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FOR IMMEDIATE RELEASE

KODATEF® (tafenoquine) approved in Australia; first malaria prevention drug in more than two decades

SYDNEY, AUSTRALIA 18th September, 2018: 60 Degrees Pharmaceuticals (60P) and Biocelect Pty Ltd announced today approval in Australia by the Therapeutic Goods Administration (TGA) of KODATEF® (tafenoquine) tablets for the prevention of malaria in patients aged 18 years and older. This is the first time in more than 20 years that the TGA approved a new drug for the prevention of malaria. 60P and Biocelect have partnered together on the commercialisation of KODATEF® for malaria prevention in travellers from Australia to countries where malaria is present.

TGA approval follows a warning at the first World Malaria Congress in Melbourne that progress in eliminating malaria has slowed and there is a threat that malaria will return in areas where it was eradicated. In addition, antimalarial drug resistance is a growing concern. Malaria remains widespread in many countries including Australia's near neighbours such as Papua New Guinea, Vanuatu, Solomon Islands and various South East Asian countries.

"KODATEF® 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. KODATEF kills the parasites in both the blood and liver stages, including the dormant liver phase seen with P. vivax", said Karl Herz, Managing Director of Biocelect.

"KODATEF® provides the travel medicine community the option to prescribe an antimalarial which provides protection in all of the malaria endemic zones, while utilizing what is considered by many physicians to be a more compliant dosing regimen", said Geoffrey Dow, Ph.D., CEO of 60P.

Each year over 4 million Australians travel to areas where malaria is present[2,3], including those travelling for leisure, business, visiting friends and relatives, foreign aid work and government or military assignments. KODATEF® has the potential to protect these travellers from the devastating and life-threatening effects of malaria. Approximately 500 Australians[4] contract malaria every year, largely through foreign travel, and suffer severe symptoms that generally require hospitalization and without treatment it can be fatal.

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The Australian subsidiary of 60P, Biocelect and Sydney-based consulting company Biointelect were all closely involved in the development and approval of KODATEF®. “Helping develop a drug that prevents all types of malaria and seeing it through to approval in both the U.S. and Australia is an incredible achievement, especially for a neglected tropical disease. This is the first step in the longer-term goal of this team to participate in the effort to eliminate malaria globally”, said Karl Herz.

The marketing approval of KODATEF® is the culmination of years of scientific discovery and research in the U.S. and Australia by experts in the field of malariology and infectious disease. Tafenoquine was originally discovered by scientists at the U.S. Walter Reed Army Institute of Research (WRAIR). The approval was based on a concerted effort by the U.S. Army Medical Research and Materiel Command (USAMRMC) and 60P, involving over 21 clinical trials and more than 3,100 trial subjects, to develop tafenoquine as a weekly prophylactic (prevention) drug for the prevention of malaria.

KODATEF® is supplied in 100 mg tablets for oral use only. KODATEF® will be available with a doctor's prescription. As with other antimalarial medicines for prophylaxis, it will be available privately and is not subsidised on the Pharmaceutical Benefits Scheme (PBS). 60P and Biocelect have committed to the TGA to perform post-marketing safety surveillance studies that will gather further data on this important tool against malaria.

After an initial loading dose prior to travelling, KODATEF® is intended to be taken once a week, with only one dose required on return from the malaria-affected region. This convenience may make it more likely that travellers will adhere to the drug regimen. For KODATEF® dosing information, refer to the regimen below or the KODATEF® Approved Product Information, contained at the end of this announcement.

Important Safety Information

Dosing Regimen for KODATEF®

Loading Dose	Before travelling to a malarious area	200 mg (two of the 100 mg tablets) once daily for three days.
Maintenance Dose	While in the malarious area	200 mg (two of the 100 mg 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 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.

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Contraindications

KODATEF® should not be administered to:

- Individuals with G6PD deficiency or unknown G6PD status due to the risk of haemolytic anaemia.
- Pregnancy and Lactation.
- Subjects with current or history of psychosis.
- 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.

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 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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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.

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.

Use in hepatic impairment

KODATEF® 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

KODATEF® 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.

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.

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.

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About malaria

Malaria, a life-threatening disease transmitted through the bite of an infected mosquito, caused an estimated 429,000 fatalities and 212 million clinical cases in 2015, according to the U.S. Centres for Disease Control and Prevention (CDC). Malaria cases among travellers returning to the U.S. have been trending upwards.

About KODATEF®

Tafenoquine is an 8-aminoquinoline chemically derived from primaquine, with activity against all types of malaria. It was first synthesized by scientists at WRAIR in 1978. 60P entered into a cooperative research and development agreement with the U.S. Army Medical Materiel Development Activity (USAMMDA) in 2014 to develop tafenoquine as a weekly prophylactic drug for the prevention of malaria. Since malaria is the top infectious disease threat to U.S. military service members overseas, the military maintains a robust antimalarial drug development effort through internal research and commercial partnerships. The TGA approval is a culmination of more than 30 years of research and development with the USAMRMC, from the discovery of tafenoquine at WRAIR through the current collaboration between 60P and USAMMDA. Further information is available on www.biocelect.com.

