



 **Arakoda**TM
(tafenoquine) tablets,
for oral use

**Product
Monograph**

ArakodaTM tablets are indicated for the prophylaxis of malaria in patients aged 18 years and older.

 **Sixty
Degrees
Pharma**





Table of Contents

Introduction.....	1
Malaria.....	3
Arakoda™ (tafenoquine) - Mechanism of Action.....	8
Arakoda™ (tafenoquine) - Chemistry.....	9
Arakoda™ (tafenoquine) - Pharmacological Properties.....	10
Arakoda™ (tafenoquine) - Indication.....	12
Arakoda™(tafenoquine) - Clinical Studies.....	13
Arakoda™ (tafenoquine) - Efficacy.....	15
Arakoda™ (tafenoquine) - Adverse Reactions.....	18
Non-Clinical Toxicology Studies.....	22
Warnings and Precautions.....	23
Use in Specific Populations.....	25
Contraindications.....	27
Dosage and Administration.....	28
Patient Counseling Information.....	30
Dosage Forms and Strengths, Product Presentation and Storage.....	31
References.....	32

Introduction

Malaria is one of the most serious, life-threatening infectious diseases. The disease is caused by infection with one of several species of parasites belonging to the genus *Plasmodium* via the bite of an infected female *Anopheles* mosquito (Figure 1).¹

Malaria is not only a constant threat to people living in malaria-endemic regions, but also to international travelers.² An estimated 25-30 million global travelers visit malaria-endemic tropic and subtropic regions annually. This results in an estimated 30,000 malaria infected travelers each year.³

Malaria symptoms can develop as early as seven days after initial exposure in a malaria-endemic region and as late as several months or more after departure.^{4,5}

Infected individuals initially present with low-grade fever, shaking chills and muscle aches. These symptoms can progress to drenching sweats, high fever and exhaustion.⁴ In untreated or partially treated individuals, malaria infection can progress to severe malaria, which is often fatal.⁴

In addition, some species of malaria parasites can remain in the liver long-term as dormant “hypnozoites”. These can awaken and emerge from the liver to cause relapsing malaria months or years after the initial infection.

Until now, no antimalarial drug was active against both the parasites that cause the initial malaria infection and the dormant hypnozoites that cause relapsing malaria. The typical regimen to prevent malaria has needed to include multiple drugs for different phases of malaria prevention

(during travel and also after travel to a malaria-endemic region).⁵

As a result, non-adherence is an important disadvantage of current antimalarial prophylactic drugs, in addition to *Plasmodium* spp. resistance and adverse side effects.



Figure 1. *Anopheles* mosquito

The main disadvantages of current prophylactic drugs include resistance, adverse effects, and non-adherence to prescribed medicine.^{5,6,7}

60° Pharmaceuticals

60° Pharmaceuticals (60P) is a growth-oriented specialty pharmaceutical company that applies cutting-edge biological science and applied research to further therapies for the prevention and treatment of tropical diseases, including malaria.⁸

60P was founded in 2010 with a mission to realize new ways to improve and extend people’s lives by discovering, developing, and distributing new best-in-class medicines.⁸

60P’s preventive treatment regimens for travel are aimed at being straightforward, thereby enabling travelers to be more compliant (before, during, and after travel). They also are designed to permit travel to any region where malaria occurs, no matter what species of *Plasmodium* parasite is the cause.⁸

Arakoda™ (tafenoquine)

Arakoda™ was developed by 60P for the prevention of malaria in individuals traveling to endemic areas.

It is the first approved antimalarial agent that is active against dormant hypnozoites and all blood and liver stages of the malaria life cycle. It is indicated for the prophylaxis of malaria in patients aged 18 years and older for up to 6 months of continuous dosing. Arakoda™ is contraindicated in glucose-6-phosphate dehydrogenase (G6PD) deficiency or where G6PD status is unknown, during breastfeeding when the infant is found to be G6PD deficient or if G6PD status is unknown, in patients with a history of psychotic disorders or current psychotic symptoms, and in patients with known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of Arakoda™.⁹

Arakoda™ has been extensively studied for over 20 years in more than 25 clinical studies. Varying doses of different Arakoda™ formulations (early capsule and the marketed tablet formulation) were employed in these studies.¹⁰

