deficient. Consideration should be given to the long half-life for tafenoquine as the drug may be present in the systemic circulation for 3 months following treatment with tafenoquine (see Section 5.2 PHARMACOKINETIC PROPERTIES).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of tafenoquine on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of tafenoquine. The clinical status of the patient and the adverse event profile of tafenoquine should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

The adverse drug reaction profile in patients aged 16 years and older was evaluated in 3 randomised, double-blind studies including a total 483 patients administered 300 mg tafenoquine in a single oral dose co-administered with chloroquine phosphate (600 mg free base on Days 1 and 2 with 300 mg free base on Day 3). Two of these studies were placebo-controlled and the third was an active-controlled study. The safety profile was also informed by supportive clinical studies, some of which included healthy volunteers who received the indicated dose. In the clinical development program supporting the approval of the single 300 mg dose, a total of 810 subjects received a single dose of tafenoquine 300 mg (>4,000 subjects received tafenoquine including other doses or regimens).

Adverse reactions are listed below by MedDRA body system organ class and by frequency.

The frequency categories used are:

Very common	$\geq$ 1 in 10
Common	$\geq$ 1 in 100 and < 1 in 10
Uncommon	$\geq$ 1 in 1,000 and < 1 in 100
Rare	< 1 in 1,000

System organ class	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders		Haemoglobin decreased Elevated methaemoglobin		
Immune system disorders				Hypersensitivity reactions (e.g. urticaria, angioedema)
Psychiatric disorders		Insomnia	Anxiety	Abnormal dreams
Nervous system disorders		Headache Dizziness	Somnolence	
Eye disorders			Photophobia Vortex keratopathy	
Gastrointestinal disorders		Nausea Vomiting		
Hepatobiliary disorders			Alanine aminotransferase increased	
Renal and urinary disorders		Blood creatinine increased		

Paediatric population

The paediatric clinical trial data is limited to 60 patients (2 to 15 years of age) in TAF113577 trial. The adverse effects profile in this trial was similar to that observed previously in the adult population. However, vomiting was reported in 12/60 (20%) of patients who received the recommended doses of either 150 mg tablets or 50 mg tablets as a single dose. Of these patients, 5 patients vomited, and 2 patients spat out the medication within 60 minutes of administration requiring re-dosing.

There is no clinical trial experience in children <2 years of age.

No post-market data are currently available.

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 https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Haemolysis and methaemoglobinaemia may be encountered in an overdose.

Treatment

There is no specific treatment for an overdose with tafenoquine. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Further management should be as clinically indicated or as recommended by the national poisons centre.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: P01BA07

Mechanism of action

Tafenoquine, an 8-aminoquinoline, eradicates *P. vivax* liver hypnozoites, preventing the relapse of malaria. The molecular target of tafenoquine is not known.

Clinical trials

Combination with Chloroquine

Adults and adolescents

The TAF112582 trial was a double-blind, randomised, controlled clinical trial of 522 adults positive for *P. vivax* in 3 regions (Asia, Africa, and Latin America). All patients received chloroquine phosphate (600 mg free base on Days 1 and 2 and 300 mg free base on Day 3) to treat the acute *P.vivax* malaria and were randomised to one of the following: a one-time dose of tafenoquine (two 150 mg tablets) on Day 1 or Day 2 (N=260), primaquine 15 mg once daily for 14 days starting Day 2 (N=129), or placebo (N=133). Patients included in the study had a mean age of 35 (range 15-79 years), were primarily male (75%), and from the following regions: 70% South America (Brazil and Peru), 20% Southeast Asia (Thailand, Cambodia and the Philippines), and 11% Africa (Ethiopia). All patients enrolled in the study had a positive blood film for *P. vivax*. Those with mixed malaria infections were excluded.

The primary endpoint was recurrence-free efficacy 6 months post-dosing for tafenoquine added to chloroquine compared to chloroquine alone. Patients were considered recurrence-free if they

demonstrated initial parasite clearance, took no anti-malarial medications, and were confirmed parasite-free at the final assessment (i.e., absence of relapse or new infection).

Due to the risk of haemolytic anaemia, patients were excluded from the study if they had a G6PD enzyme level <70% of the site median value for G6PD normals. An assay validation study determined G6PD eligibility requirements for the pivotal trials and found global median G6PD activity was 8.2 IU/gHb, with 70% of median at 5.7 IU/gHb (at 30ºC using Trinity® assay). Regional G6PD values (70% of median) were similar across the studied regions: 5.8 for South America, 5.6 for SE Asia, 5.7 for Africa). In this trial, the minimum G6PD enzyme level of any subject was 5.4 IU/gHb.

The recurrence-free efficacy rates at 6 months amongst treatment groups are presented for the overall population in Table 2. The risk of recurrence for tafenoquine plus chloroquine was reduced by 70% compared to chloroquine alone.

