February 2025

IMPORTANT PRESCRIBING INFORMATION

Subject:	**Temporary importation of unapproved KODATEF® (tafenoquine succinate) tablets from Australia to address shortage of the FDA approved ARAKODA® (tafenoquine) tablets in the U.S.**

Dear Health Care Provider,

The purpose of this letter is to inform you that FDA approved tafenoquine, which is marketed under the brand name ARAKODA® and used for malaria prevention, will temporarily be out of stock due to a delay in completion of commercial validation of updated packaging formats. We understand the importance of continuity in malaria prophylaxis for your patients and have taken steps to ensure an alternative drug for prophylaxis is available during this time.

To prevent a drug shortage, 60 Degrees Pharma is coordinating with the Food and Drug Administration (FDA) to provide the availability of tafenoquine under the brand name KODATEF®, which is labeled for and distributed in Australia for malaria prevention. However, FDA has not approved KODATEF® for marketing in the United States.

KODATEF® is identical to ARAKODA® in terms of its active ingredient, dosage, and indication for use.

Description of Product and Packaging	
Product Name	KODATEF® (TAFENOQUINE SUCCINATE) ORAL FILM-COATED TABLETS
Product Packaging	100 mg film-coated tablets are packed in blister cards. Each blister card contains eight film-coated tablets. Each carton contains 16 film-coated tablets (two blister cards)
Product Code	258
NDC	71475-258-03
Lot Number	110939
Expiry Date	09/2027

Key Information about unapproved KODATEF®:

1. Active Ingredient: Tafenoquine (same as ARAKODA®).
2. Indication: Malaria prophylaxis, consistent with the approved use of ARAKODA®.
3. Product Packaging: KODATEF® is distributed as two blister cards, contained in a cardboard carton (not serialized and not child-resistant). The carton includes statements "Keep out of reach of children." The carton does not enclose a prescribing information insert.
4. There is a QR code on the box that reads out the lot number, GTIN, expiry information, and serial number. There is also a barcode on the box which when scanned reads out the GS-1 number.
5. Availability: KODATEF® will be available through Infuserve America, a specialty pharmacy distributor. You can direct patients to www.infuserve.com or by calling 800-886-9222.
6. There is an enclosure titled "Comparison of ARAKODA® (FDA-Approved Product) and KODATEF® (Imported Product) Prescribing Information (PI) after the KODATEF prescribing information at the end of this letter. Page 5 of this enclosure described the tablet characteristics. Pages 44 and 45 provides a comparison of carton and blister pack labels and appearance.

While this substitution is being provided as a temporary solution, we are actively working to resolve the supply constraints for FDA approved ARAKODA® and anticipate its return to availability by April 1st, 2025.

Prescriber Information:

KODATEF 100 mg film-coated tablets are packed in blister cards. Each blister card contains eight film-coated tablets. Each carton contains 16 film-coated tablets (two blister cards).

ARAKODA and KODATEF are identical in composition and appearance. The dosing requirements are the same. The potential risks are the same for both named brands.

It Is Important to Note:

1. A barcode is available on the KODATEF box that when read provides the product ID and manufacturer. This barcode does not provide the serialization number to identify individual units as is normally done for US Pharma products.

2. KODATEF does not have a medication guide. Please refer to the ARAKODA medication guide that can be found at the ARAKODA.com website.

3. Be sure that patients are tested for glucose-6-phosphate dehydrogenase deficiency prior to use.

4. The KODATEF outer carton is not child resistant.

Reporting Adverse Events

Health care providers and patients are encouraged to report adverse events in patients taking KODATEF to 60 Degrees Pharmaceuticals at 1-888-834-0225.

Adverse events, medication errors or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting Program either online, by regular mail, or by fax:

- Complete and submit the report online: https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program
- Regular mail or Fax: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form or submit by fax to 1-800-FDA-0178 (1-800-332-0178).

For any questions or concerns, please do not hesitate to contact our Medical Information Team at 888-834-0225 or micc.60P@4Cpharma.com. Additional resources and prescribing information for KODATEF® can be accessed at ARAKODA.com.

This letter is not intended as a complete description of the benefits and risks related to the use of KODATEF®. Please refer to the enclosed full prescribing information.

We deeply appreciate your understanding and cooperation in ensuring your patients continue to have access to appropriate malaria prevention options. Thank you for your commitment to their health and well-being.

Sincerely,

Geoff Dow

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Enclosure(s):

KODATEF® Full Prescribing Information
Comparison of Arakoda® (FDA-Approved Product) and Kodatef® (Imported Product) Prescribing Information (PI)

▼ 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 PI – KODATEF® (TAFENOQUINE SUCCINATE) ORAL FILM-COATED TABLETS

1 NAME OF THE MEDICINE

Tafenoquine succinate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KODATEF film-coated tablets contain 125.5 mg of the active ingredient tafenoquine succinate equivalent to 100 mg of tafenoquine free base.

For the full list of excipients, see subsection 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Each KODATEF tablet is a dark pink, capsule shaped, film-coated tablet debossed with "TQ100" onone side and plain on the other. The film-coated tablets are for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Malaria Prophylaxis

KODATEF (tafenoquine) is an antimalarial indicated for the prevention of malaria in adults 18 years of age and above for up to 6 months of continuous dosing (see **subsection 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials**).

4.2 Dose and method of administration

The recommended dosing regimen for KODATEF is shown in Table 1.

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

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

KODATEF film-coated tablets should be swallowed whole and not chewed or broken apart. KODATEF film-coated tablets canbe taken with or without food although KODATEF taken with food may be associated with better gastrointestinal tolerance.

Dosage adjustment for persons with renal impairment, hepatic impairment and dialysis has not beenstudied in clinical trials.

KODATEF is NOT intended for treatment of acute malaria. Relevant clinical guidelines should be used for management of acute malaria, including subjects who develop acute malaria while taking KODATEF for prophylaxis or in instances of relapse of malaria following cessation of prophylaxiswith KODATEF.

Malaria prophylaxis with KODATEF consists of loading, maintenance and terminal dosing. KODATEF should only be used for a maximum of 6 months of continuous dosing. No more than a total of 28 doses should be consumed in a 6 month period.

There are no data on repeated use of KODATEF for malaria prophylaxis after the initial use.

Table 1: Dosing Regimen for KODATEF

Loading Dose	Before travelling to a malarious area	200 mg (two of the 100 mg film-coated tablets) once daily for three days.
Maintenance Dose	While in the malarious area	200 mg (two of the 100 mg film-coated tablets) once weekly – start seven days after the last loading dose.
Final (Terminal) Dose	In the week following exit from the malarious area	Single 200 mg dose (two of the 100 mg film-coated tablets) 7 days after the last maintenance dose.

Individuals need to complete the full course of KODATEF including loading and terminal doses. If leaving the malarious area before the start of the maintenance regimen, a single terminal dose should be taken 7 days after the last dose of the loading regimen.

Missed Doses:

Table 2: Missed Doses of KODATEF

Dose(s) Missed	**How to Replace Missed Dose(s):**
1 Loading dose	1 dose of 200 mg (2 of the 100 mg film-coated tablets) so that a total of 3 daily loading doses have been taken. Begin maintenance dose 1 week after the last loading dose.
2 Loading doses	2 doses of 200 mg (2 of the 100 mg film-coated tablets) on 2 consecutive days so that a total of 3 daily loading doses have been taken. Begin maintenance dose 1 week after the last loading dose.
1 Maintenance (weekly) dose	1 dose of 200 mg (2 of the 100 mg film-coated tablets) on any day up to the time of the next scheduled weekly dose.
2 Maintenance (weekly) doses	1 dose of 200 mg (2 of the 100 mg film-coated tablets) on any day up to the time of the next scheduled weekly dose.
3 or more Maintenance (weekly) doses	2 doses of 200 mg (2 of the 100 mg film-coated tablets), taken as 200 mg (2 of the 100 mg film-coated tablets) once daily for 2 days up to the time of the next weekly dose.
Terminal prophylaxis dose	1 dose of 200 mg (2 of the 100 mg film-coated tablets) as soon as remembered.

4.3 CONTRAINDICATIONS

- Individuals with G6PD deficiency or unknown G6PD status due to the risk of haemolytic anaemia (subsection 4.4 – see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Pregnancy and Lactation (see subsection 4.6 – FERTILITY, PREGNANCY AND LACTATION).
- Subjects with current or history of psychosis (see subsection 4.4 - SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any other component of KODATEF formulation. Due to the long half-life of tafenoquine (up to 17 days), hypersensitivity reactions may be delayed in onset and/or duration.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

G6PD enzyme deficiency

G6PD deficiency should be excluded before prescribing KODATEF due to the risk of haemolytic anaemia in patients with G6PD deficiency. Physicians need to be aware of residual or unrecognised risk of haemolysis due to limitations of the G6PD tests. In clinical trials, declines in haemoglobin levels have been reported in patients with normal G6PD enzyme levels. Monitor patients for clinical signs or symptoms of haemolysis. Advise patients to discontinue KODATEF and seek medical attention if signs of haemolysis occur.

Psychiatric Effects

In patients receiving KODATEF in clinical trials, adverse psychiatric reactions included sleep disturbances (2.5%), depression/depressed mood (0.3%), and anxiety (0.2%). KODATEF was discontinued in one subject with a reported adverse reaction of suicide attempt (0.1%) deemed unrelated to KODATEF by the Investigator. Subjects with a history of psychiatric disorders were excluded from the pivotal clinical study (trial 033) supporting the use of KODATEF for prophylaxisof malaria. Serious psychiatric disorders such as psychosis and depression have been associated withsome quinoline anti-malarial agents.

KODATEF should not be used in subjects with a history of serious psychosis or current psychotic symptoms, delusions or hallucinations. If psychosis or other serious psychiatric events occur whiletaking KODATEF, urgent medical advice should be sought.

Haematological effects

Haemoglobin decreases by 0.66 g/dL have been frequently reported in clinical trials of KODATEF. Asymptomatic elevations in methaemoglobin, characteristically increases to >1% but below 10% (alevel associated with hypoxia), have been observed in the clinical trials of KODATEF. Discontinuation of KODATEF treatment is recommended if signs and symptoms of methaemoglobinaemia occur, followed by medical advice and appropriate medical therapy.

Gastrointestinal effects

Gastrointestinal effects including diarrhoea (13% of subjects), vomiting (4%), and gastroesophagealreflux disorder (2%), occurred at a greater frequency in KODATEF-treated subjects than in placebosubjects in clinical trials. Administration of KODATEF with food may ameliorate these gastrointestinal effects.

Use in hepatic impairment

Tafenoquine pharmacokinetics have not been studied in patients with hepatic impairment. Patients with serum levels of ALT >60 U/L and total bilirubin levels >2.0 mg/dL were excluded or infrequently entered in the pivotal clinical trials (mean ALT = 28 U/L, SD=12; mean total bilirubin =0.5 mg/dL, SD=0.3).

Use in renal impairment

Tafenoquine pharmacokinetics have not been studied in patients with renal impairment. Patients withserum creatinine >1.8 mg/dL were excluded from the pivotal clinical trials.

Use in the elderly

Clinical trials did not include sufficient numbers of subjects 65 years of age and over to determine ifthey respond differently than younger subjects.

Paediatric use

Safety and effectiveness in children have not been established.

Effects on laboratory tests

The use of KODATEF may influence the results of certain laboratory tests including biochemical parameters of the liver and kidneys and haematology parameters. These changes, which are expected due to the oxidative nature of 8-aminoquinoline drugs, generally remain within the normal laboratory range of each parameter. Biochemical parameter changes may include mild ALT elevations (> 60 U/L) and serum creatinine elevations > 1.8 mg/dL. Change in haematology parameters, may specifically include a reduction of haemoglobin > 0.66 g/dL and methaemoglobin increases to >1%.

Methaemoglobin does not increase to as much as 10%, a level associated with hypoxia.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

KODATEF may inhibit drug transporters in the kidney. Since inhibition of these transporters may lead to increased exposure to medications that they excrete, when KODATEF is co-administered withprocainamide, it may be advisable to re-evaluate the safety and/or efficacy of procainamide.

Tafenoquine inhibited the in vitro transport of [14C] metformin via OCT2, MATE1, and MATE2-K. Clinical predictions indicate there may be a potential, but low risk of lactic acidosis in subjects who receive tafenoquine and metformin concomitantly, due to an increased exposure to metformin arising from this interaction.

Treatment with Other Potentially Haemolytic Drugs

Drugs including dapsone may cause haemolysis in G6PD-normal individuals. It is possible that dapsone in combination with KODATEF might cause haemolysis in G6PD-normal individuals. If dapsone is co-administered with KODATEF, monitor urine for dark colour and perform periodic checks of hematocrit.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Tafenoquine had no effects on mating, estrous cycles, sperm motility, sperm count or morphology in rats dosed with tafenoquine at up to 15 mg/kg/day (approximately 6 times the clinical exposure based on AUC). However, the number of corpora lutea was decreased at 15 mg/kg/day, resulting in lower numbers of implantations and viable foetuses. There was no effect on fertility at 5 mg/kg/day (approximately 2 times the clinical exposure based on AUC).

Use in pregnancy – Pregnancy Category C

KODATEF is contraindicated in pregnancy because the G6PD status of the foetus is unknown.

KODATEF was not teratogenic in the rat or rabbit. However, KODATEF may cause foetal harm when administered to a pregnant woman if the foetus is G6PD-deficient and should not be taken in pregnancy. There are no adequate and well-controlled trials in pregnant women. If pregnancy is detected while taking KODATEF, discontinue KODATEF and seek medical advice.

Furthermore, females of reproductive potential should use effective contraception during malaria prevention administration and for five half- lives (three months) after the end of treatment.

The effects of tafenoquine on labour and delivery are unknown.