Arakoda™ has been extensively studied for over 20 years in more than 25 clinical studies.¹⁰

The key clinical trials, including more than 600 healthy non-immune individuals without prior exposure to malaria and 200 healthy semi-immune individuals,¹¹ demonstrated the ability of Arakoda™ to offer safe and clinically significant protection against all species of malaria parasites in the population for whom prophylaxis is needed. This wide-range of activity demonstrates the prophylactic potential of Arakoda™ in

African, Oceanian, and Southeast Asian malaria-endemic regions.¹¹

Key clinical trials have demonstrated the ability of Arakoda™ to offer clinically significant protection. This wide-range of activity demonstrates the prophylactic potential of Arakoda™ in malaria-endemic regions.¹¹

Clinical data also show the ability of Arakoda™ to prevent relapsing malaria, thereby demonstrating its potential to simplify the dosing regimen to **one prophylactic drug** before, during, and after travel to a malaria-endemic region.¹¹

Clinical studies show the ability of Arakoda™ to prevent malaria relapse, demonstrating its potential to simplify the complete prophylactic regimen to one prophylactic drug.¹¹

Arakoda™ oral administration consists of a brief 3-day loading dose before traveling, followed by once-weekly dosing while in a malaria-endemic region, and one dose following exit from the region.

Malaria

Disease Burden and Epidemiology

Malaria is a major international public health problem, causing an estimated 216 million infections worldwide and 445,000 deaths in 2016, according to the World Health Organization Malaria Report 2017.¹² Most cases occurred in Africa (90%), followed by Southeast Asia (7%), and the Eastern Mediterranean region (2%).¹²

As well as being a constant threat to people living in malaria-endemic regions (Figure 2), malaria is also a threat to international travelers.^{2,12} An estimated 25-30 million global travelers visit malaria-endemic tropic and subtropic regions annually, resulting in an estimated 30,000 travel-related malaria infections.³

Although there have been improvements in global malaria control, the incidence of malaria in travelers has increased during the last decade.^{2,3}

The risk of acquiring malaria for travelers differs from area to area, and depends on the intensity of transmission within the malaria-endemic region, the season of travel, and the itinerary of travel.¹³ Individuals at risk of malaria infection in endemic regions include travelers visiting friends and relatives, international business travelers, and tourists.³

An estimated 25-30 million global travelers visit malaria-endemic tropic and subtropic regions annually, resulting in an estimated 30,000 travel-related malaria infections.³

