SUMMARY OF PRODUCT CHARACTERISTICS

KOZENIS

tafenoquine

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

The 150 mg tablet is pink, capsule-shaped, and debossed with ‘GS J11’ on one side.

CLINICAL INFORMATION

Indications

KOZENIS in combination with chloroquine is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria.

Dosage and Administration

Pharmaceutical Form

Film-coated tablets.

All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing *KOZENIS (see Contraindications, Warnings and Precautions)*.

KOZENIS should be co-administered with chloroquine on the first or second day of chloroquine administration.

KOZENIS should be taken with food to increase systemic absorption *(see Pharmacokinetics)*.

In the event of vomiting within 60 minutes after dosing, a repeat dose should be given. Re-dosing should not be attempted more than once and is not recommended if vomiting occurs 60 minutes or longer after initial dosing.

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

Concomitant use of *KOZENIS* with dihydroartemisinin-piperaquine is not recommended *(see Clinical Studies)*. The efficacy and safety of *KOZENIS* with antimalarials other than chloroquine have not been established. Consideration should be given to official guidance on

the appropriate use of antimalarial medicinal products in areas where chloroquine is not recommended.

Method of Administration

Adults, adolescents, and children weighing greater than 35 kg

A single 300 mg dose (two 150 mg *KOZENIS* tablets) is recommended.

Elderly (65 years or older)

There are limited data available on the use of *KOZENIS* in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients *(see Pharmacokinetics).*

Renal Impairment

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

Hepatic Impairment

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

Contraindications

KOZENIS is contraindicated in the following:

- G6PD deficiency or unknown G6PD status *(see Warnings and Precautions).*
- Pregnancy *(see Pregnancy).*
- Breastfeeding an infant who is G6PD deficient or if the G6PD status of the infant is unknown *(see Lactation).*
- Patients with known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any component of the formulation of *KOZENIS*.

Warnings and Precautions

Haemolytic anaemia and G6PD deficiency

Due to the risk of haemolytic anaemia in patients with G6PD deficiency or unknown G6PD status, G6PD testing must be performed before prescribing *KOZENIS (see Contraindications)*. Withhold *KOZENIS* from patients with G6PD enzyme levels <70% of normal *(see Clinical Studies)*. 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 Adverse Reactions)*. 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 *KOZENIS (see Adverse Reactions)*. 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 *KOZENIS*, 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 *KOZENIS* to patients with a current or past history of serious psychiatric disorders.

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.

Interactions

KOZENIS is an inhibitor of human transporters OCT2 and MATE *in vitro*, potentially resulting in increased exposure to their substrates (e.g., dofetilide) (*see Pharmacokinetics)*. 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).

Pregnancy and Lactation

Fertility

Animal studies indicate no adverse effects of *KOZENIS* on male or female fertility at concentrations comparable to those achieved at the recommended human dose *(see Non-Clinical information).*

Pregnancy

KOZENIS 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.

The effect of *KOZENIS* on human pregnancy is unknown. No fetotoxicity was observed in pregnant rats at doses equivalent to the clinical exposure based on body surface area comparisons. However, there were increased abortions in pregnant rabbits at doses equivalent to 0.4 times the clinical exposure based on body surface area comparisons *(see Non-Clinical information).*

Women of child-bearing potential should have a pregnancy test prior to starting treatment with *KOZENIS* and avoid becoming pregnant for 3 months after taking *KOZENIS*.

Lactation

It is not known whether *KOZENIS* is excreted in human milk. *KOZENIS* should not be used during breastfeeding when the infant has G6PD deficiency or the status is unknown as haemolytic anaemia may occur *(see Contraindications).*

KOZENIS 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 *KOZENIS (see Pharmacokinetics).*

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Clinical trial data

The adverse drug reaction profile in patients aged 16 years and older was evaluated in 3 randomized, 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 *KOZENIS* 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	≥ 1 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 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

Based on data from the TAF113577 trial (n=60), in paediatric patients aged at least 2 years (weighing at least 5 kg) to 15 years, there were no additional types of adverse reactions beyond those observed in the adult population. However, vomiting was reported in 20% (12/60) of patients who received the recommended doses of either 150 mg tablets or 50 mg tablets once daily. Of these patients, 5 patients vomited, and 2 patients spat out the medication within 60 minutes of administration requiring re-dosing.