Tafenoquine resulted in dose related abortions when given orally to pregnant rabbits during organogenesis (gestational day 6 to 18), at doses of 7 mg/kg (about 4.5 times the clinical dose on a mg/m^2/week basis) 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 but no foetotoxicity, at the high dose (equivalent to 10 times the clinical dose on a mg/m^2/week basis). There was no evidence of malformations in either species.

Use in lactation

Women taking KODATEF should stop breastfeeding. A G6PD-deficient infant may be at risk for haemolytic anaemia from exposure to KODATEF through breast milk. Check infant's G6PD status before breastfeeding recommences.

In rats given oral doses of tafenoquine during gestation and lactation, decreased body weight gain, slightly delayed eye opening and decreased rearing activity of offspring, associated with maternal toxicity were observed at 18 mg/kg/day (approximately 8 times the clinical exposure based on AUC).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following adverse reactions are discussed in greater detail in other sections of the Product Information:

Gastrointestinal Effects (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). Haematological Effects (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). Drug-Drug Interactions (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Treatment with Other Potentially Haemolytic Drugs (**see Section 4.5 INTERACTIONS WITH OTHER**

MEDICINES AND OTHER FORMS OF INTERACTIONS).

Clinical Trial Experience

The safety of tafenoquine was studied in clinical trials at various doses and regimens in 3,184 subjects. The recommended KODATEF malaria prevention regimen was evaluated in 825 subjects in 5 controlled clinical trials (Trials 043, 045, 030, 033, and 057). The mean duration of exposure to KODATEF in these five clinical trials was 21 weeks (range 10-29 weeks). Trial 043, 045 and 030 were conducted in healthy, semi-immune, indigenous African volunteers in Ghana or Kenya and wereplacebo-controlled; a mefloquine arm was included in Trials 045 and 030 as a benchmark. Possible asymptomatic parasitaemia was cleared prior to initial receipt of trial drugs in these African studies.

Trial 033, an active comparator (mefloquine) controlled trial was conducted in healthy Australian soldiers deployed in East Timor (now Timor Leste) for a peace-keeping operation at which time trialdrugs were administered. A placebo-controlled Trial 057 was a renal and ophthalmic safety trial conducted in healthy volunteers in the United States and United Kingdom. The mean age of the subjects included in the five trials was 29 years (range 17 to 69 years); 84% were male. The number of randomised placebo subjects in these trials plus one other (Trial 044) was 396. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may notreflect the rates observed in practice.

Serious Adverse Events and Treatment Discontinuations

A total of 49 serious adverse events (SAEs) were reported in tafenoquine-treated subjects (5.9 per 100 subjects) compared to 23 SAEs in placebo-treated subject (5.8 per 100 subjects). Of the 49 SAEs in tafenoquine-treated subjects, only 23 were SAEs that were considered "treatment-related"(includes unlikely, possibly, or probably treatment-related). Of these 23 SAEs: seven were an eye disorder, 5 were decreased glomerular filtration rate, 4 were an infection or infestation, 4 were gastrointestinal disorders, 2 were a nervous system disorder, and 1 was a blood/lymphatic tissue disorder. Of the 23 SAEs in placebo subjects, 10 were considered "treatment-related", affecting 9 subjects. Of these 10 treatment-related SAEs: 1 was an eye disorder, 2 were decreased glomerular filtration rate, 3 were an infection or infestation, 1 was a gastrointestinal disorder, 1 was a nervous system disorder, and 2 were general disorders and administration site conditions.

The most common treatment-related adverse reactions leading to treatment discontinuation in tafenoquine-treated subjects were increased ALT (6 subjects), decreased haemoglobin (3 subjects),and decreased GFR (2 subjects). Only 1 or 2 subjects were discontinued due to AEs in other body systems. The most common treatment-related adverse reactions leading to treatment discontinuation in placebo-treated subjects were increased ALT (1 subject), decreased haemoglobin (1 subject), and decreased platelet count (1 subject). In addition, 1 placebo-treated subject was discontinued for headache and 1 for metamorphopsia.

Eye Findings

Vortex keratopathy (specifically, corneal deposits that can only be detected during a medical examination) was reported in 21% to 93% of subjects receiving KODATEF for 3-6 months in thethree trials that included ophthalmic evaluations. The vortex keratopathy did not result in any apparent functional visual changes, including no loss of night vision, and resolved within 1 year after drug cessation in all subjects. Retinal abnormalities were noted in less than 1% of subjects receiving KODATEF. A total of 7 ocular adverse events were reported to regulatory authorities, 5 reports of vortex keratopathy after the initial findings and 2 reports of retinal disorders.

Laboratory Abnormalities

Methaemoglobinemia: Asymptomatic methaemoglobin elevations were observed in 13% of subjects receiving KODATEF.

Haemoglobin decrease: Haemoglobin decreases of ≥3 g/dL were observed in 2.3% of subjects receiving KODATEF.

Common Adverse Events

Adverse reactions occurring in ≥1% of subjects in the KODATEF group in the active-control Trial033 conducted in military personnel deployed to malaria endemic areas are presented in Table 3.

Table 3: Selected Adverse Reactions Occurring in ≥1% of Subjects ReceivingKODATEF in Trial 033 (Deployed Subjects)

Adverse Reaction	KODATEF[1] (n=492) %	Mefloquine[2] (n=162) %
Nervous system Disorders	22	27
Headache[3]	15	19
Dizziness[4]	1	1
Ear and labyrinth Disorders	7	11
Motion sicknesss[5]	5	6
Musculoskeletal and connective tissue disorders	29	30
Adverse Reaction	**KODATEF[1] (n=492) %**	**Mefloquine[2] (n=162) %**
Back pain	14	15
Gastrointestinal disorders	36	41
Diarrhea	18	20
Nausea	7	9
Vomiting	5	6
Psychiatric disorders	5	4
Any sleep symptom[6]	4	4
Insomnia	2	1
Abnormal dreams[7]	2	2
Anxiety[8]	1	0

[1] KODATEF was administered as 200 mg daily for 3 days, then 200 mg weekly.
[2] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly.
[3] Includes headache, sinus headache, migraine and tension headache.
[4] Includes dizziness and dizziness postural.
[5] Includes motion sickness, vertigo and vertigo positional.
[6] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.
[7] Includes abnormal dreams, nightmares.
[8] Includes anxiety disorder, panic attack and stress.

Adverse reactions occurring in ≥1% of subjects in the KODATEF group in the placebo-controlledpooled data from Trials 043, 045, 030 and 057 are presented in Table 4.

Table 4 Selected Adverse Reactions Occurring in ≥1% of Subjects ReceivingKODATEF in Pooled Trials 043, 045, 030, and 057 (Non-Deployed Subjects)[1]

Adverse Reaction	KODATEF[2] (n=333) %	Placebo (n=295) %	Mefloquine[3] (n=147) %
Nervous system Disorders	35	34	47
Headache[4]	32	32	44
Dizziness[5]	5	3	10
Musculoskeletal and connective tissue disorders	27	26	37
Back pain	14	9	11
Gastrointestinal disorders	31	33	46
Diarrhoea	5	3	1
Nausea	5	2	2
Vomiting	2	2	1

Investigations	8	7	11
ALT increased/abnormal	4	2	3
Psychiatric disorders	2	1	2
Any sleep symptom[6]	1	1	0
Insomnia	1	1	0
Depression/depressed mood	1	0	0

[1] Trials 045 and 030 included mefloquine arm in addition to placebo.
[2] KODATEF was administered as 200 mg daily for 3 days, then 200 mg weekly.
[3] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly.
[4] Includes headache, sinus headache, migraine and tension headache.
[5] Includes dizziness and dizziness postural.
[6] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.

Adverse Events Reported in < 1% of Subjects Receiving KODATEF in Trials 030, 033, 043, 045 ***and 057***

The following selected adverse reactions were reported in subjects receiving KODATEF in Trials030, 033, 043, 045 and 057 at a rate of less than 1%.

Blood and lymphatic system disorders: haemolytic anaemia, anaemia, thrombocytopenia.

Ear and labyrinth disorders: hyperacusis, Meniere's disease.

Eye disorders: night blindness, photophobia, blurred vision, visual acuity reduced, visual impairment, vitreous floaters.

Hepatobiliary disorders: hyperbilirubinaemia, jaundice cholestatic.

Immune system disorders: hypersensitivity.

Investigations: blood bilirubin increased, blood creatinine increased, glomerular filtration ratedecreased.

Nervous system disorders: amnesia, coordination abnormal, hyperesthesia, hypoesthesia, somnolence, syncope, tremor, visual field defect.

Psychiatric disorders: agitation, neurosis.

Skin and subcutaneous tissue disorders: urticaria.

Reporting suspected adverse events

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

There were no reported cases of KODATEF overdose. However, based on clinical experience with individual doses above 200 mg, early symptoms of KODATEF overdose are likely to be gastrointestinal (nausea, vomiting, diarrhoea, and abdominal pain). Haematologic events (haemolytic anaemia and methaemoglobinaemia), may also be seen. Haemolytic anaemia is also to be expected if normal KODATEF doses are administered in error to subjects deficient in G6PD.

Patients should contact their health care provider if they have darker lips or urine (see Section 5 PHARMACOLOGICAL PROPERTIES), as these may be signs of haemolysis or methaemoglobinaemia.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tafenoquine kills the developing asexual, developing exoerythrocytic, and latent hypnozoites ofmalaria

parasites. The mechanism of action is unknown, but is hypothesised to involve redox reactions.

Safety Pharmacology

In vitro studies with tafenoquine suggested potential effect on heart conductance, as it inhibited hERGtail current in a dose-dependent manner (IC_{50} 0.51 µg/mL) and at 100-fold higher concentrations (46.4 µg/mL) caused a non-specific effect on the conduction through heart purkinje fibres of the dog. In vivo, tafenoquine caused systemic vasodilation when given by IV infusion to anaesthetised dogs but at oral doses up to 16 mg/kg had no cardiovascular effect in the conscious dog. The dog $AUC_{0\text{-}1\ week}$ of 116 µg.hr/mL following 16 mg/kg is approximately five-times higher than the clinical AUCfollowing a clinical dose of 600 mg.

The effect of tafenoquine on the QT interval was evaluated in a trial of healthy adult subjects. In this trial, subjects received once daily 400 mg (2 times the approved recommended dosage) doses of tafenoquine for 3 days. The results suggest that the mean increase in the QTcF interval for tafenoquine is less than 20 msec.

Clinical trials

The use of KODATEF for prophylaxis of malaria is supported by single pivotal trial 033.

Trial 033 compared tafenoquine with mefloquine for the prophylaxis of both *Plasmodium falciparum* (*Pf*) and *Plasmodium vivax* (*Pv*) malaria in healthy non-immune Australian soldiers deployed to East Timor (now Timor-Leste).

The trial was carried out from 1999-2000. All applicable ethical and informed consent proceduresweare appropriately undertaken.

The trial was divided into two phases. The first, or prophylactic phase, consisted of a 26-week periodduring deployment where subjects received prophylactic trial medication (tafenoquine 200 mg or mefloquine 250 mg). At the end of the deployment to the malarious area and once the subjects had returned to barracks in Townsville, Australia, the subjects entered a 24-week relapse follow-up phase.During this follow-up phase, subjects who had been on mefloquine prophylaxis received 14-days of primaquine (15 mg bid) while subjects on tafenoquine prophylaxis received placebo capsules for 14 days.

Subjects with documented G6PD enzyme deficiency or a history of psychiatric disorders and/or seizures were excluded, as well as subjects with any significant medical history or concurrent medicalcondition. All subjects (N=654) were healthy at baseline with an age range of 18-47 years. Mean age was 25±5 years in the tafenoquine group and 26±6 years in mefloquine group. Subjects were mostly male (97%) and of white ethnicity (99%).

The primary efficacy endpoint was prophylactic failure (Table 5): parasitologic and clinical failure during the 26-week prophylactic phase. The protocol-defined principal efficacy analysis was based onthe per-protocol (PP) population, which consisted of all randomised subjects who satisfied inclusion/exclusion criteria and subsequently adhered to the protocol. A very high compliance to trial drugs was observed in the trial – 100% for the loading dose, 99% for the weekly regimens and 96% during the relapse follow-up phase. No subject was a prophylactic failure during the prophylactic phase. Historic control data indicate that 7.9% of subjects would have become infected (6.9% with *Pv*,1.0% with *Pf*) under those conditions.

Table 5: Prophylactic Outcome During the Prophylactic Treatment Phase (PPPopulation) for Trial 033

Prophylactic Outcome	**Treatment Group**	
	Tafenoquine 200 mg[a]	**Mefloquine 250 mg**[b]
Number of Subjects	462	153
Prophylactic failure, n (%)	0 (0%)	0 (0%)

Prophylactic Outcome	Treatment Group	
	Tafenoquine 200 mg[a]	Mefloquine 250 mg[b]
Prophylactic Success, n (%)	462 (100%)	153 (100%)
Treatment Difference (Tafenoquine – Mefloquine) [95% confidence interval]	0% [-2%,1%]	

a Subjects received a loading dose of tafenoquine 200 mg per day for 3 days, followed by tafenoquine 200 mg once a week for the 26-week prophylactic phase. Subjects who entered the follow-up phase received placebo bid for 14 days.

b Subjects received a loading dose of mefloquine 250 mg per day for 3 days, followed by mefloquine 250 mg once a week for the 26-week prophylactic phase. Subjects who entered the follow-up phase received primaquine 15 mg bid for 14 days.

In the 24 week follow up phase after leaving the endemic region, and after receiving no further drug (tafenoquine group), or standard post-exposure prophylaxis with primaquine (mefloquine group), there were four cases of Pv malaria in the tafenoquine group and one case of Pv malaria in the mefloquine group (Table 6Table 6).