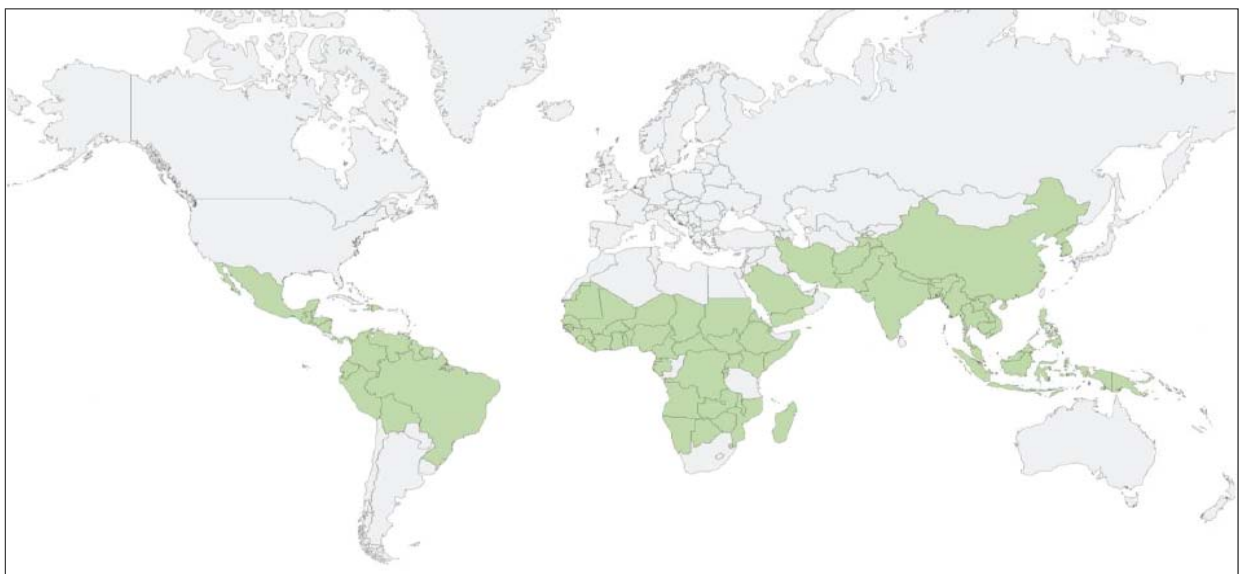


Figure 2. Malaria-endemic regions^{1,2}

Malaria infection in non-immune travelers - such as military personnel and employees from mining, oil, and gas companies and tourists - is potentially lethal.¹³

It is estimated that in approximately 1% of all non-immune travelers, who acquired malaria infection in high-risk areas, it is a fatal disease.¹³

Malaria infection in non-immune travelers is potentially lethal.¹³

Economic Burden of Malaria in Travelers

In addition to being a significant economic burden on malaria-endemic regions, malaria contributes substantial costs to non-endemic countries.

These include direct costs through the provision of care and indirect costs from lost productivity due to malaria. The direct costs of hospitalization per malaria-infected traveler returning from an endemic region were estimated to range between \$10,000 and \$24,000, depending on the severity of malaria and days in hospital.^{14,15}

The indirect costs associated with sick leave due to malaria infection per infected traveler were estimated to be between \$605 and \$2550.^{14,15} The societal cost of death due to malaria infection was estimated to be around \$412,000 per death.¹⁵

Malaria Parasites

Malaria is caused by five species of parasites belonging to the genus *Plasmodium*. Four of these - *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* – are malaria parasite species that are spread from one person to another via the bite of an infected female *Anopheles* mosquito. In recent years, human cases of malaria due to *P. knowlesi* have also been reported. This species of malaria parasites does not seem to spread from person to person. *P. knowlesi* infection may occur in people when an *Anopheles* mosquito, infected with *P. knowlesi* after biting a monkey, then bites a human.¹

Of these five malaria parasites, *P. falciparum* and *P. vivax* cause most of malaria-associated morbidity and mortality.¹⁶

P. falciparum is most prevalent throughout sub-Saharan Africa and is responsible for most deaths from malaria. *P. vivax* is primarily found in Southeast Asia, Central and South America, Ethiopia, and Madagascar.^{12,17}

Despite its reputation as a benign infection, *P. vivax* contributes significantly to the global disease morbidity. In 2016, this form of malaria caused an estimated 8.55 million cases globally. Severe cases and deaths due to *P. vivax* malaria have been reported from all endemic regions.^{12,17}

P. falciparum and P. vivax cause most of malaria-associated morbidity and mortality.¹⁶

Malaria Parasite Life Cycle

Plasmodium spp. have a complex life cycle that alternates between female *Anopheles* mosquitoes and the human host (Figure 3).^{18,19}

The life cycle starts when a *Plasmodium*-infected mosquito injects sporozoites – along with its anticoagulating saliva – into the host’s skin during a blood meal. These sporozoites are the infective, motile stage of *Plasmodium* spp. A proportion of sporozoites reaches and penetrates blood vessels and enters the bloodstream to invade the liver. Inside liver cells, sporozoites transform to a liver stage over a period of 2-10 days. These liver stage forms are also known as exoerythrocytic forms, which develop into merozoites. One single sporozoite can form tens of thousands of merozoites inside liver cells, which are then released into the bloodstream.^{18,19}

P. vivax and *P. ovale* parasites can also stay dormant in the liver. These dormant forms are called hypnozoites and can emerge from

the liver years after the initial infection to cause relapsing malaria.^{18,19}

Once released into the bloodstream, free merozoites invade red blood cells within minutes. Over the following 48 hours, merozoites replicate inside the red blood cells (erythrocytic forms). This results in hemolysis of invaded red blood cells and explosive release of asexual *Plasmodium* parasites that can invade new host cells. This leads to the exponential growth of the parasite population in the human host.^{18,19}

A fraction of these parasites develop into gametocytes, the form of the malaria parasite that infects a mosquito when it takes a blood meal. Once ingested by a mosquito during a blood meal, the gametocytes become fertilized zygotes and develop into sporozoites. These sporozoites then travel to the mosquito’s salivary glands, ready to infect a new host and start a new round of its life cycle.^{18,19}