Table 2. Recurrence-free efficacy at 6 months – Overall Population[a]

	Tafenoquine/ Chloroquine (n = 260)	**Primaquine/ Chloroquine[d] (n = 129)**	**Chloroquine (n = 133)**
Recurrence-free efficacy[b] (95% CI)	62% (55, 69)	70% (60, 77)	28% (20, 36)
HR[c] - (95% CI) difference from chloroquine p value	0.30 (0.22, 0.40) <0.001	0.26 (0.18, 0.39) <0.001	

a. Microbiologic intent to treat population; survival analysis
b. Kaplan-Meier Estimate
c. Hazards ratio of the risk of recurrence versus chloroquine alone obtained from a Cox's proportional hazards model with treatment and region as covariates.
d. Statistical comparisons for efficacy cannot be made between tafenoquine/chloroquine and primaquine/chloroquine as the study was not powered for this comparison.

Paediatric patients

An open-label, single arm, multicentre trial (TAF113577) evaluated tafenoquine in the treatment of paediatric patients with *P. vivax* malaria. Sixty patients (aged at least 2 to 15 years) with confirmed *P. vivax* infection and greater than or equal to 70% normal G6PD levels were treated with chloroquine phosphate according to local guidelines followed by a weight-based dose of tafenoquine on Day 1 (as a single dose taken with food). Patients included in the study were from South America (Colombia) and Southeast Asia (Vietnam) and all *P. falciparum* negative at baseline. The trial was open for patients aged 6 months to 2 years (weighing at least 5 kg), but no patients in this weight group were enrolled.

The efficacy data from this trial is limited as the study was uncontrolled and was not intended as an efficacy study. Its objective was to test the dispersible formulation of tafenoquine and to develop an algorithm for weight-based dosing in young infants through a population pharmacokinetic analysis.

All enrolled patients (N=60) had microscopically confirmed *P. vivax* parasitaemia at baseline and 58/60 (97%) were successfully dosed.

Results for recurrence-free efficacy at 4 months post-dosing were based on the microbiologic intent to treat population (n=60). The overall Kaplan Meier Estimate of the recurrence-free rate over 4 months was 95% (95% CI: 85%, 98%).

Table 3: Recurrence free survival over 4 months of follow up (mITT population)

	TQ 100 mg (n=14)	**TQ 150 mg (n=5)**	**TQ 200 mg (n=22)**	**TQ 300 mg (n=19)**	**Total (n=60)**
Recurrence-free efficacy at 4 months					
Subjects, n (%)	12(86)	4 (80)	20 (91)	17 (89)	53 (88)
Recurrence-free efficacy rate at 4 months[a]					
Subjects with confirmed recurrence prior to or at 4 months n (%)	1 (7)	0	2 (9)	0	3 (5)
Estimate					95%
95% CI					85%, 98%

Note: Weight bands were: TQ 100 mg: >10 - ≤20 kg (Cohort 2 and 3); TQ 150 mg: >10 - ≤20 kg (Cohort 1); TQ 200 mg: >20 - ≤35 kg; TQ 300 mg: >35 kg.
Tafenoquine was given in combination with chloroquine for all doses.

a. Kaplan-Meier Estimate.

Combination with Dihydroartemisinin-Piperaquine

A double-blind, randomised, placebo-controlled trial (Study 200894) evaluated the efficacy and safety of tafenoquine co-administered with dihydroartemisinin-piperaquine (DHA-PQP) for the radical cure of *P.vivax* malaria. The 150 male patients included in the trial had a mean age of 29 (range 21-49) years and contracted *P.vivax* in the Papua region of Indonesia. All patients received open-label DHA-PQP (three or four 320/40 mg tablets dosed according to weight) on Days 1 through 3 and were randomised to one of the following: tafenoquine (two 150 mg tablets) on Days 1 or 2 (n = 50) or primaquine (one 15 mg tablet) daily for 14 days starting on Day 1 or 2 (n = 50) or placebo (n = 50).

The recurrence-free efficacy rates at 6 months among treatment groups are presented in Table 4. Tafenoquine in combination with DHA-PQP was not associated with a clinically relevant reduction in recurrence over 6 months.

Table 4. Recurrence-free efficacy at 6 months – Overall Population[a]

	Tafenoquine/ DHA-PQP (n = 50)	Primaquine/ DHA-PQP (n = 50)	DHA/PQP (n = 50)
Recurrence-free efficacy[b] (95% CI)	21% (11, 34)	52% (37, 65)	11% (4, 22)
HR[c] - (95% CI) difference from DHA/PQP	0.44 (0.29, 0.69)	0.26 (0.16, 0.43)	

DHA-PQP = dihydroartemisinin-piperaquine

a. Microbiologic intent to treat population

b. Kaplan-Meier Estimate

c. Hazard ratio of the risk of recurrence versus DHA-PQP alone obtained from a Cox's proportional hazards model.