Table 6: Prophylactic Outcome During the post-exposure Phase (PP Population) forTrial 033

Prophylactic Outcome	Tafenoquine 200 mg	Mefloquine 250 mg followed by primaquine
Number of Subjects	462	153
Prophylactic Success	458 (99.1%)	152 (99.3%)
Prophylactic Failure	4 (0.9%)	1 (0.7%)
Treatment Difference (Tafenoquine – Mefloquine)	0.21%	
95% CI	(-1.32%, 1.74%)	

The failure rate due to *Pv* relapse was 0.9% for the tafenoquine group and 0.7% for the primaquine group. The time to relapse after the last dose of tafenoquine or mefloquine was 12-20 weeks for the 4tafenoquine failures and 12 weeks for the 1 mefloquine-then-primaquine failure. All 5 cases were *Pv* malaria.

The relapse follow-up was extended for another 6 months (a total of 12 months post-prophylactic phase). There were 3 more cases of malaria in the tafenoquine group and one case of malaria in the mefloquine/primaquine group during this 6-month extension, bringing to a total of 7 *Pv* relapses in thetafenoquine group and 2 *Pv* relapses in the mefloquine/primaquine group during the 12 months relapse follow-up after the end of prophylactic phase.

5.2 PHARMACOKINETIC PROPERTIES

A population PK analysis in healthy subjects was conducted consolidating clinical PK data fromTrials 001, 002, 003, 004, 005, 014, 015, 033, 044 and 058. Covariates common to all 10 trials were age, weight, race, sex and meal schedule. The analysis comprised 866 participants across the trials. The total analysis population was 93.3% male; median age 25 years, mean weight

75.0 kg and 72.3% Caucasian/white. The majority of participants (89.4%) took tafenoquine underfed conditions (i.e., after a meal).

A one-compartment PK model with first-order absorption and elimination processes was specified in the NONMEM control file and was parameterised in terms of apparent CL/F, V/Fand ka. Key pharmacokinetic parameters from the population PK analysis and from Trial 051 data are shown in Table 7.

Table 7: Key Pharmacokinetic Parameters for Tafenoquine

Parameter	Value
*Volume of distribution/F	2470 L (inter-individual variability = 24%)
*Clearance/F	4.17 L/hour (inter-individual variability = 24%)
*k_a	0.359 L/hour (inter-individual variability = 54%)
*Half-life ($t_{½}$)	17 days
**$t_{max,ss}$	7.0 hours
*$C_{max,ss}$	Approximately 300 ng/mL
*$C_{min,ss}$	>80 ng/mL will be present in >95% of individuals

*From population PK analysis
**From Trial 051
SS=steady state.

Absorption

Tafenoquine plasma concentrations were generally higher following administration of a single dose of tafenoquine under fed compared with fasting conditions, with mean fed: fasted ratios of 1.41 (AUC) and 1.31 (C_{max}). T_{max} and $t_{½}$ were similar under fasting and fed states. However, population PK analyses demonstrated that after the recommended regimen of 200 mg/day times 3 days for loading followed by 200 mg weekly, trough tafenoquine values even in the non-fed state were above the valueof 80 ng/mL (the minimum target trough value for prevention of symptomatic malaria in non-immuneindividuals) by the end of the loading dose. By the sixth weekly dose, exposure in the fasted state is predicted to equal exposure in the fed state.

Distribution

In healthy male volunteers administered one dose of 100 mg, 200 mg, or 400 mg while fasting, bloodand calculated RBC concentrations were 2.0 and 3.4 times higher than corresponding plasma concentrations, and there was no change in RBC accumulation over time. In humans, >99.5% of tafenoquine is bound to plasma protein.

Metabolism

In human biomaterials studied in vitro, minimal metabolism of tafenoquine occurred. When tafenoquine 400 mg per day for three days was administered to humans, only parent tafenoquine wasextractable in plasma drawn 80 hours after the first dose.

Excretion

The major route of excretion in the rat, dog and monkey was via the faeces and to a lesser extent via the urine. Overall excretion of radioactivity in animals was slow. In bile-cannulated animals, equal amounts were recovered in bile and faeces in dogs (20% of dose in 7 days) and 5% of dose in bile and75% of dose in faeces in rats in 4 days. Human radiolabeled mass balance studies have not been conducted to characterise the clinical excretion of tafenoquine.

Dose-PK relationships

Following administration of a single dose to healthy males, AUC and Cmax were dose-proportional. When healthy volunteers received 10 weekly administrations of 200 mg without a loading dose while fasting, the accumulation ratio was approximately 4.

PK-PD relationships

Trials in non-immune persons (those without prior malaria exposure), a population similar to the population for which malaria prevention is intended, showed that symptomatic breakthrough of malaria only occurred when tafenoquine plasma concentrations were <50 ng/mL. Consequently, a precautionary plasma concentration of 80 ng/mL was selected as the minimum target trough value for prevention of symptomatic malaria development in non-immune individuals. Population PK analysispredicts that the recommended prevention regimen will achieve trough levels >80 ng/mL in >95% ofsubjects.

Drug-drug interactions

Tafenoquine does not significantly inhibit or induce CYP2D6, CYP3A4, CYP2C9 or CYP1A2, sincein phase 1 trials, the PK parameters of the CYP2D6 substrate desipramine, the CYP3A4 substrate midazolam, the CYP2C9 substrate Flurbiprofen and the CYP1A2 substrate caffeine were unaffected by co-administration of tafenoquine.

Tafenoquine was a potent inhibitor of renal multidrug and toxin extrusion transporters (MATE) and organic cation transporter 2 in vitro. Since inhibition of these transporters may lead to increased exposure to medications that they excrete, when tafenoquine is co-administered with procainamide, itmay be advisable to re-evaluate safety and/or efficacy of procainamide.

Tafenoquine inhibited the in vitro transport of [14C] metformin via OCT2, MATE1, and MATE2-K. Risk assessments based on systemic concentrations of tafenoquine at therapeutic doses, compared with the

metformin IC_{50} values derived from in vitro transporter inhibition studies, were conducted and indicated a potential, but low, drug interaction risk with OCT2,

MATE1 and/or MATE2K substrates. Clinical predictions indicate there may be a potential, but low, risk of lactic acidosis in subjects who receive tafenoquine and metformin concomitantly, dueto an increased exposure to metformin arising from this interaction.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The mutagenic and clastogenic potential of tafenoquine has been assessed in bacterial gene mutationassays and in vitro gene mutation assays in mammalian cells (mouse lymphoma cells and Chinese hamster ovary cells), in vitro chromosome aberration assays in Chinese hamster ovary cells, and onemouse in vivo micronucleus study. Based on these studies, tafenoquine is not considered to present agenotoxic risk to humans.

Carcinogenicity

Two two-year oral carcinogenicity studies were performed; 1 in the mouse and 1 in the rat. Oral administration of doses up to 1.0 mg/kg/day (approximately 0.3 times the clinical exposure based onAUC) for 2 years produced no clear evidence of an increase in the incidence of tumours in treated mice of either sex. Tafenoquine administration was associated with an increase in the incidence of renal tumours and hyperplasia in male rats following administration of 1.0 and/or 2.0 mg/kg/day (0.5 times the clinical exposure based on AUC). The exact mechanism behind renal tumor development is unknown but may be the result of multi-factorial, non-genotoxic modes of action, possibly potentiated by chronic progressive nephropathy (CPN). CPN is a spontaneous age-related disease that occurs at a high incidence in rat strains used in preclinical toxicology studies, exhibiting apredisposition in male rats. The relevance of these findings for a carcinogenic risk in humans is unclear.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

KODATEF also contains:

- Microcrystalline cellulose.
- Mannitol.
- Magnesium stearate.
- Hypromellose.
- Titanium dioxide.
- Iron oxide red and
- Macrogol 400.

6.2 INCOMPATIBILITIES

Refer to subsection 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in original container. Dispense only in the original carton.

6.5 NATURE AND CONTENTS OF CONTAINER

KODATEF 100 mg film-coated tablets are packed in polyamide aluminium and PVC formable laminate backedblisters with a peelable polyethylene terephthalate aluminium foil and paper cover. Each blister card

contains eight film-coated tablets. Each carton contains 8 or 16 film-coated tablets (one or two blister cards).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

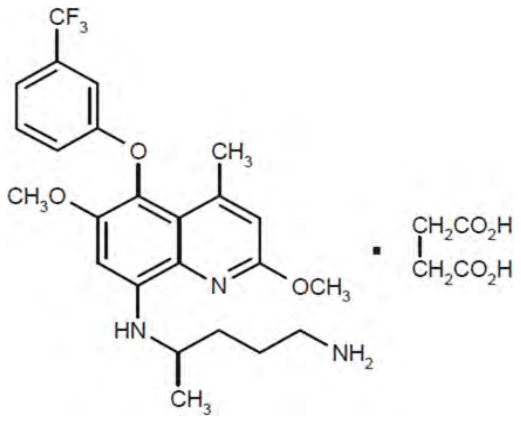
In Australia, any unused medicine or waste material should be disposed of by taking to your localpharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemical name: 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline succinate.

Structural formula



Molecular weight

463.49 (free base anhydrous)

581.58 (succinate salt)

Molecular Formula

$C_{24}H_{28}F_3N_3O_3 \cdot C_4H_6O_4$

Tafenoquine succinate, is an off-white to pink/orange/brown crystalline powder and exhibits the highest solubility at pH 1 (25°C and 37°C), pH 2 (37°C) and pH 4 (37°C), and negligible solubility at all other tested pH values at 25°C and 37°C.

CAS number

106635-80-7 (tafenoquine free base) and 106635-81-8 (tafenoquine succinate) (Source Chemical Book).

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

Biocelect Pty Ltd
Level 29,
66 Goulburn Street,
SYDNEY,
NSW 2000

Customer enquiries and Medical Information: 1300 848 628

Website: www.biocelect.com/products/kodatef

9 DATE OF FIRST APPROVAL

12 September 2018

10 DATE OF REVISION

12 May 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All relevant sections	Changed from tablets to film-coated tablets
2 QUALITATIVE AND QUANTITATIVE COMPOSITION	Text updated.
6.1 LIST OF EXCIPIENTS	Excipient names amended to AANs.
6.4 SPECIAL PRECAUTIONS FOR STORAGE	Text updated.
6.7 PHYSICOCHEMICAL PROPERTIES	Text updated.
8 Sponsor	Update to sponsor address

Comparison of ARAKODA™ (FDA-Approved Product) and KODATEF® (Imported Product) Prescribing Information (PI)

The below table provides a side by side comparison of the related sections of the prescribing information for Arakoda™ and Kodatef®. While the text may not be identical in some places, the meaning and instructions are the same. If the text had different or new information in one of the PIs, the text is shown in red.

ARAKODA- tafenoquine tablet, film coated **ARAKODA™ (tafenoquine) tablets, for oral use**	**KODATEF® (TAFENOQUINE SUCCINATE)** **ORAL FILM-COATED TABLETS**
To report SUSPECTED ADVERSE REACTIONS, contact 60 Degrees Pharmaceuticals at 1-888- 834-0225 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.	**HEALTHCARE PROFESSIONALS ARE ASKED TO REPORT ANY SUSPECTED ADVERSE EVENTS AT WWW.TGA.GOV.AU/REPORTING-PROBLEMS**
1 INDICATIONS AND USAGE ARAKODA is indicated for the prophylaxis of malaria in patients aged 18 years and older.	**4.1 Therapeutic indications** ***Malaria Prophylaxis*** KODATEF (tafenoquine) is an antimalarial indicated for the prevention of malaria in adults 18 years of age and above for up to 6 months of continuous dosing.
2 DOSAGE AND ADMINISTRATION 2.1 Tests to be Performed Prior to ARAKODA Dose Initiation All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA *[see Contraindications (4), Warnings and Precautions (5.1)]*. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with ARAKODA *[see Use in Specific Populations (8.1 and 8.3)]*.	**4.2 Dose and method of administration** The recommended dosing regimen for KODATEF is shown in Table 1. All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing tafenoquine (subsection 4.3 CONTRAINDICATIONS and subsection 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Pregnancy should be excluded prior to the use of tafenoquine in females of child bearing potential (subsection 4.3 CONTRAINDICATIONS and subsection 4.6 - FERTILITY, PREGNANCY AND LACTATION).

ARAKODA- tafenoquine tablet, film coated ARAKODA™ (tafenoquine) tablets, for oral use	KODATEF® (TAFENOQUINE SUCCINATE) ORAL FILM-COATED TABLETS
2.2 Recommended Dosage and Administration Instructions The recommended dosage of ARAKODA is described in Table 1 below. ARAKODA can be administered for up to 6 months of continuous dosing.	**4.2 Dose and method of administration *(continued)*** KODATEF film-coated tablets should be swallowed whole and not chewed or broken apart. KODATEF filmcoated tablets can be taken with or without food although KODATEF taken with food may be associated with better gastrointestinal tolerance. Dosage adjustment for persons with renal impairment, hepatic impairment and dialysis has not been studied in clinical trials. KODATEF is NOT intended for treatment of acute malaria. Relevant clinical guidelines should be used for management of acute malaria, including subjects who develop acute malaria while taking KODATEF for prophylaxis or in instances of relapse of malaria following cessation of prophylaxis with KODATEF. Malaria prophylaxis with KODATEF consists of loading, maintenance and terminal dosing. KODATEF should only be used for a maximum of 6 months of continuous dosing. No more than a total of 28 doses should be consumed in a 6 month period. There are no data on repeated use of KODATEF for malaria prophylaxis after the initial use.