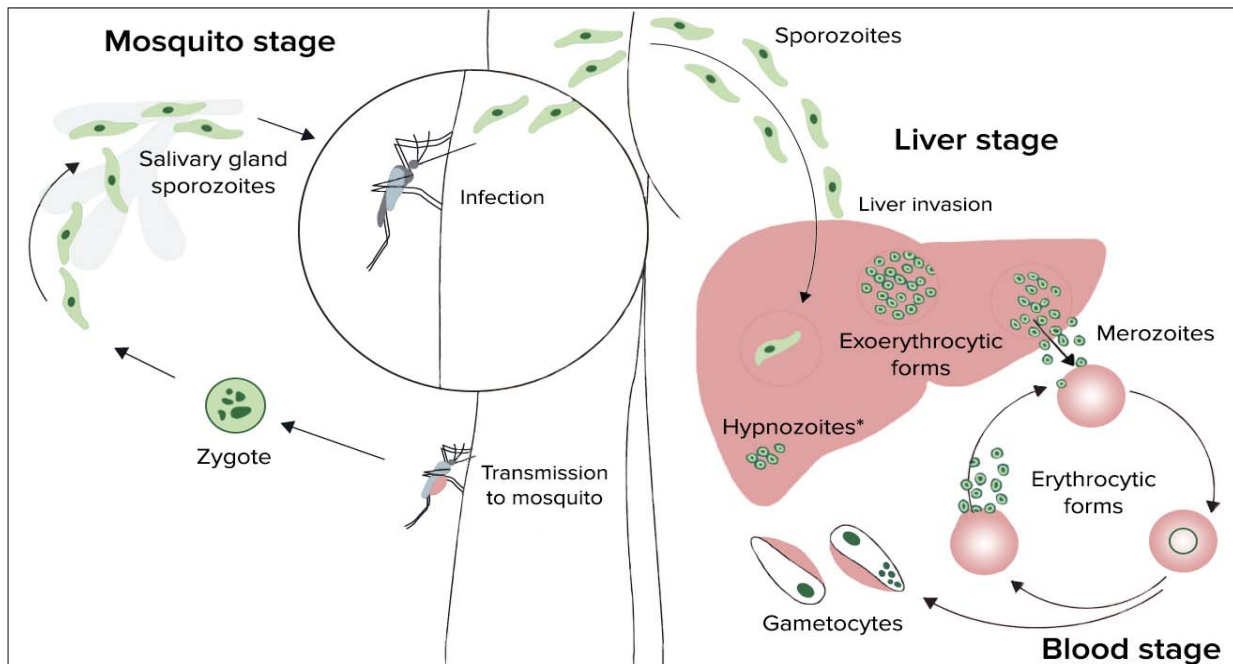


Figure 3. Malaria parasite life cycle²⁰

***Only *P. vivax* and *P. ovale* also stay in the liver as dormant hypnozoites.^{18,19}**

Malaria Symptoms and Pathogenesis

Malaria infection can be uncomplicated or severe (complicated),⁴ depending on the parasite species and whether the person has been previously infected.^{4,5}

Malaria symptoms can develop as early as seven days (usually ≥ 14 days) after initial exposure in a malaria-endemic region and as late as several months or more after departure.^{4,5}

Malaria symptoms can develop as early as seven days after initial exposure in a malaria-endemic region and as late as several months or more after departure.^{4,5}

Uncomplicated malaria can be caused by all *Plasmodium* species. The symptoms of uncomplicated malaria are nonspecific - such as low-grade fever, shaking chills, profuse sweating, headache, nausea, vomiting, diarrhea, and anemia (deficiency of red blood cells or a low level of hemoglobin in the blood).⁴

In untreated or partially treated individuals, malaria infection can progress to severe malaria, which may lead to death. Severe malaria is usually caused by infection with *P. falciparum*, although it can also be caused by *P. vivax* and *P. knowlesi*.⁴

Complications of severe malaria include severe anemia and signs of end-organ damage – such as coma (cerebral malaria), lung complications, hypoglycemia (low glucose blood levels), or acute kidney injury.⁴