Overdose

Haemolysis and methaemoglobinaemia may be encountered in an overdose.

There is no specific treatment for an overdose with *KOZENIS*. 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, where available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Microbiology

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

Cardiac Electrophysiology

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

Pharmacokinetics

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.

Elimination

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

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 IC50 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.

Clinical Studies

Combination with Chloroquine

Adults and Adolescents

The TAF112582 trial was a double-blind, randomized, controlled clinical trial of 522 adults positive for *P. vivax* in 3 regions (Asia, Africa, and Latin America). All subjects received chloroquine phosphate (600 mg free base on Days 1 and 2 with 300 mg free base on Day 3) to treat the acute infection and were randomized to one of the following: a one-time dose of *KOZENIS* (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).

The primary endpoint was recurrence-free efficacy 6 months post-dosing for *KOZENIS* 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 1. The risk of recurrence for *KOZENIS* plus chloroquine was reduced by 70% compared to chloroquine alone.

Table 1. Recurrence-free efficacy at 6 months – Overall Population[a]

	***KOZENIS* / 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 *KOZENIS*/chloroquine and primaquine/chloroquine as the study was not powered for this comparison.

Combination with Dihydroartemisinin-Piperaquine

A double-blind, randomised, placebo-controlled trial (Study 200894) evaluated the efficacy and safety of tafenoquine coadministered with dihydroartemisinin-piperaquine 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 dihydroartemisinin-piperaquine (three or four 320/40-mg tablets dosed according to weight) on Days 1 through 3 and were randomised to one of the following: *KOZENIS* (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 2. *KOZENIS* in combination with dihydroartemisinin-piperaquine was not associated with a clinically relevant reduction in recurrence over 6 months.

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

	***KOZENIS*/ 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.

NON-CLINICAL INFORMATION

Carcinogenesis/mutagenesis

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 (normalized $AUC_{0\text{-}8\ weeks}$ 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.

Tafenoquine was not mutagenic in Ames bacterial mutation tests, mouse lymphoma assays, or in a micronucleus study in rats.

Reproductive Toxicology

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. At 15 mg/kg/day, in the presence of maternal toxicity, there was reduced fertility in female rats; the number of corpora lutea, and hence numbers of implantations and numbers of viable foetuses was approximately 18% lower than controls.

Tafenoquine given orally to pregnant rats during organogenesis at doses of 3, 10 or 30 mg/kg/day produced maternal toxicity (decreased body weight gain, enlarged spleen, and reduced food intake) at ≥10 mg/kg/day in rats but no fetotoxicity at the high dose (equivalent to the clinical exposure based on body surface area comparisons). Tafenoquine resulted in dose-related abortions when given orally to pregnant rabbits during organogenesis (Gestation Days 6 to 18) at doses of 7 mg/kg (about 0.4 times the clinical exposure based on body surface area comparisons) and above. However, doses higher than 7 mg/kg were also associated with maternal toxicity (mortality and reduced body weight gain).

In a pre- and postnatal development study in rats, 18 mg/kg/day (equivalent to about 0.6 times the clinical dose based on body surface area comparisons) administered throughout pregnancy and lactation produced maternal toxicity and decreased offspring body weight gain (not observed at maturity) associated with a delay in eye opening and decrease in motor activity.

It is unknown if tafenoquine crosses the placenta.

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.

PHARMACEUTICAL INFORMATION

List of Excipients

Microcrystalline cellulose

Mannitol

Magnesium stearate

Opadry® Pink (film coat)

Shelf Life

The expiry date is indicated on the packaging.

Storage

Store in the original package to protect from moisture.

The storage conditions are detailed on the packaging.

Nature and Contents of Container

KOZENIS 150 mg film-coated tablets are supplied in either:

- Child-resistant aluminium foil blister strip.
- High density polyethylene (HDPE) opaque bottles with child resistant closure and containing a silica gel desiccant canister.

Incompatibilities

No incompatibilities have been identified.

Use and Handling

Do not break or crush the 150 mg tablets.

Read the Instructions for Use before starting the therapy.

Not all presentations are available in every country.

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