Table 1: Recommended Dosage of ARAKODA in Patients (18 Years of Age and Older)

Regimen Name	**Timing**	**Dosage**
Loading regimen	For each of the 3 days before travel to a malarious area	200 mg (2 of the 100 mg tablets) once daily for 3 days
Maintenance regimen	While in the malarious area	200 mg (2 of the 100 mg tablets) once weekly – start 7 days after the last loading regimen dose
Terminal prophylaxis regimen	In the week following exit from the malarious area	200 mg (2 of the 100 mg tablets) taken one time, 7 days after the last maintenance dose

- Administer ARAKODA with food. *[see Clinical Pharmacology (12.3)]*.
- Swallow the tablet whole. Do not break, crush or chew the tablets.
- Complete the full course of ARAKODA including the loading dose and the terminal dose.

Table 1: Dosing Regimen for KODATEF

Loading Dose	Before travelling to a malarious area	200 mg (two of the 100 mg film-coated tablets) once daily for three days.
Maintenance Dose	While in the malarious area	200 mg (two of the 100 mg film-coated tablets) once weekly – start seven days after the last loading dose.
Final (Terminal) Dose	In the week following exit from the malarious area	Single 200 mg dose (two of the 100 mg film-coated tablets) 7 days after the last maintenance dose.

Individuals need to complete the full course of KODATEF including loading and terminal doses. If leaving the malarious area before the start of the maintenance regimen, a single terminal dose should be taken 7 days after the last dose of the loading regimen.

Table 2: How to Replace Missed Doses of ARAKODA

Dose(s) Missed	How to Replace Missed Dose(s):
1 Loading dose	1 dose of 200 mg (2 of the 100 mg tablets) so that a total of 3 daily loading doses have been taken. Begin maintenance dose 1 week after the last loading dose.
2 Loading doses	2 doses of 200 mg (2 of the 100 mg tablets) on 2 consecutive days so that a total of 3 daily loading doses have been taken. Begin maintenance dose 1 week after the last loading dose.
1 Maintenance (weekly) dose	1 dose of 200 mg (2 of the 100 mg tablets) on any day up to the time of the next scheduled weekly dose.
2 Maintenance (weekly) doses	1 dose of 200 mg (2 of the 100 mg tablets) on any day up to the time of the next scheduled weekly dose.
3 or more Maintenance (weekly) doses	2 doses of 200 mg (2 of the 100 mg tablets), taken as 200 mg (2 of the 100 mg tablets) once daily for 2 days up to the time of the next weekly dose.
Terminal prophylaxis dose	1 dose of 200 mg (2 of the 100 mg tablets) as soon as remembered.

Table 2: Missed Doses of KODATEF

Dose(s) Missed	How to Replace Missed Dose(s):
1 Loading dose	1 dose of 200 mg (2 of the 100 mg film-coated tablets) so that a total of 3 daily loading doses have been taken. Begin maintenance dose 1 week after the last loading dose.
2 Loading doses	2 doses of 200 mg (2 of the 100 mg film-coated tablets) on 2 consecutive days so that a total of 3 daily loading doses have been taken. Begin maintenance dose 1 week after the last loading dose.
1 Maintenance (weekly) dose	1 dose of 200 mg (2 of the 100 mg film-coated tablets) on any day up to the time of the next scheduled weekly dose.
2 Maintenance (weekly) doses	1 dose of 200 mg (2 of the 100 mg film-coated tablets) on any day up to the time of the next scheduled weekly dose.
3 or more Maintenance (weekly) doses	2 doses of 200 mg (2 of the 100 mg film-coated tablets), taken as 200 mg (2 of the 100 mg film-coated tablets) once daily for 2 days up to the time of the next weekly dose.
Terminal prophylaxis dose	1 dose of 200 mg (2 of the 100 mg film-coated tablets) as soon as remembered.

ARAKODA- tafenoquine tablet, film coated **ARAKODA™ (tafenoquine) tablets, for oral use**	**KODATEF® (TAFENOQUINE SUCCINATE)** **ORAL FILM-COATED TABLETS**
3 DOSAGE FORMS AND STRENGTHS ARAKODA tablets are dark pink, film-coated, capsule-shaped tablets debossed with 'TQ100' on one side containing 100 mg of tafenoquine.	**3 PHARMACEUTICAL FORM** Each KODATEF tablet is a dark pink, capsule shaped, film-coated tablet debossed with "TQ100" on one side and plain on the other. The film-coated tablets are for oral administration.
4 CONTRAINDICATIONS **ARAKODA is contraindicated in:** • patients with G6PD deficiency or unknown G6PD status due to the risk of hemolytic anemia *[see Warnings and Precautions (5.2)]*. • breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if the G6PD status of the infant is unknown *[see Warnings and Precautions (5.3), Use in Specific Populations (8.2)]*. • patients with a history of psychotic disorders or current psychotic symptoms (i.e., hallucinations, delusions, and/or grossly disorganized behavior) *[see Warnings and Precautions (5.4)]* • patients with known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of ARAKODA *[see Warnings and Precautions (5.5)]*.	**4.3 CONTRAINDICATIONS** • Individuals with G6PD deficiency or unknown G6PD status due to the risk of haemolytic anaemia (subsection 4.4 - see SPECIAL WARNINGS AND PRECAUTIONS FOR USE). • Pregnancy and Lactation (see subsection 4.6 - FERTILITY, PREGNANCY AND LACTATION). • Subjects with current or history of psychosis (see subsection 4.4 - SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
5 WARNINGS AND PRECAUTIONS **5.5 Hypersensitivity Reactions** Serious hypersensitivity reactions (e.g., angioedema and urticaria) have been observed with administration of tafenoquine. Hypersensitivity reactions have been reported in clinical trials of ARAKODA *[see Adverse Reactions (6.1)]*. Discontinue prophylaxis with ARAKODA and institute appropriate therapy if hypersensitivity reactions occur *[see Warnings and Precautions (5.6)]*. ARAKODA is contraindicated in patients who develop hypersensitivity to tafenoquine or any component of ARAKODA or other 8-aminoquinolines *[see Contraindications (4)]*.	• Known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any other component of KODATEF formulation. Due to the long half-life of tafenoquine (up to 17 days), hypersensitivity reactions may be delayed in onset and/or duration.

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5 WARNINGS AND PRECAUTIONS **5.1 Hemolytic Anemia** Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing ARAKODA *[see Contraindications (4)]*. Due to the limitations with G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Treatment with ARAKODA is contraindicated in patients with G6PD deficiency or unknown G6PD status *[see Contraindications (4)]*. In clinical trials, declines in hemoglobin levels were reported in some G6PD-normal patients *[see Adverse Reactions (6.1)]*. Monitor patients for clinical signs or symptoms of hemolysis *[see Warnings and Precautions (5.6)]*. Advise patients to discontinue ARAKODA and seek medical attention if signs of hemolysis occur.	**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** ***G6PD enzyme deficiency*** G6PD deficiency should be excluded before prescribing KODATEF due to the risk of haemolytic anaemia in patients with G6PD deficiency. Physicians need to be aware of residual or unrecognised risk of haemolysis due to limitations of the G6PD tests. In clinical trials, declines in haemoglobin levels have been reported in patients with normal G6PD enzyme levels. Monitor patients for clinical signs or symptoms of haemolysis. Advise patients to discontinue KODATEF and seek medical attention if signs of haemolysis occur.

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5.2 G6PD Deficiency in Pregnancy and Lactation Potential Harm to the Fetus The use of ARAKODA during pregnancy may cause hemolytic anemia in a G6PD-deficient fetus. Even if a pregnant woman has normal levels of G6PD, the fetus could be G6PD deficient. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception during treatment and for 3 months after the last dose of ARAKODA. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy *[see Use in Specific Populations (8.1 and 8.3)]*.	**4.6 FERTILITY, PREGNANCY AND LACTATION** ***Use in pregnancy – Pregnancy Category C*** KODATEF is contraindicated in pregnancy because the G6PD status of the foetus is unknown. KODATEF was not teratogenic in the rat or rabbit. However, KODATEF may cause foetal harm when administered to a pregnant woman if the foetus is G6PD-deficient and should not be taken in pregnancy. There are no adequate and well-controlled trials in pregnant women. If pregnancy is detected while taking KODATEF, discontinue KODATEF and seek medical advice. Furthermore, females of reproductive potential should use effective contraception during malaria prevention administration and for five half- lives (three months) after the end of treatment. The effects of tafenoquine on labour and delivery are unknown. ***<Note this animal data included in this section of 8.1 of the KODAFEF PI is presented in Section 8.1 of the ARAKODA PI>*** Tafenoquine resulted in dose related abortions when given orally to pregnant rabbits during organogenesis (gestational day 6 to 18), at doses of 7 mg/kg (about 4.5 times the clinical dose on a mg/m^2/week basis) 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 but no foetotoxicity, at the high dose (equivalent to 10 times the clinical dose on a mg/m^2/week basis). There was no evidence of malformations in either species.

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Potential Harm to the Breastfeeding Infant A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown *[see Contraindications (4)]*. Advise the woman with a G6PD-deficient infant or if the G6PD status of the infant is unknown not to breastfeed during treatment with ARAKODA and for 3 months after the final dose *[see Use in Specific Populations (8.2)]*.	***Use in lactation*** Women taking KODATEF should stop breastfeeding. A G6PD-deficient infant may be at risk for haemolytic anaemia from exposure to KODATEF through breast milk. Check infant's G6PD status before breastfeeding recommences. In rats given oral doses of tafenoquine during gestation and lactation, decreased body weight gain, slightly delayed eye opening and decreased rearing activity of offspring, associated with maternal toxicity were observed at 18 mg/kg/day (approximately 8 times the clinical exposure based on AUC).
5.3 Methemoglobinemia Asymptomatic elevations in methemoglobin have been observed in the clinical trials of ARAKODA *[see Adverse Reactions (6.1)]*. Institute appropriate therapy if signs or symptoms of methemoglobinemia occur *[see Warnings and Precautions (5.6)]*. Carefully monitor individuals with nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase deficiency. Advise patients to discontinue ARAKODA and seek medical attention if signs of methemoglobinemia occur.	***Haematological effects*** Haemoglobin decreases by 0.66 g/dL have been frequently reported in clinical trials of KODATEF. Asymptomatic elevations in methaemoglobin, characteristically increases to >1% but below 10% (a level associated with hypoxia), have been observed in the clinical trials of KODATEF. Discontinuation of KODATEF treatment is recommended if signs and symptoms of methaemoglobinaemia occur, followed by medical advice and appropriate medical therapy.

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5.4 Psychiatric Effects In patients receiving ARAKODA in clinical trials, psychiatric adverse reactions included sleep disturbances (2.5%), depression/depressed mood (0.3%), and anxiety (0.2%) *[see Adverse Reactions (6.1)]*. ARAKODA was discontinued in a subject with an adverse reaction of suicide attempt (0.1%). Subjects with a history of psychiatric disorders were excluded from three of five ARAKODA trials in which mefloquine was included as a comparator. Psychosis was reported in three patients with a history of psychosis or schizophrenia who received tafenoquine doses (350 mg to 500 mg single dose, or 400 mg daily for 3 days) different from the approved ARAKODA regimen. Safety and effectiveness of ARAKODA have not been established at doses or regimens other than the approved regimen; use of ARAKODA at doses or regimens other than a 200-mg weekly dose is not approved by FDA. ARAKODA is contraindicated in patients with a history of psychotic disorders or current psychotic symptoms *[see Contraindication (4)]*. If psychotic symptoms (hallucinations, delusions, or grossly disorganized thinking or behavior) occur, consider discontinuation of ARAKODA and prompt evaluation by a mental health professional as soon as possible. Other psychiatric symptoms, such as changes in mood, anxiety, insomnia, and nightmares, should be promptly evaluated by a medical professional if they are moderate and last more than three days or are severe *[see Warnings and Precautions (5.6)]*.	**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** ***Psychiatric Effects*** In patients receiving KODATEF in clinical trials, adverse psychiatric reactions included sleep disturbances (2.5%), depression/depressed mood (0.3%), and anxiety (0.2%). KODATEF was discontinued in one subject with a reported adverse reaction of suicide attempt (0.1%) deemed unrelated to KODATEF by the Investigator. Subjects with a history of psychiatric disorders were excluded from the pivotal clinical study (trial 033) supporting the use of KODATEF for prophylaxis of malaria. Serious psychiatric disorders such as psychosis and depression have been associated with some quinoline anti-malarial agents. KODATEF should not be used in subjects with a history of serious psychosis or current psychotic symptoms, delusions or hallucinations. If psychosis or other serious psychiatric events occur while taking KODATEF, urgent medical advice should be sought.