The clinical symptoms of malaria are caused by the erythrocytic or blood stage parasites. The release of merozoites and malaria endotoxin from lysed red blood cells activates the immune system and leads to the production of high levels of tumor necrosis factor alpha (TNF α). This molecule, along with others in a cascade, is responsible for fever and other pathological effects during infection.⁴

Particularly in *P. falciparum* malaria, infected red blood cells become “sticky” 12-15 hours after invasion. These “sticky” red blood cells attach to blood vessel walls and clump with other infected and uninfected red blood cells. This can lead to the obstruction of capillaries, which blocks blood flow and may cause life-threatening complications when vital organs are affected.^{4,20}

*In untreated or partially treated individuals, malaria infection can progress to severe malaria, which may lead to death. Severe malaria is usually caused by infection with *P. falciparum*, although it can also be caused by *P. vivax* or *P. knowlesi*.⁴*

Arakoda™ (tafenoquine) Prophylaxis to Prevent Malaria

The main disadvantages of current antimalarial prophylaxis are adverse side effects and non-adherence to the prescribed regimen. Complicated regimens or daily medication were reported as the main reasons for non-compliance to the current prophylactic regimens.^{6,7}

The discovery of the broad-spectrum activity of Arakoda™ against the blood and liver stages of malaria parasites (Figure 4) has enabled the subsequent development of Arakoda™ as a prophylactic for the prevention of malaria.^{9,21,22}

The finding of its additional activity against latent hypnozoites led to the potential of Arakoda™ to prevent malaria relapse and to simplify the complete dosing regimen to one prophylactic drug.^{9,21,22}

Arakoda™ is a long-half-life derivative of primaquine. The recognition of Arakoda's long half-life allowed the establishment of an effective once-weekly dosing and short post-exposure regimen, which anticipates increased compliance to its prescribed regimen.⁹

Based on this rationale, and the clinical findings to date, the prophylactic application of Arakoda™ to prevent malaria presents an effective and clinically significant option for all malaria-endemic regions.⁹

Arakoda™ is indicated for the prophylaxis of malaria in patients aged 18 years and older⁹ for up to 6 months of continuous dosing.⁹

Based on the clinical findings of Arakoda™, the prophylactic application of Arakoda™ to prevent malaria presents an effective and clinically significant option for malaria-endemic region.⁹



Arakoda™ (tafenoquine) - Mechanism of Action

Arakoda™ (tafenoquine) is an 8-aminoquinoline antimalarial which is active against exoerythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *Plasmodium* species.⁹

The activity of Arakoda™ against dormant exoerythrocytic liver stages of the parasites, prevents the later development of the erythrocytic forms that result in relapsing malaria (Figure 4).⁹

The molecular target of Arakoda™ is not known.⁹

Arakoda™ is an antimalarial agent that is active against all stages of Plasmodium species that include the hypnozoite (dormant stage) in the liver.⁹

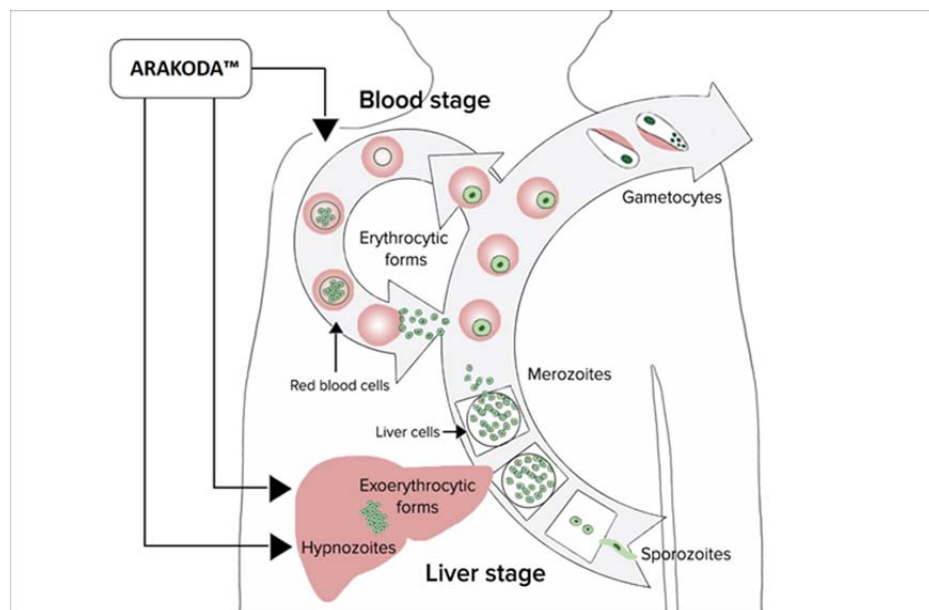


Figure 4. Arakoda™ is active against exoerythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *Plasmodium* species that include *P. falciparum* and *P. vivax*⁹