Cardiac Electrophysiology

At a cumulative dose of 1200 mg (400 mg/day for 3 days; 4 times the maximum recommended dose), tafenoquine did not prolong the QT interval to any clinically relevant extent.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Maximum plasma concentrations were generally observed 12 to 15 hours following oral administration. Plasma AUC increased 41% and C_{max} increased 31% for tafenoquine administration with a high fat meal compared to the fasted state.

Distribution

Tafenoquine is highly plasma protein bound (>99.5%) and widely distributed (apparent oral volume of distribution >1,500 L). Following single and multiple oral dose administration, tafenoquine whole blood concentrations were on average 67% higher than corresponding plasma values, reflecting preferential partitioning of drug in the erythrocytes.

Metabolism

Tafenoquine undergoes very slow metabolism, and drug-related material is excreted slowly, both unchanged and as metabolites. Tafenoquine is the principal circulating drug-related component and there are no major systemic metabolites in humans.

Excretion

The clearance of oral tafenoquine is approximately 3 L/h based on plasma concentrations. The average terminal half-life is approximately 15 days. Definitive elimination data in humans has not been generated, although slow elimination of drug related material in urine is evident. In nonclinical species drug-related material is eliminated slowly in both urine and faeces (which includes some biliary secretion).

Special Patient Populations

Paediatric patients

The pharmacokinetics of tafenoquine following administration of dispersible 50 mg tablets was evaluated in the TAF113577 trial. The trial included patients aged 2 to 15 years. Pharmacokinetic modelling was performed to predict the dose and exposures for patients by weight. Weight based dosing of paediatric patients provides comparable exposure to that associated with the administration of a single 300 mg dose in adults and adolescents aged 16 years or older. Based on the dose-ranging trial TAF112582 Part 1, the median AUC for the tafenoquine 300 mg dose in an adult weighing 60 kg was predicted to be 96 mcg.hr/mL (95% Prediction Interval (PI) 55-162 mcg.hr/mL).

Table 5. Predicted tafenoquine exposures across weight groups

Weight Group (kg)	Tafenoquine Dose (mg)	$AUC_{0-\infty}$ (mcg.hr/mL) Median (90% PI)
≥ 5 to ≤ 10	50	73.8 (46.9 – 117)
> 10 to ≤ 20	100	87.5 (55.4 – 139)
> 20 to ≤ 35	200	110.7 (70.9 – 174)
> 35	300	85.7 (50.6 – 151)

However, no children < 2 years of age and weighing ≤10 kg could be recruited in the trial; therefore the use tafenoquine in this age group is not recommended.

Elderly patients (> 65 years old)

No formal studies have been conducted in elderly patients. In a population pharmacokinetic analysis in 675 subjects aged 15 to 79 years, there was no indication of an effect of age on the pharmacokinetics of tafenoquine.

Renal impairment

No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of tafenoquine.

Hepatic impairment

No formal studies have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of tafenoquine.

Drug Interaction Studies

Tafenoquine demonstrated *in vitro* inhibition of several CYPs including 1A2, 2A6, 2C8, 2C9 and 3A4 enzymes. Clinical studies have shown no clinically significant effects on the pharmacokinetics of substrates of CYP1A2 (caffeine), CYP2D6 (desipramine), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam, chloroquine) following oral administration of tafenoquine.

Tafenoquine inhibited *in vitro* transport of metformin via human OCT2, MATE1 and MATE2-K transporters. Assessments based on systemic concentrations (unbound Cmax) of tafenoquine at therapeutic doses, compared with the IC_{50} values derived from *in vitro* transporter inhibition studies,

were conducted and indicated a potential, but small, drug interaction risk with OCT2 and MATE substrates.

Concomitant administration of tafenoquine and chloroquine in man resulted in no clinically significant interaction.

Tafenoquine administered concomitantly with dihydroartemisinin-piperaquine (40 mg /320 mg tablets given on Day 1, and then again at 24 hours and 48 hours post first dose) increased exposure of tafenoquine AUC0-inf 12% and Cmax 38%. This change was not considered clinically relevant. There was no significant change in dihydroartemisinin or piperaquine exposure.

Concomitant administration of tafenoquine with artemether-lumefantrine (20 mg/120 mg tablets, on Day 1, and then at 8, 24, 36, 48 and 60 hours post first dose) reduced the exposure of the dihydroartemisinin metabolite of artemether by 23% and 16% for AUC(0-tau) and Cmax respectively. This change was not considered clinically significant. There was no significant change in tafenoquine, lumefantrine or artemether exposure.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tafenoquine did not cause gene mutations or chromosomal damage in two definitive *in vitro* tests (bacterial mutation assay and mouse lymphoma L5178Y cell assay), or in an *in vivo* oral rat micronucleus test.