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5.5 Hypersensitivity Reactions Serious hypersensitivity reactions (e.g., angioedema and urticaria) have been observed with administration of tafenoquine. Hypersensitivity reactions have been reported in clinical trials of ARAKODA *[see Adverse Reactions (6.1)]*. Discontinue prophylaxis with ARAKODA and institute appropriate therapy if hypersensitivity reactions occur *[see Warnings and Precautions (5.6)]*. ARAKODA is contraindicated in patients who develop hypersensitivity to tafenoquine or any component of ARAKODA or other 8-aminoquinolines *[see Contraindications (4)]*.	**4.3 CONTRAINDICATIONS** Known hypersensitivity to tafenoquine, other 8-minoquinolines, or any other component of KODATEF formulation. Due to the long half-life of tafenoquine (up to 17 days), hypersensitivity reactions may be delayed in onset and/or duration.
5.6 Delayed Adverse Reactions, Including Hemolytic Anemia, Methemoglobinemia, Psychiatric Effects, and Hypersensitivity Reactions Adverse reactions including hemolytic anemia, methemoglobinemia, psychiatric effects, and hypersensitivity reactions were reported with the use of ARAKODA or tafenoquine in clinical trials *[see Warnings and Precautions (5.1, 5.3, 5.4, 5.5)]*. Due to the long half-life of ARAKODA (approximately 17 days), psychiatric effects, hemolytic anemia, methemoglobinemia, and signs or symptoms of hypersensitivity reactions that may occur could be delayed in onset and/or duration. Advise patients to seek medical attention if signs of hypersensitivity occur *[see Clinical Pharmacology (12.3)]*.	Delayed adverse reactions are discussed in other individual sections for these adverse effects.
This is not presented in ARAKODA label	**4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES** The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

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6 ADVERSE REACTIONS The following clinically significant adverse reactions observed with ARAKODA are discussed in detail in the Warnings and Precautions section: • Hemolytic Anemia *[see Warnings and Precautions (5.2)]* • Methemoglobinemia *[see Warnings and Precautions (5.3)]* • Psychiatric Effects *[see Warnings and Precautions (5.4)]* • Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*	**4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)** The following adverse reactions are discussed in greater detail in other sections of the Product Information: Gastrointestinal Effects (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Haematological Effects (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Drug-Drug Interactions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Treatment with Other Potentially Haemolytic Drugs (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).
GI effects were not included in ARAKODA adverse drug reaction warnings section.	**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** ***Gastrointestinal effects*** Gastrointestinal effects including diarrhoea (13% of subjects), vomiting (4%), and gastroesophageal reflux disorder (2%), occurred at a greater frequency in KODATEF-treated subjects than in placebo subjects in clinical trials. Administration of KODATEF with food may ameliorate these gastrointestinal effects.
6.1 Clinical Trials Experience ***< Due to the length and summary tables in this section, these data are provided after this table.>***	**5 PHARMACOLOGICAL PROPERTIES** ***Clinical trials*** ***< Due to the length and summary tables in this section, these data are provided after this table.>***

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7 DRUG INTERACTIONS **7.1 Effect of ARAKODA on Organic Cation Transporter-2 (OCT2) and Multidrug and Toxin Extrusion (MATE) Substrates** The effect of coadministration of tafenoquine on the pharmacokinetics of OCT2 and MATE substrates in humans is unknown. However, in vitro observations suggest the potential for increased concentrations of these substrates *[see Clinical Pharmacology (12.3)]* which may increase the risk of toxicity of these drugs. Avoid coadministration of ARAKODA with OCT2 and MATE substrates (e.g., dofetilide, metformin). If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction if needed based on approved product labeling of the coadministered drug.	**4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS** KODATEF may inhibit drug transporters in the kidney. Since inhibition of these transporters may lead to increased exposure to medications that they excrete, when KODATEF is co-administered with procainamide, it may be advisable to re-evaluate the safety and/or efficacy of procainamide. Tafenoquine inhibited the in vitro transport of [14C] metformin via OCT2, MATE1, and MATE2-K. Clinical predictions indicate there may be a potential, but low risk of lactic acidosis in subjects who receive tafenoquine and metformin concomitantly, due to an increased exposure to metformin arising from this interaction. *Treatment with Other Potentially Haemolytic Drugs* Drugs including dapsone may cause haemolysis in G6PD-normal individuals. It is possible that dapsone in combination with KODATEF might cause haemolysis in G6PD-normal individuals. If dapsone is coadministered with KODATEF, monitor urine for dark colour and perform periodic checks of hematocrit.

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8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** **Risk Summary** The use of ARAKODA during pregnancy may cause hemolytic anemia in a fetus who is G6PD-deficient. Treatment with ARAKODA during pregnancy is not recommended. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy *[see Warnings and Precautions (5.2)]*. Available data with use of ARAKODA in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal studies, there were increased abortions, with and without maternal toxicity when tafenoquine was given orally to pregnant rabbits at and above doses equivalent to about 0.4 times the clinical exposure based on body surface area comparisons. No fetotoxicity was observed at doses about 1.5 times the clinical exposure (based on body surface area comparisons) in a similar study in rats. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **Clinical Considerations** *Disease-Associated Maternal and/or Embryo/Fetal Risk:* Malaria during pregnancy increases the risk for adverse pregnancy outcomes, including maternal anemia, prematurity, spontaneous abortion and stillbirth.	**4.6 FERTILITY, PREGNANCY AND LACTATION** ***Use in pregnancy – Pregnancy Category C*** KODATEF is contraindicated in pregnancy because the G6PD status of the foetus is unknown. KODATEF was not teratogenic in the rat or rabbit. However, KODATEF may cause foetal harm when administered to a pregnant woman if the foetus is G6PD-deficient and should not be taken in pregnancy. There are no adequate and well-controlled trials in pregnant women. If pregnancy is detected while taking KODATEF, discontinue KODATEF and seek medical advice. Furthermore, females of reproductive potential should use effective contraception during malaria prevention administration and for five half- lives (three months) after the end of treatment. The effects of tafenoquine on labour and delivery are unknown.

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Data ***Animal Data:*** 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. 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 (about 1.5 times the clinical exposure based on body surface area comparisons). There was no evidence of malformations in either species. 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.	***Effects on Fertility*** Tafenoquine resulted in dose related abortions when given orally to pregnant rabbits during organogenesis (gestational day 6 to 18), at doses of 7 mg/kg (about 4.5 times the clinical dose on a mg/m2/week basis) 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 but no foetotoxicity, at the high dose (equivalent to 10 times the clinical dose on a mg/m2/week basis). There was no evidence of malformations in either species.

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8.2 Lactation **Risk Summary** A breastfed infant with G6PD deficiency is at risk for hemolytic anemia from exposure to ARAKODA. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown *[see Contraindications (4) and Clinical Considerations]*. There is no information regarding the presence of ARAKODA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. In a breastfed infant with normal G6PD, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARAKODA and any potential effects on the breastfed infant from ARAKODA or from the underlying maternal condition. **Clinical Considerations** Check the infant's G6PD status before maternal breastfeeding commences. If an infant is G6PD-deficient, exposure to ARAKODA during breastfeeding may result in hemolytic anemia in the infant; therefore, advise the woman with an infant who has G6PD deficiency or whose G6PD status is unknown, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose of ARAKODA.	**4.6 FERTILITY, PREGNANCY AND LACTATION** ***4.5 Use in lactation*** Women taking KODATEF should stop breastfeeding. A G6PD-deficient infant may be at risk for haemolytic anaemia from exposure to KODATEF through breast milk. Check infant's G6PD status before breastfeeding recommences. In rats given oral doses of tafenoquine during gestation and lactation, decreased body weight gain, slightly delayed eye opening and decreased rearing activity of offspring, associated with maternal toxicity were observed at 18 mg/kg/day (approximately 8 times the clinical exposure based on AUC).

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8.3 Females and Males of Reproductive Potential **Pregnancy Testing** Verify the pregnancy status in females of reproductive potential prior to initiating treatment with ARAKODA. *[see Dosage and Administration (2.2), Warnings and Precautions, (5.2), and Use in Specific Populations (8.1)]*. **Contraception** ARAKODA may cause hemolytic anemia in a G6PD-deficient fetus *[see Warnings and Precautions (5.2), Use in Specific Populations (8.1)]*. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception for 3 months after the final dose of ARAKODA.	**See Section 4.6 above.**
8.4 Pediatric Use Safety and effectiveness of ARAKODA in pediatric patients have not been established.	***Paediatric use*** Safety and effectiveness in children have not been established.
8.5 Geriatric Use Clinical trials of ARAKODA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients *[see Clinical Pharmacology (12.3)]*.	***Use in the elderly*** Clinical trials did not include sufficient numbers of subjects 65 years of age and over to determine if they respond differently than younger subjects.
8.6 Renal Impairment The pharmacokinetics of ARAKODA have not been studied in patients with renal impairment. If ARAKODA is administered to such patients, monitoring for adverse reactions associated with ARAKODA is needed *[see Warnings and Precautions (5), Adverse Reactions (6)]*.	***Use in renal impairment*** Tafenoquine pharmacokinetics have not been studied in patients with renal impairment. Patients with serum creatinine >1.8 mg/dL were excluded from the pivotal clinical trials.

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8.7 Hepatic Impairment The pharmacokinetics of ARAKODA have not been studied in patients with hepatic impairment. If ARAKODA is administered to such patients, monitoring for adverse reactions associated with ARAKODA is needed *[see Warnings and Precautions (5), Adverse Reactions (6)]*.	***Use in hepatic impairment*** Tafenoquine pharmacokinetics have not been studied in patients with hepatic impairment. Patients with serum levels of ALT >60 U/L and total bilirubin levels >2.0 mg/dL were excluded or infrequently entered in the pivotal clinical trials (mean ALT = 28 U/L, SD=12; mean total bilirubin = 0.5 mg/dL, SD=0.3).
10 OVERDOSAGE There were no reported cases of ARAKODA overdose. Hemoglobin decline and methemoglobinemia may be encountered in an overdose with ARAKODA. Treatment of overdosage consists of institution of appropriate symptomatic and/or supportive therapy.	**4.9 OVERDOSE** There were no reported cases of KODATEF overdose. However, based on clinical experience with individual doses above 200 mg, early symptoms of KODATEF overdose are likely to be gastrointestinal (nausea, vomiting, diarrhoea, and abdominal pain). Haematologic events (haemolytic anaemia and methaemoglobinaemia), may also be seen. Haemolytic anaemia is also to be expected if normal KODATEF doses are administered in error to subjects deficient in G6PD. Patients should contact their health care provider if they have darker lips or urine (see Section 5 PHARMACOLOGICAL PROPERTIES), as these may be signs of haemolysis or methaemoglobinaemia. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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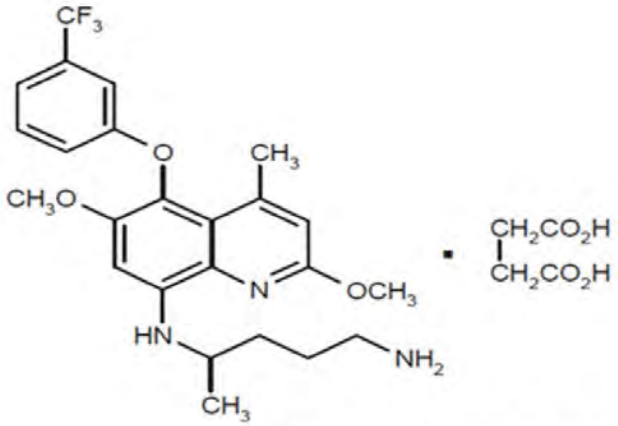
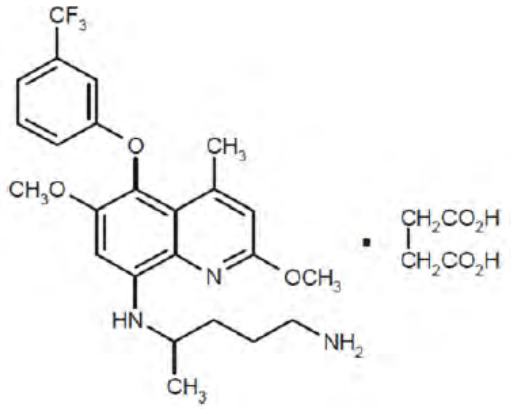
11 DESCRIPTION ARAKODA contains tafenoquine succinate, an antimalarial agent for oral administration. The structural formula of tafenoquine succinate is:  **Figure 1: Tafenoquine Succinate Structure** The chemical name of tafenoquine succinate is (±)-8-[(4-amino-1-methylbutyl) amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl) phenoxy]quinoline succinate. The molecular formula of tafenoquine succinate is $C_{24}H_{28}F_3N_3O_3 \cdot C_4H_4O_4$ and its molecular weight is 581.6 as the succinate salt (463.49 as free base). Each ARAKODA tablet contains 100 mg of tafenoquine (equivalent to 125.5 mg of tafenoquine succinate). Inactive ingredients include magnesium stearate, mannitol, and microcrystalline cellulose. The tablet film coating inactive ingredients include: hypromellose, iron oxide red, macrogol/polyethylene glycol and titanium dioxide.	**6.7 PHYSICOCHEMICAL PROPERTIES** ***Chemical structure*** **Chemical name:** 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline succinate. ***Structural formula***  ***Molecular weight*** 463.49 (free base anhydrous) 581.58 (succinate salt) ***Molecular Formula*** $C_{24}H_{28}F_3N_3O_3 \cdot C_4H_4O_4$ Tafenoquine succinate, is an off-white to pink/orange/brown crystalline powder and exhibits the highest solubility at pH 1 (25°C and 37°C), pH 2 (37°C) and pH 4 (37°C), and negligible solubility at all other tested pH values at 25°C and 37°C. ***CAS number*** 106635-80-7 (tafenoquine free base) and 106635-81-8 (tafenoquine succinate) (Source Chemical Book).

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<Excipients are listed directly above>	**6.1 LIST OF EXCIPIENTS** KODATEF also contains: • Microcrystalline cellulose. • Mannitol. • Magnesium stearate. • Hypromellose. • Titanium dioxide. • Iron oxide red and • Macrogol 400.
12 CLINICAL PHARMACOLOGY **12.1 Mechanism of Action** Tafenoquine is an 8-aminoquinoline antimalarial drug *[see Microbiology (12.4)]*.	**5 PHARMACOLOGICAL PROPERTIES** **5.1 PHARMACODYNAMIC PROPERTIES** ***Mechanism of action*** Tafenoquine kills the developing asexual, developing exoerythrocytic, and latent hypnozoites of malaria parasites. The mechanism of action is unknown, but is hypothesised to involve redox reactions.