Arakoda™ (tafenoquine) - Chemistry

Tafenoquine succinate, an 8-aminoquinoline antimalarial, is available as a tablet for oral administration. The structural formula of tafenoquine succinate is:

8-[(4-Amino-1-methylbutyl) amino]-2,6-dimethoxy-4-methyl-5-[3(trifluoromethyl)phenoxy] quinolone succinate (Figure 5).

The empiric formula of tafenoquine succinate is $C_{24}H_{28}F_3N_3O_3 \cdot C_4H_6O_4$.

The molecular weight of tafenoquine as the free base (anhydrous) is 463.49 and of tafenoquine succinate is 581.6.

The active ingredient in Arakoda™ tablets is tafenoquine succinate. Arakoda™ tablets contain 125.5 mg of tafenoquine succinate equivalent to 100 mg free base per tablet. Arakoda™ tablets also contain the excipients microcrystalline cellulose, mannitol, and magnesium stearate. The tablet film coating inactive ingredients include: hypromellose, iron oxide red, macrogol/polyethylene glycol, and titanium dioxide.⁹

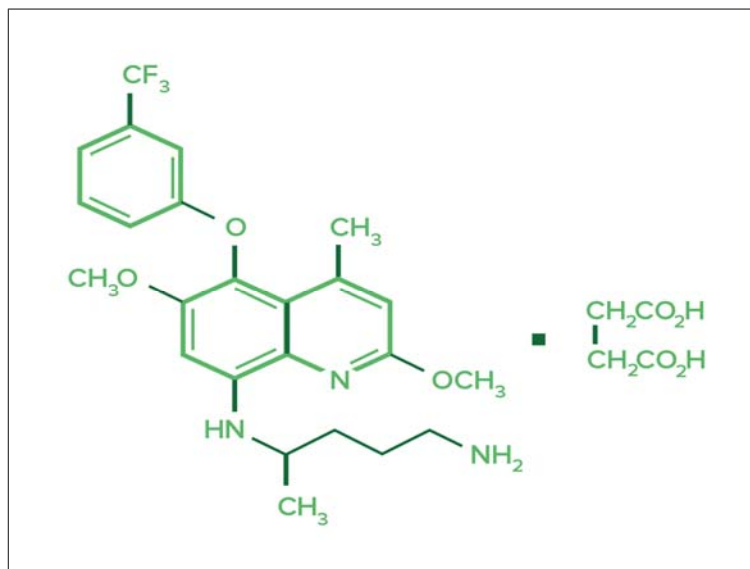


Figure 5. Arakoda™ chemical structure⁹



Arakoda™ (tafenoquine) – Pharmacological Properties

Arakoda™ has been studied for over 20 years in more than 25 clinical trials. Varying doses of different Arakoda™ formulations (early capsule and the marketed tablet formulation) were employed in these studies.¹⁰

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.⁹

Pharmacokinetics

Absorption

A food effect study was not conducted with the 100 mg Arakoda™ tablet. In the majority of clinical trials, tafenoquine was administered under fed conditions.⁹

Table 1 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).⁹

Following administration of a single dose of tafenoquine orally under fasted conditions in healthy adult subjects, AUC and C_{max} 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 4.4.⁹

Table 1. 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)⁹

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.