About Biocelect

Biocelect, founded in 2014, is actively involved in the sourcing, in-licencing and commercialisation of pharmaceutical products that will meet the unmet medical needs of patients in Australia and the region. Biocelect combined with its companion company Biointelect (www.biointelect.com) has an experienced team that can provide a range of bespoke partnering solutions to local and international companies looking to launch their products in Australia and the region.

About 60P

60P, founded in 2010, focuses on discovering, developing and distributing new medicines for treatment and prevention of tropical diseases, including malaria and dengue. 60P's mission is supported through in-kind funding from the U.S. Department of Defence. The company also collaborates with prominent research organizations in the U.S., Australia and Singapore. In addition, 60P has been funded by Knight Therapeutics Inc. (TSX:GUD), a Canadian specialty pharmaceutical company that obtained FDA approval for Impavido, a product for leishmaniasis which is a tropical disease. 60P is headquartered in Washington D.C., with a subsidiary in Australia. For more information about KODATEF® visit www.biocelect.com. In August 2018, 60P received U.S. FDA licensure and marketing approval for Tafenoquine under a different brand name; for more information visit the company's website, 60degreespharma.com.

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The statements contained herein may include prospects, statements of future expectations and other forward-looking statements that are based on management's current views and assumptions and involve known and unknown risks and uncertainties. Actual results, performance or events may differ materially from those expressed or implied in such forward-looking statements.

The statements expressed herein are those of 60P and do not necessarily represent those of the U.S. Department of Defence, or Department of the Army.

1 Cullen KA, Mace KE, Arguin PM. Malaria Surveillance-United States, 2013 MMWR Surveillance Summary 2016:65 (No.SS-2);1-22 DOI: http://dx.doi.org/10.15585/mmwr.SS6502a1

2 www.who.int/ith/2017-ith-chapter7

3 www.tra.gov.au/Archive-TRA-Old-site/Research/Australians-travelling-overseas/Outbound-tourism-statistics/outbound-tourism-statistics

4 www.health.nsw.gov.au/Infectious/factsheets/pages/malaria.aspx

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▼ **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 TABLETS

1 NAME OF THE MEDICINE

Tafenoquine succinate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KODATEF tablets contain 125.5 mg/tablet of the active ingredient tafenoquine succinate equivalent to 100 mg of tafenoquine free base.

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.

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 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 tablets should be swallowed whole and not chewed or broken apart. KODATEF 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: Dosing Regimen for KODATEF

Loading Dose	Before travelling to a malarious area	200 mg (two of the 100 mg tablets) once daily for three days.
Maintenance Dose	While in the malarious area	200 mg (two of the 100 mg 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 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 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.

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 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.

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 methaemoglobinemia occur, followed by medical advice and appropriate medical therapy.

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.

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 with serum 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 if they 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 $\geq$ 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 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 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 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 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 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 Receiving KODATEF 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
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.

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 of malaria 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 hERG tail 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 AUC following 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 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 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) 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.

PHARMACOKINETIC PROPERTIES

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.

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 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.

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.

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.

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.

Dose-PK relationships

Following administration of a single dose to healthy males, AUC and C_{max} 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 analysis predicts that the recommended prevention regimen will achieve trough levels >80 ng/mL in >95% of subjects.

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 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, due to an increased exposure to metformin arising from this interaction.

5.2 PRECLINICAL SAFETY DATA

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.

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, 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 a predisposition 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 (E171).
- Iron oxide red (E172) and
- Macrogol/polyethylene glycol 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 Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below +30°C. Protect from moisture. Dispense only in the original carton.

6.5 NATURE AND CONTENTS OF CONTAINER

KODATEF 100 mg tablets are packed in polyamide aluminum and PVC formable laminate backed blisters with a peelable polyethylene terephthalate aluminum foil and paper cover. Each blister card contains eight tablets. Each carton contains 8 or 16 tablets (one or two blister cards).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

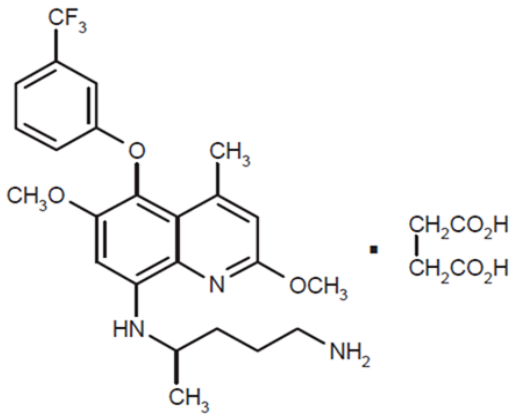
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

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

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

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 4, 51 Rawson Street
Epping
NSW 2121
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

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information