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12.2 Pharmacodynamics **Cardiac Electrophysiology** The effect of tafenoquine on the QT interval was evaluated in a study of healthy adult subjects. In this study, subjects received once daily 400 mg (2 times the approved recommended dosage) doses of tafenoquine for 3 days. The results suggest that the mean increase in the QTcF interval for tafenoquine is less than 20 msec. ***<The in vitro hERG study data presented in the KODATEF PI is not included in the ARAKODA PI>***	***Safety Pharmacology*** The effect of tafenoquine on the QT interval was evaluated in a trial of healthy adult subjects. In this trial, subjects received once daily 400 mg (2 times the approved recommended dosage) doses of tafenoquine for 3 days. The results suggest that the mean increase in the QTcF interval for tafenoquine is less than 20 msec. In vitro studies with tafenoquine suggested potential effect on heart conductance, as it inhibited hERG tail current in a dose-dependent manner (IC50 0.51 μ g/mL) and at 100-fold higher concentrations (46.4 µg/mL) caused a non-specific effect on the conduction through heart purkinje fibres of the dog. In vivo, tafenoquine caused systemic vasodilation when given by IV infusion to anaesthetised dogs but at oral doses up to 16 mg/kg had no cardiovascular effect in the conscious dog. The dog AUC0-1 week of 116 µg.hr/mL following 16 mg/kg is approximately five-times higher than the clinical AUC following a clinical dose of 600 mg.

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12.3 Pharmacokinetics **Absorption** A food effect study was not conducted with the 100 mg ARAKODA tablet. In majority of the clinical trials, tafenoquine was administered under fed conditions. Table 5 provides the pharmacokinetics of tafenoquine following single dose administration of 200 mg ARAKODA (two 100-mg ARAKODA tablets) in 65 healthy adult subjects under fed conditions. In this study, ARAKODA was administered with a high-calorie, high-fat meal (approximately 1000 calories with 19% protein, 31% carbohydrate, and 50% fat). **Table 5. Mean (%CV) Pharmacokinetic Parameters of Tafenoquine Following Single Oral Administration of Two 100-mg ARAKODA Tablets Under Fed Conditions in Healthy Adult Subjects (N=65)** **Parameter** / **Value** C_{max} — 147 ng/mL (20.7%)[a] T_{max} — 14 hr (6 - 72 hr)[b] AUC_{inf} — 70 hr*mcg/mL (24.6%)[a, c] [a] Coefficient of Variance (CV) [b] Median and (Range) [c] Plasma tafenoquine AUC_{inf} increased by 41% when tafenoquine was administered as an investigational capsule formulation with a high-calorie, high-fat meal compared with the fasted state. Following administration of a single dose of tafenoquine orally under fasted conditions in healthy adult subjects, AUC and C increased dose proportionally over the dose range from 100 mg to 400 mg. When healthy adult subjects received once-weekly administrations of 200 mg tafenoquine orally for ten weeks without a loading dose under fasting conditions, the mean plasma accumulation ratio of tafenoquine was approximately 4.4.	**5.2 PHARMACOKINETIC PROPERTIES** ***Absorption*** Tafenoquine plasma concentrations were generally higher following administration of a single dose of tafenoquine under fed compared with fasting conditions, with mean fed: fasted ratios of 1.41 (AUC) and 1.31 (Cmax). Tmax and t½ were similar under fasting and fed states. However, population PK analyses demonstrated that after the recommended regimen of 200 mg/day times 3 days for loading followed by 200 mg weekly, trough tafenoquine values even in the non-fed state were above the value of 80 ng/mL (the minimum target trough value for prevention of symptomatic malaria in non-immune individuals) by the end of the loading dose. By the sixth weekly dose, exposure in the fasted state is predicted to equal exposure in the fed state. ***Dose-PK relationships*** Following administration of a single dose to healthy males, AUC and Cmax were dose-proportional. When healthy volunteers received 10 weekly administrations of 200 mg without a loading dose while fasting, the accumulation ratio was approximately 4.

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Specific Populations The pharmacokinetics of tafenoquine were not significantly impacted by age, sex, ethnicity, and body weight. The effect of renal or hepatic impairment on tafenoquine pharmacokinetics is unknown.	A population PK analysis in healthy subjects was conducted consolidating clinical PK data from Trials 001, 002, 003, 004, 005, 014, 015, 033, 044 and 058. Covariates common to all 10 trials were age, weight, race, sex and meal schedule. The analysis comprised 866 participants across the trials. The total analysis population was 93.3% male; median age 25 years, mean weight 75.0 kg and 72.3% Caucasian/white. The majority of participants (89.4%) took tafenoquine under fed conditions (i.e., after a meal). A one-compartment PK model with first-order absorption and elimination processes was specified in the NONMEM control file and was parameterised in terms of apparent CL/F, V/F and ka. Key pharmacokinetic parameters from the population PK analysis and from Trial 051 data are shown in Table 7. Table 7: Key Pharmacokinetic Parameters for Tafenoquine **Parameter** / **Value** *Volume of distribution/F — 2470 L (inter-individual variability = 24%) *Clearance/F — 4.17 L/hour (inter-individual variability = 24%) *K_a — 0.359 L/hour (inter-individual variability = 54%) *Half-life ($t_{½}$) — 17 days **$t_{max,ss}$ — 7.0 hours *$C_{max,ss}$ — Approximately 300 ng/mL *$C_{min,ss}$ — >80 ng/mL will be present in >95% of individuals *From population PK analysis **From Trial 051 SS=steady state.

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12.3 Pharmacokinetics **Distribution** Tafenoquine is greater than 99.5% bound to protein in humans. The apparent volume of distribution of tafenoquine in healthy adult subjects is 2470 L [Inter-Individual Variability (IIV): 24.1 %]. **Elimination** The apparent oral clearance of tafenoquine is approximately 4.2 L/hr (IIV: 23.6 %) in healthy adult subjects. The mean terminal half-life following administration of ARAKODA is approximately 16.5 days (range: 10.8 days to 27.3 days) in healthy adult subjects. ***Excretion*** The full excretion profile of tafenoquine in humans is unknown.	**5.2 PHARMACOKINETIC PROPERTIES** ***Distribution*** In healthy male volunteers administered one dose of 100 mg, 200 mg, or 400 mg while fasting, blood and calculated RBC concentrations were 2.0 and 3.4 times higher than corresponding plasma concentrations, and there was no change in RBC accumulation over time. In humans, >99.5% of tafenoquine is bound to plasma protein. ***Excretion*** The major route of excretion in the rat, dog and monkey was via the faeces and to a lesser extent via the urine. Overall excretion of radioactivity in animals was slow. In bile-cannulated animals, equal amounts were recovered in bile and faeces in dogs (20% of dose in 7 days) and 5% of dose in bile and 75% of dose in faeces in rats in 4 days. Human radiolabeled mass balance studies have not been conducted to characterise the clinical excretion of tafenoquine.
Metabolism Negligible metabolism of tafenoquine was observed in vitro in human liver microsomes and hepatocytes. Following administration of tafenoquine orally, once daily for three days to healthy adult subjects, unchanged tafenoquine represented the only notable drug-related component in plasma at approximately 3 days following the first dose of tafenoquine.	***Metabolism*** In human biomaterials studied in vitro, minimal metabolism of tafenoquine occurred. When tafenoquine 400 mg per day for three days was administered to humans, only parent tafenoquine was extractable in plasma drawn 80 hours after the first dose.

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12.3 Pharmacokinetics **Drug Interaction Studies** ***Clinical Studies*** No clinically significant effects on the pharmacokinetics of substrates of cytochrome P450 isoenzymes (CYP)1A2 (caffeine), CYP2D6 (desipramine), CYP2C9 (flurbiprofen), or CYP3A4 (midazolam) were observed following coadministration with tafenoquine in healthy adult subjects. ***In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically*** Tafenoquine inhibited metformin transport via human OCT2, MATE1 and MATE2-K transporters *[see Drug Interactions (7)]*. Tafenoquine is not an inhibitor of human breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), Organic anion transporter 1/3 (OAT1 or OAT3), Organic anion transporting polypeptide 1B1/1B3 (OATP1B1 or OATP1B3) mediated transport at clinically relevant concentrations. Tafenoquine is also not a substrate of human OATP1B1 or OATP1B3 at clinically relevant concentrations. It is inconclusive as to whether tafenoquine is a substrate of P-gp and/or BCRP mediated transport.	**5.2 PHARMACOKINETIC PROPERTIES** ***Drug-drug interactions*** Tafenoquine does not significantly inhibit or induce CYP2D6, CYP3A4, CYP2C9 or CYP1A2, since in phase 1 trials, the PK parameters of the CYP2D6 substrate desipramine, the CYP3A4 substrate midazolam, the CYP2C9 substrate Flurbiprofen and the CYP1A2 substrate caffeine were unaffected by co-administration of tafenoquine. Tafenoquine was a potent inhibitor of renal multidrug and toxin extrusion transporters (MATE) and organic cation transporter 2 in vitro. Since inhibition of these transporters may lead to increased exposure to medications that they excrete, when tafenoquine is co-administered with procainamide, it may be advisable to re-evaluate safety and/or efficacy of procainamide. Tafenoquine inhibited the in vitro transport of [14C] metformin via OCT2, MATE1, and MATE2-K. Risk assessments based on systemic concentrations of tafenoquine at therapeutic doses, compared with the metformin IC50 values derived from in vitro transporter inhibition studies, were conducted and indicated a potential, but low, drug interaction risk with OCT2, MATE1 and/or MATE2K substrates. Clinical predictions indicate there may be a potential, but low, risk of lactic acidosis in subjects who receive tafenoquine and metformin concomitantly, due to an increased exposure to metformin arising from this interaction.

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12.4 Microbiology **Mechanism of Action** Tafenoquine, an 8-aminoquinoline antimalarial, is active against all the stages of *Plasmodium* species that include the hypnozoite (dormant stage) in the liver. Studies in vitro with the erythrocytic forms of *Plasmodium falciparum* suggest that tafenoquine may exert its effect by inhibiting hematin polymerization and inducing apoptotic like death of the parasite. In addition to its effect on the parasite, tafenoquine causes red blood cell shrinkage in vitro. The molecular target of tafenoquine is not known. **Antimicrobial activity** Tafenoquine is active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *Plasmodium* species that include *P. falciparum* and *P. vivax.* The activity of tafenoquine against the pre-erythrocytic liver stages of the parasite, prevents the development of the erythrocytic forms of the parasite *[see Clinical Studies (14)]*. **Resistance** A potential for development of resistance of *Plasmodium* species to tafenoquine was not evaluated. Studies with the erythrocytic forms of *P. falciparum* strains/isolates suggest a potential for cross-resistance with primaquine, an 8-aminoquinoline. Clinical relevance of such findings is not known.	**5.1 PHARMACODYNAMIC PROPERTIES** **Mechanism of action** Tafenoquine kills the developing asexual, developing exoerythrocytic, and latent hypnozoites of malaria parasites. The mechanism of action is unknown, but is hypothesised to involve redox reactions.

ARAKODA- tafenoquine tablet, film coated ARAKODA™ (tafenoquine) tablets, for oral use	KODATEF® (TAFENOQUINE SUCCINATE) ORAL FILM-COATED TABLETS
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** **Carcinogenesis** Two-year oral carcinogenicity studies were conducted in rats and mice. Renal cell adenomas and carcinomas were increased in male rats at doses 1 mg/kg/day and above (0.5 times the clinical exposure based on AUC comparisons). Tafenoquine was not carcinogenic in mice. The relevance of these findings to a carcinogenic risk in humans is unclear.	**5.3 PRECLINICAL SAFETY DATA** ***Carcinogenicity*** Two two-year oral carcinogenicity studies were performed; 1 in the mouse and 1 in the rat. Oral administration of doses up to 1.0 mg/kg/day (approximately 0.3 times the clinical exposure based on AUC) for 2 years produced no clear evidence of an increase in the incidence of tumours in treated mice of either sex. Tafenoquine administration was associated with an increase in the incidence of renal tumours and hyperplasia in male rats following administration of 1.0 and/or 2.0 mg/kg/day (0.5 times the clinical exposure based on AUC). The exact mechanism behind renal tumor development is unknown but may be the result of multi-factorial, nongenotoxic modes of action, possibly potentiated by chronic progressive nephropathy (CPN). CPN is a spontaneous age-related disease that occurs at a high incidence in rat strains used in preclinical toxicology studies, exhibiting a predisposition in male rats. The relevance of these findings for a carcinogenic risk in humans is unclear.
Mutagenesis Tafenoquine did not cause mutations or chromosomal damage in 2 definitive in vitro tests (bacterial mutation assay and mouse lymphoma L5178Y cell assay) or in an in vivo oral rat micronucleus test.	***Genotoxicity*** The mutagenic and clastogenic potential of tafenoquine has been assessed in bacterial gene mutation assays and in vitro gene mutation assays in mammalian cells (mouse lymphoma cells and Chinese hamster ovary cells), in vitro chromosome aberration assays in Chinese hamster ovary cells, and one mouse in vivo micronucleus study. Based on these studies, tafenoquine is not considered to present a genotoxic risk to humans.

ARAKODA- tafenoquine tablet, film coated ARAKODA™ (tafenoquine) tablets, for oral use	KODATEF® (TAFENOQUINE SUCCINATE) ORAL FILM-COATED TABLETS
Impairment of 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 fetuses, implantation sites, and corpora lutea at 15 mg/kg in the presence of maternal toxicity (mortality, piloerection, rough coat, and reduced body weight).	***Effects on fertility*** Tafenoquine had no effects on mating, estrous cycles, sperm motility, sperm count or morphology in rats dosed with tafenoquine at up to 15 mg/kg/day (approximately 6 times the clinical exposure based on AUC). However, the number of corpora lutea was decreased at 15 mg/kg/day, resulting in lower numbers of implantations and viable foetuses. There was no effect on fertility at 5 mg/kg/day (approximately 2 times the clinical exposure based on AUC). **4.6 FERTILITY, PREGNANCY AND LACTATION** Tafenoquine resulted in dose related abortions when given orally to pregnant rabbits during organogenesis (gestational day 6 to 18), at doses of 7 mg/kg (about 4.5 times the clinical dose on a mg/m2/week basis) 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 but no foetotoxicity, at the high dose (equivalent to 10 times the clinical dose on a mg/m2/week basis). There was no evidence of malformations in either species.