Carcinogenicity

Two-year oral carcinogenicity studies were conducted in rats and mice. Tafenoquine was not carcinogenic in mice but was carcinogenic in rats inducing an increase in the incidence of renal cell tumours and hyperplasia in high dose (2 mg/kg/day) and mid dose (1 mg/kg/day) males compared with controls (normalised $AUC_{0\text{-}8\ weeks}$ equivalent to 5.0 and 2.4 times the human dose per $AUC_{0\text{-}\infty}$ based on a single 300 mg dose, respectively). Given the single dose administration of tafenoquine, these findings are not considered to represent a carcinogenicity risk to humans.

Animal toxicology and/or pharmacology

Tafenoquine has been evaluated in repeat dose toxicity studies of up to 13 weeks in duration in CD-1 mice, 26 weeks in Sprague Dawley rats, 52 weeks in beagle dogs and in a PK study in rhesus monkeys. Principal findings were haematological (e.g., decreased haemoglobin, increased methaemoglobin), pulmonary (e.g., increased numbers of foamy macrophages and the presence of eosinophilic material in alveoli), hepatic (e.g., increased liver weight, subacute inflammation), and renal toxicity (e.g., renal tubular lesions). The majority of these effects was both dose- and duration-dependent, and reversible upon cessation of treatment. The risk of clinically relevant toxicity outside of the known risk of haematologic effects associated with 8-aminoquinolines is low considering the single dose administration of tafenoquine.

Microbiology

Tafenoquine has demonstrated schizontocidal activity against *Plasmodium vivax* in animal models.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

150 mg film-coated tablets:

Microcrystalline Cellulose

Mannitol

Magnesium Stearate

Hypromellose

Titanium Dioxide

Iron Oxide Red

Macrogol

50 mg film-coated dispersible tablets:

Microcrystalline Cellulose

Hyprolose

Sucralose

Magnesium Stearate

Iron oxide yellow

Macrogol

Polyvinyl alcohol

Purified talc

Titanium dioxide

6.2 INCOMPATIBILITIES

No incompatibilities have been identified.

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 in the original package to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

150 mg tablets supplied in:

- Child-resistant aluminium foil blister strip.

The pack contains 2 tablets.

50 mg dispersible tablets supplied in:

- Child-resistant, aluminum foil, perforated blister strip, containing 2 tablets on one side and 1 tablet plus a dummy pocket on the other side.

The pack contains 10 blisters, with a total of 30 tablets (bulk pack), to support weight-based dosing of multiple patients.

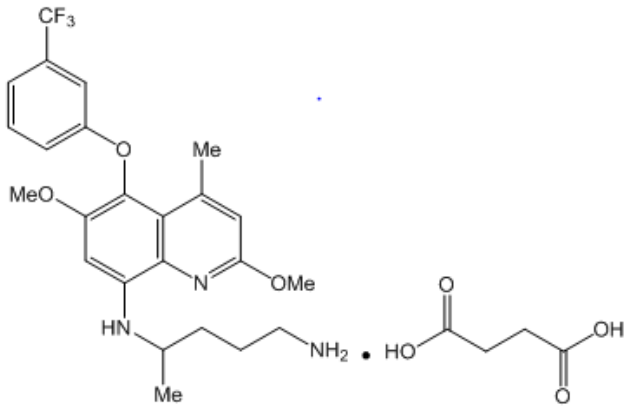
Not all presentations will be distributed in Australia.

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: $C_{24}H_{28}F_3N_3O_3$. $C_4H_6O_4$

Molecular Weight: 581.58 as the succinate salt.
463.49 as free base.

Tafenoquine succinate is a pale green or pale orange to orange solid. The pKa values for tafenoquine succinate are 10.0 and 3.0, and it is sparingly soluble at pH 2 and practically insoluble at and above pH 6 in aqueous buffer. Tafenoquine succinate contains one chiral centre and is produced as a racemate.

CAS number

CAS Registry Number: 106635-81-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd,

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

Australia

9 DATE OF FIRST APPROVAL (ARTG ENTRY)

13 September 2018

10 DATE OF REVISION

9 March 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Addition of information for 50 mg dispersible table
3	Addition of description for 50 mg dispersible tablet
4.1	Update to indication to include patients aged 2 year and older
4.2	Addition of paediatric dosing information
4.8	Addition of adverse effects information for the paediatric population
5.1	Addition of clinical trial data from TAF113577
5.2	Addition of paediatric pharmacokinetic data from study TAF113577
5.2	Clarification of dosing in studies with dihydroartemisinin-piperaquine and artemether-lumefantrine
6.1	Addition of excipients for dispersible tablets
6.5	Addition of pack information for dispersible tablets
-	Minor editorial updates throughout the document

Version 5.0