ARAKODA- tafenoquine tablet, film coated ARAKODA™ (tafenoquine) tablets, for oral use	KODATEF® (TAFENOQUINE SUCCINATE) ORAL FILM-COATED TABLETS
16 HOW SUPPLIED/STORAGE AND HANDLING **How Supplied** ARAKODA tablets contain 100 mg of tafenoquine (equivalent to 125.5 mg of tafenoquine succinate) and are dark pink, film-coated, capsule-shaped, and debossed with 'TQ100' on one side. ARAKODA tablets are packed in blister packs or bottles. For the blister pack presentation, ARAKODA tablets are packed in polyamide aluminum and PVC formable laminate backed blisters with a polyethylene terephthalate aluminum foil cover. Each blister card contains 8 tablets. Each package contains 2 blister cards (16 tablets) housed in a contiguous outer paperboard child-resistant carton component (NDC 71475-257-01). For the bottle presentation, ARAKODA tablets are packed in 40 cc, 33 mm white high density polyethylene bottles with a 33 mm polypropylene screw-top child resistant cap with an induction seal liner. Each bottle contains 8 tablets (NDC 71475-257-02). **Storage** Store at less than 30°C (86°F). Protect from moisture. Dispense only in the original carton or bottle.	**6.5 NATURE AND CONTENTS OF CONTAINER** **KODATEF 100 mg film-coated tablets are packed in polyamide aluminium and PVC formable laminate backed blisters with a peelable polyethylene terephthalate aluminium foil and paper cover. Each blister card contains eight film-coated tablets. Each carton contains 16 film-coated tablets (two blister cards).** **6.4 SPECIAL PRECAUTIONS FOR STORAGE** Store below 30°C. Store in original container. Dispense only in the original carton.
Manufactured for: 60° Pharmaceuticals, LLC. 1025 Connecticut Ave., NW, Suite 1000 Washington DC 20036	**8 SPONSOR** Biocelect Pty Ltd Level 29, 66 Goulburn Street, SYDNEY, NSW 2000 Website: www.biocelect.com/products/kodatef

ARAKODA- tafenoquine tablet, film coated **ARAKODA™ (tafenoquine) tablets, for oral use**	**KODATEF® (TAFENOQUINE SUCCINATE)** **ORAL FILM-COATED TABLETS**
17 PATIENT COUNSELING INFORMATION **<see ARAKODA PI>**	There is no equivalent section in the KODATEF PI
Medication Guide **<see ARAKODA PI>**	No medication guide is provided.
The ARAKODA PI does not have an equivalent warning.	**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** ***Effects on laboratory tests*** The use of KODATEF may influence the results of certain laboratory tests including biochemical parameters of the liver and kidneys and haematology parameters. These changes, which are expected due to the oxidative nature of 8-aminoquinoline drugs, generally remain within the normal laboratory range of each parameter. Biochemical parameter changes may include mild ALT elevations (> 60 U/L) and serum creatinine elevations > 1.8 mg/dL. Change in haematology parameters, may specifically include a reduction of haemoglobin > 0.66 g/dL and methaemoglobin increases to >1%. Methaemoglobin does not increase to as much as 10%, a level associated with hypoxia.
The ARAKODA PI does not have equivalent section.	**5.2 PHARMACOKINETIC PROPERTIES** ***PK-PD relationships*** Trials in non-immune persons (those without prior malaria exposure), a population similar to the population for which malaria prevention is intended, showed that symptomatic breakthrough of malaria only occurred when tafenoquine plasma concentrations were <50 ng/mL. Consequently, a precautionary plasma concentration of 80 ng/mL was selected as the minimum target trough value for prevention of symptomatic malaria development in non-immune individuals. Population PK analysis predicts that the recommended prevention regimen will achieve trough levels >80 ng/mL in >95% of subjects.

ARAKODA – Clinical Trial Summaries

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of tafenoquine was studied in clinical trials at various doses and regimens in 3,184 subjects. The recommended ARAKODA regimen was evaluated in 825 subjects in 5 controlled clinical trials (Trials 1, Trial 2, Trial 3, Trial 4 and Trial 5). The mean duration of exposure to ARAKODA in these five clinical trials was 21 weeks (range 10-29 weeks). Trial 1, 2 and 4 were conducted in healthy semi-immune volunteers in Ghana or Kenya and were placebo-controlled; a mefloquine arm was included in Trials 2 and 4 as a benchmark. Trial 3, an active comparator (mefloquine) controlled trial was conducted in healthy soldiers deployed in East Timor (Timor Leste). A placebo-controlled Trial 5 was conducted in healthy volunteers in the United States and United Kingdom. The mean age of the subjects included in the five trials was 29 years (range 17 to 69 years); 84% were male.

Adverse Reactions Reported with ARAKODA in Trial 3 and Pooled Trials 1, 2, 4, and 5

Adverse reactions occurring in ≥1% of subjects in the ARAKODA group in the placebo controlled pooled Trials 1, 2, 3, and 4 are presented in Table 3.

Table 3: Selected Adverse Reactions Occurring in ≥1% of Subjects Receiving ARAKODA in Pooled Trials 1, 2, 4, and 5 (Non-Deployed Subjects)

Adverse Reaction	ARAKODA[1] (n=333) %	Placebo (n=295) %	Mefloquine[2] (n=147) %
Nervous system Disorders	35	34	47
Headache[3]	32	32	44
Dizziness[4]	5	3	10
Musculoskeletal and connective tissue disorders	27	26	37
Back pain	14	9	11
Gastrointestinal disorders	31	33	46
Diarrhea	5	3	1
Nausea	5	2	2
Vomiting	2	2	1
Investigations	8	7	11
Alanine Aminotransferase (ALT) increased/abnormal	4	2	3
Psychiatric disorders	2	1	2

[1] ARAKODA was administered as 200 mg daily for 3 days, then 200 mg weekly
[2] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly
[3] Includes headache, sinus headache, migraine and tension headache.
[4] Includes dizziness and dizziness postural
[5] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.

Adverse Reaction	ARAKODA[1] (n=333) %	Placebo (n=295) %	Mefloquine[2] (n=147) %
Any sleep symptom[5]	1	1	0
Insomnia	1	1	0
Depression/depressed mood	1	0	0

[1] ARAKODA was administered as 200 mg daily for 3 days, then 200 mg weekly
[2] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly
[3] Includes headache, sinus headache, migraine and tension headache.
[4] Includes dizziness and dizziness postural
[5] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.

Adverse reactions occurring in ≥1% of subjects in the ARAKODA group in the active control Trial 3 conducted in military personnel deployed to malaria endemic areas are presented in Table 4.

Table 4: Selected Adverse Reactions Occurring in ≥1% of Subjects Receiving ARAKODA in Trial 3 (Deployed Subjects)

Adverse Reaction	ARAKODA[1] (n=492) %	Mefloquine[2] (n=162) %
Nervous system Disorders	22	27
Headache[3]	15	19
Dizziness[4]	1	1
Ear and labyrinth Disorders	7	11
Motion sicknesss[5]	5	6
Musculoskeletal and connective tissue disorders	29	30
Back pain	14	15
Gastrointestinal disorders	36	41
Diarrhea	18	20
Nausea	7	9
Vomiting	5	6
Psychiatric disorders	5	4
Any sleep symptom[6]	4	4
Insomnia	2	1
Abnormal dreams[7]	2	2
Anxiety[8]	1	0

[1] ARAKODA was administered as 200 mg daily for 3 days, then 200 mg weekly
[2] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly
[3] Includes headache, sinus headache, migraine and tension headache.
[4] Includes dizziness and dizziness postural
[5] Includes motion sickness, vertigo and vertigo positional.
[6] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.
[7] Includes abnormal dreams, nightmares
[8] Includes anxiety disorder, panic attack and stress.

Clinically Significant Adverse Reactions in Trials 1 to 5 (Overall Safety Population) Clinically significant adverse reactions with ARAKODA (200 mg daily for 3 days, followed by 200 mg weekly) in Trials 1 to 5 (n= 825) are described below:

Ocular Adverse Reactions

Vortex keratopathy was reported in 21% to 93% of subjects receiving ARAKODA in the trials which included ophthalmic evaluations (Trials 3, 5, and Trial 6 (NCT # 01290601), an active-control trial in patients from Thailand with *P. vivax* malaria. The keratopathy did not result in any apparent functional visual changes and resolved within one year after drug cessation in all patients. Retinal abnormalities were noted in less than 1% of subjects receiving ARAKODA.

A total of 7 serious ocular adverse reactions (SARs) were reported in ARAKODA-treated subjects in the trials which included ophthalmic evaluations: 5 reports of keratopathy and two reports of retinal disorders.

Laboratory Abnormalities

Methemoglobinemia: Asymptomatic methemoglobin elevations were observed in 13% of subjects receiving ARAKODA.

Hemoglobin decrease: Hemoglobin decreases of ≥ 3 g/dL were observed in 2.3% of subjects receiving ARAKODA.

Adverse Reactions Reported in < 1% of Subjects Receiving ARAKODA in Trials 1 to 5.

The following selected adverse reactions were reported in subjects receiving ARAKODA in Trials 1 to 5 at a rate of less than 1%.

Blood and lymphatic system disorders: hemolytic anemia, anemia, thrombocytopenia

Ear and labyrinth disorders: hyperacusis, Meniere's disease

Eye disorders: night blindness, photophobia, blurred vision, visual acuity reduced, visual impairment, vitreous floaters

Hepatobiliary disorders: hyperbilirubinemia, jaundice cholestatic

Immune system disorders: hypersensitivity

Investigations: blood bilirubin increased, blood creatinine increased, glomerular filtration rate decreased

Nervous system disorders: amnesia, coordination abnormal, hyperesthesia, hypoesthesia, somnolence, syncope, tremor, visual field defect

Psychiatric disorders: agitation, neurosis

Skin and subcutaneous tissue disorders: urticaria.

14 CLINICAL STUDIES

Clinical Trials 1, 2, and 3

Three double-blind, randomized, controlled studies have been performed to evaluate the efficacy of ARAKODA.

Trial 1 (NCT #02491606) was a Phase IIb, placebo-controlled study conducted in Kenya, an area of holoendemic *P. falciparum* malaria. After taking a three-day presumptive course of halofantrine to eliminate any existing parasitemia, subjects were randomized into one of four groups (placebo and three different ARAKODA dosing groups; one group received 200 mg once daily for 3 days, then a maintenance regimen of weekly dose of 200 mg for 10-15 weeks). Sixty-one percent of subjects were male. The mean age was 32.4 years (range 17-55). Subjects were evaluated for parasitemia by weekly blood smears. Protective efficacy at 15 weeks was defined based on the reduced incidence of parasitemia during the prophylaxis phase relative to placebo. The results in the intention-to-treat population, which included all subjects who received three doses of halofantrine and were randomized, are shown in Table 6 below.

Table 6: Incidence of Parasitemia and Protective Efficacy of ARAKODA at 15 weeks for Trial 1

	Placebo	**ARAKODA[1]**
Number of subjects	62	61
Subjects free of parasitemia	5 (8.1%)	46 (75.4)
Subjects with parasitemia	54 (87.1%)	7 (11.5%)
Subjects with missing data	3 (4.8%)	8 (13.1%)
Protective efficacy [98.3% CI][2]	–	73.3% [54.0%, 84.5%]

[1] 200 mg once daily for 3 days, then 200 mg weekly for 10-15 weeks

[2] Protective efficacy is reduced incidence of parasitemia relative to placebo (0: no protection; 1: full protection); CI: confidence interval. Bonferroni adjustment was used for multiple comparisons. Missing outcome was considered a failure due to parasitemia for this analysis.

Trial 2 (NCT #02488902) was a comparison of tafenoquine to placebo for prophylaxis in healthy semi-immune residents of a malarious region in Ghana. After treating existing parasitemia with quinine/doxycycline/primaquine, subjects were randomized into prophylactic groups including ARAKODA and placebo. Patients were administered a loading regimen of daily drug or placebo for 3 days followed by a maintenance regimen of weekly drug or placebo for 12 weeks. For the ARAKODA and placebo groups, males were 65% of the total population. The mean age was 38.4 years and 53.5 years for males and females, respectively, as women in reproductive ages were excluded from the study. The mean weight was 55.4 kg and 47.5 kg for males and females, respectively. Subjects were evaluated for parasitemia by weekly blood smears. Parasitemia required a blood smear positive for asexual stage of *P. falciparum*. The incidence of parasitemia at week 12 for all randomized subjects who received at least one dose of ARAKODA or placebo is presented in Table 7 below.

Table 7: Incidence of Parasitemia and Protective Efficacy of ARAKODA at Week 12 for Trial 2

	Placebo	**ARAKODA[1]**
Number of subjects	94	93
Subjects free of parasitemia	6 (6.4%)	68 (73.1%)
Subjects with parasitemia	86 (91.5%)	12 (12.9%)
Subjects with missing data	2 (2.1%)	13 (14.0%)
Protective efficacy [98.75% CI][2]	–	71.3% [55.8%, 81.4%]

[1] 200 mg once daily for 3 days, then 200 mg weekly for 12 weeks
[2] Protective efficacy is reduced incidence of parasitemia relative to placebo; CI: confidence interval. Bonferroni adjustment was used for multiple comparisons. Missing outcome was considered a failure due to parasitemia for this analysis.

Trial 3 compared ARAKODA with mefloquine for the prophylaxis of both *P. falciparum* and *P. vivax* malaria in healthy non-immune soldiers deployed to East Timor (now Timor-Leste). No subject developed malaria during the 26-week prophylactic phase. Subjects were exposed to *P. vivax* and there is a high likelihood that the study subjects were also exposed to *P. falciparum*. Since the precise degree of exposure to malaria in study subjects is unknown, this study provides only supportive evidence of efficacy.

Clinical Trial 7
In a randomized, double-blind, placebo-controlled trial (Trial 7) in healthy, non-immune volunteers, ARAKODA was shown to have prophylactic activity directed against blood-stage *P. falciparum* parasites. Twelve subjects received ARAKODA (200 mg once daily for 3 days, then 200 mg on 10 day) and 4 subjects received placebo. On Day 13, subjects were inoculated with erythrocytes containing viable *P. falciparum* parasites. Fifteen subjects (93.8%) were of white race. The mean age was 27.5 years (range 20-42). The mean body weight was 72.3 kg (range 56-97.7). The efficacy endpoint was parasitemia by Day 34; parasitemia was based on detection of *P. falciparum* 18S ribosomal DNA by real time polymerase chain reaction assay (PCR). There was a statistically significant difference in malaria incidence between the two groups; 4/4 (100%) subjects in the placebo group had detectable parasites from Day 17 compared to 0/12 (0%) subjects on ARAKODA were PCR negative at all visits ($p<0.0005$).

KODATEF – Clinical Trial Summaries

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

The safety of tafenoquine was studied in clinical trials at various doses and regimens in 3,184 subjects. The recommended KODATEF malaria prevention regimen was evaluated in 825 subjects in 5 controlled clinical trials (Trials 043, 045, 030, 033, and 057). The mean duration of exposure to KODATEF in these five clinical trials was 21 weeks (range 10-29 weeks). Trial 043, 045 and 030 were conducted in healthy, semi-immune, indigenous African volunteers in Ghana or Kenya and were placebo-controlled; a mefloquine arm was included in Trials 045 and 030 as a benchmark. Possible asymptomatic parasitaemia was cleared prior to initial receipt of trial drugs in these African studies.

Trial 033, an active comparator (mefloquine) controlled trial was conducted in healthy Australian soldiers deployed in East Timor (now Timor Leste) for a peace-keeping operation at which time trial drugs were administered. A placebo-controlled Trial 057 was a renal and ophthalmic safety trial conducted in healthy volunteers in the United States and United Kingdom. The mean age of the subjects included in the five trials was 29 years (range 17 to 69 years); 84% were male. The number of randomised placebo subjects in these trials plus one other (Trial 044) was 396. Because clinical trials are conducted under widely v arying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Serious Adverse Events and Treatment Discontinuations

A total of 49 serious adverse events (SAEs) were reported in tafenoquine-treated subjects (5.9 per 100 subjects) compared to 23 SAEs in placebo-treated subject (5.8 per 100 subjects). Of the 49 SAEs in tafenoquine-treated subjects, only 23 were SAEs that were considered “treatment-related” (includes unlikely, possibly, or probably treatment-related). Of these 23 SAEs: seven were an eye disorder, 5 were decreased glomerular filtration rate, 4 were an infection or infestation, 4 were gastrointestinal disorders, 2 were a nervous system disorder, and 1 was a blood/lymphatic tissue disorder. Of the 23 SAEs in placebo subjects, 10 were considered treatment-related” affecting 9 subjects. Of these 10 treatment-related SAEs: 1 was an eye disorder, 2 were decreased glomerular filtration rate, 3 were an infection or infestation, 1 was a gastrointestinal disorder, 1 was a nervous system disorder, and 2 were general disorders and administration site conditions.

The most common treatment-related adverse reactions leading to treatment discontinuation in tafenoquine-treated subjects were increased ALT (6 subjects), decreased haemoglobin (3 subjects), and decreased GFR (2 subjects). Only 1 or 2 subjects were discontinued due to AEs in other body systems. The most common treatment-related adverse reactions leading to treatment

discontinuation in placebo-treated subjects were increased ALT (1 subject), decreased haemoglobin (1 subject), and decreased platelet count (1 subject). In addition, 1 placebo-treated subject was discontinued for headache and 1 for metamorphopsia.

Eye Findings

Vortex keratopathy (specifically, corneal deposits that can only be detected during a medical examination) was reported in 21% to 93% of subjects receiving KODATEF for 3-6 months in the three trials that included ophthalmic evaluations. The vortex keratopathy did not result in any apparent functional visual changes, including no loss of night vision, and resolved within 1 year after drug cessation in all subjects. Retinal abnormalities were noted in less than 1% of subjects receiving KODATEF. A total of 7 ocular adverse events were reported to regulatory authorities, 5 reports of vortex keratopathy after the initial findings and 2 reports of retinal disorders.

Laboratory Abnormalities

Methaemoglobinemia: Asymptomatic methaemoglobin elevations were observed in 13% of subjects receiving KODATEF.
Haemoglobin decrease: Haemoglobin decreases of ≥3 g/dL were observed in 2.3% of subjects receiving KODATEF.

Common Adverse Events

Adverse reactions occurring in ≥1% of subjects in the KODATEF group in the active-control Trial 033 conducted in military personnel deployed to malaria endemic areas are presented in Table 3.

Table 3: Selected Adverse Reactions Occurring in ≥1% of Subjects ReceivingKODATEF in Trial 033 (Deployed Subjects)

Adverse Reaction	KODATEF[1] (n=492) %	Mefloquine[2] (n=162) %
Nervous system Disorders	22	27
Headache[3]	15	19
Dizziness[4]	1	1
Ear and labyrinth Disorders	7	11
Motion sicknesss[5]	5	6
Musculoskeletal and connective tissue disorders	29	30
Adverse Reaction	**KODATEF[1] (n=492) %**	**Mefloquine[2] (n=162) %**
Back pain	14	15
Gastrointestinal disorders	36	41
Diarrhea	18	20
Nausea	7	9
Vomiting	5	6
Psychiatric disorders	5	4
Any sleep symptom[6]	4	4
Insomnia	2	1
Abnormal dreams[7]	2	2
Anxiety[8]	1	0

[1] KODATEF was administered as 200 mg daily for 3 days, then 200 mg weekly.
[2] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly.
[3] Includes headache, sinus headache, migraine and tension headache.
[4] Includes dizziness and dizziness postural.
[5] Includes motion sickness, vertigo and vertigo positional.
[6] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.
[7] Includes abnormal dreams, nightmares.
[8] Includes anxiety disorder, panic attack and stress.

Adverse reactions occurring in ≥1% of subjects in the KODATEF group in the placebo-controlled pooled data from Trials 043, 045, 030 and 057 are presented in Table 4.

Table 4 Selected Adverse Reactions Occurring in ≥1% of Subjects Receiving KODATEF in Pooled Trials 043, 045, 030, and 057 (Non-Deployed Subjects)[1]

Adverse Reaction	KODATEF[2] (n=333) %	Placebo (n=295) %	Mefloquine[3] (n=147) %
Nervous system Disorders	35	34	47
Headache[4]	32	32	44
Dizziness[5]	5	3	10
Musculoskeletal and connective tissue disorders	27	26	37
Back pain	14	9	11
Gastrointestinal disorders	31	33	46
Diarrhoea	5	3	1
Nausea	5	2	2
Vomiting	2	2	1
Investigations	8	7	11
ALT increased/abnormal	4	2	3
Psychiatric disorders	2	1	2
Any sleep symptom[6]	1	1	0
Insomnia	1	1	0
Depression/depressed mood	1	0	0

[1] Trials 045 and 030 included mefloquine arm in addition to placebo.
[2] KODATEF was administered as 200 mg daily for 3 days, then 200 mg weekly.
[3] Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly.
[4] Includes headache, sinus headache, migraine and tension headache.
[5] Includes dizziness and dizziness postural.
[6] Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.

Adverse Events Reported in < 1% of Subjects Receiving KODATEF in Trials 030, 033, 043, 045 *and 057*
The following selected adverse reactions were reported in subjects receiving KODATEF in Trials 030, 033, 043, 045 and 057 at a rate of less than 1%.

Blood and lymphatic system disorders: haemolytic anaemia, anaemia, thrombocytopenia.
Ear and labyrinth disorders: hyperacusis, Meniere's disease.
Eye disorders: night blindness, photophobia, blurred vision, visual acuity reduced, visual impairment, vitreous floaters.
Hepatobiliary disorders: hyperbilirubinaemia, jaundice cholestatic.
Immune system disorders: hypersensitivity.
Investigations: blood bilirubin increased, blood creatinine increased, glomerular filtration rate decreased.
Nervous system disorders: amnesia, coordination abnormal, hyperesthesia, hypoesthesia, somnolence, syncope, tremor, visual field defect.
Psychiatric disorders: agitation, neurosis.
Skin and subcutaneous tissue disorders: urticaria.
Reporting suspected adverse events
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.

5 PHARMACOLOGICAL PROPERTIES

Clinical trials

The use of KODATEF for prophylaxis of malaria is supported by single pivotal trial 033. Trial 033 compared tafenoquine with mefloquine for the prophylaxis of both Plasmodium falciparum (Pf) and Plasmodium vivax (Pv) malaria in healthy non-immune Australian soldiers deployed to East Timor (now Timor-Leste). The trial was carried out from 1999-2000. All applicable ethical and informed consent procedures were appropriately undertaken.
The trial was divided into two phases. The first, or prophylactic phase, consisted of a 26-week period during deployment where subjects received prophylactic trial medication (tafenoquine 200 mg or mefloquine 250 mg). At the end of the deployment to the malarious area and once the subjects had returned to barracks in Townsville, Australia, the subjects entered a 24-week relapse follow-up phase. During this follow-up phase, subjects who had been on mefloquine prophylaxis received 14-days of primaquine (15 mg bid) while subjects on tafenoquine prophylaxis received placebo capsules for 14 days. Subjects with documented G6PD enzyme deficiency or a history of psychiatric disorders and/or seizures were excluded, as well as subjects with any significant medical history or concurrent medical condition. All subjects (N=654) were healthy at baseline with an age range of 18-47 years. Mean age was 25±5 years in the tafenoquine group and 26±6 years in mefloquine group. Subjects were mostly male (97%) and of white ethnicity (99%). The primary efficacy endpoint was prophylactic failure (Table 5): parasitologic and clinical failure during the 26-week prophylactic phase. The protocol-defined principal efficacy analysis was based on the per-protocol (PP) population, which consisted of all randomised subjects who satisfied inclusion/exclusion criteria and subsequently adhered to the protocol. A very high

compliance to trial drugs was observed in the trial – 100% for the loading dose, 99% for the weekly regimens and 96% during the relapse follow-up phase. No subject was a prophylactic failure during the prophylactic phase. Historic control data indicate that 7.9% of subjects would have become infected (6.9% with Pv, 1.0% with Pf) under those conditions.

Table 5: Prophylactic Outcome During the Prophylactic Treatment Phase (PP Population) for Trial 033

Prophylactic Outcome	Treatment Group	
	Tafenoquine 200 mg[a]	Mefloquine 250 mg[b]
Number of Subjects	462	153
Prophylactic failure, n (%)	0 (0%)	0 (0%)

Prophylactic Outcome	Treatment Group	
	Tafenoquine 200 mg[a]	Mefloquine 250 mg[b]
Prophylactic Success, n (%)	462 (100%)	153 (100%)
Treatment Difference (Tafenoquine – Mefloquine) [95% confidence interval]	0% [-2%,1%]	

a Subjects received a loading dose of tafenoquine 200 mg per day for 3 days, followed by tafenoquine 200 mg once a week for the 26-week prophylactic phase. Subjects who entered the follow-up phase received placebo bid for 14 days.

b Subjects received a loading dose of mefloquine 250 mg per day for 3 days, followed by mefloquine 250 mg once a week for the 26-week prophylactic phase. Subjects who entered the follow-up phase received primaquine 15 mg bid for 14 days.

In the 24 week follow up phase after leaving the endemic region, and after receiving no further drug (tafenoquine group), or standard post-exposure prophylaxis with primaquine (mefloquine group), there were four cases of Pv malaria in the tafenoquine group and one case of Pv malaria in the mefloquine group (Table 6).

Table 6: Prophylactic Outcome During the post-exposure Phase (PP Population) for Trial 033

Prophylactic Outcome	Tafenoquine 200 mg	Mefloquine 250 mg followed by primaquine
Number of Subjects	462	153
Prophylactic Success	458 (99.1%)	152 (99.3%)
Prophylactic Failure	4 (0.9%)	1 (0.7%)
Treatment Difference (Tafenoquine – Mefloquine)	0.21%	
95% CI	(-1.32%, 1.74%)	

The failure rate due to *Pv* relapse was 0.9% for the tafenoquine group and 0.7% for the primaquine group. The time to relapse after the last dose of tafenoquine or mefloquine was 12-20 weeks for the 4 tafenoquine failures and 12 weeks for the 1 mefloquine-then-primaquine failure. All 5 cases were *Pv* malaria.

The relapse follow-up was extended for another 6 months (a total of 12 months post-prophylactic phase). There were 3 more cases of malaria in the tafenoquine group and one case of malaria in the mefloquine/primaquine group during this 6-month extension, bringing to a total of 7 *Pv* relapses in the tafenoquine group and 2 *Pv* relapses in the mefloquine/primaquine group during the 12 months relapse follow-up after the end of prophylactic phase.

Comparison of Arakoda™ (FDA approved product) and Kodatef® (Imported Product) Labels

ARAKODA Blister Pack – Front and Back	KODATEF Blister Pack – Front and Back