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%].⁹

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.⁹

Drug Interaction Studies

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.⁹

Metabolism

Negligible metabolism of tafenoquine was observed *in vitro* in human liver microsomes and hepatocytes.⁹

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.⁹

Specific Populations

The pharmacokinetics of tafenoquine was not significantly impacted by age, sex, ethnicity, and body weight. The effect of

Excretion

The full excretion profile of tafenoquine in humans is unknown.⁹

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.⁹

Microbiology

Antimicrobial Activity

Tafenoquine is active against exoerythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *Plasmodium* species that include *P. falciparum* and *P. vivax*.⁹

Resistance

A potential for development of resistance of *Plasmodium* species to tafenoquine was not evaluated.

renal or hepatic impairment on tafenoquine pharmacokinetics is unknown.⁹

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.⁹

Arakoda™ (tafenoquine) - Indication

Arakoda™ is an antimalarial indicated for the prophylaxis of malaria in patients aged 18 years and older.⁹





Arakoda™ (tafenoquine) - Clinical Studies

A pivotal randomized comparator-controlled clinical trial (Study 033) was conducted to evaluate the efficacy and safety of the recommended prophylaxis regimen of Arakoda™ to prevent malaria in non-immune adults traveling to a *P. falciparum* and *P. vivax* endemic area (Table 2).¹¹

Study Design and Demographics

In Study 033, two study groups received prophylactic medication during a 26-week period of deployment to a malaria-endemic region:

- 462 subjects received 200 mg Arakoda™
- 153 subjects received 250 mg mefloquine

The study was divided into three phases (Figure 6). During the first phase, each study group was administered a loading regimen of daily drug for three consecutive days. This period was followed immediately by a maintenance period, with weekly study drug

administration for 26 weeks. At the end of the 26-week deployment, the subjects entered a 24-week follow-up phase. During this phase, subjects who had received mefloquine prophylaxis were administered primaquine for two weeks, while subjects who had received Arakoda™ prophylaxis received placebo capsules for two weeks.¹¹

Patient demographics between treatment groups were similar (Table 2).

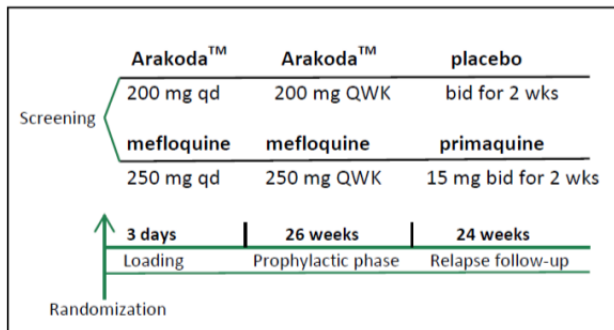


Figure 6. Study 033¹¹

Table 2. Study demographics: subjects' demographics did not differ significantly between treatment groups¹¹

	Study 033	
	Mefloquine (n=153)	Arakoda™ (n=462)
Gender M:F (%)	95:5	97:3
Age (median; years)	26	25
Weight (median; kg)	81	81

Arakoda™ (tafenoquine) - Efficacy

The results of Study 033 showed that the prophylactic success of Arakoda™ (100%, n=462) was similar to mefloquine (100%, n=153) in non-immune subjects in a malaria-endemic area (Table 3). There were no episodes of *Plasmodium* parasitemia in individuals receiving either prophylactic Arakoda™ or mefloquine during the prophylactic treatment phase of this study.⁹ Historic control data indicate that 7.9% of individuals would have become infected with malaria (6.9% with *P. vivax*, 1% with *P. falciparum*) under the conditions of Study 033.²³

During the follow-up phase of Study 033, prophylactic success of Arakoda™ (n=462) in malaria naïve individuals after they had left the malaria-endemic region was comparable to the standard of care (mefloquine followed by primaquine, n=153) (Table 4). During the 24-week follow-up phase, there were four episodes (0.9%) of *P. vivax* infection in subjects who had received Arakoda™ while still in the malaria-endemic area, and no further drug treatment after leaving the endemic region. Among subjects who received mefloquine followed by primaquine during the follow-up phase, there was one case (0.7%) of *P. vivax* infection.¹¹

These follow-up data indicate that the efficacy of post-exposure prophylaxis against *P. vivax* relapse by Arakoda™ administered up to the day of exit from the endemic region was almost identical to that of a standard 14-day post-exposure regimen of primaquine in non-immune individuals.⁹

These data indicate Arakoda™ offers an effective prophylactic option to prevent malaria in non-immune adults.

The data demonstrate Arakoda™ offers an effective prophylactic option to prevent malaria.¹¹

Table 3. Prophylactic outcome during prophylactic treatment in Study 033¹¹

Study	Treatment	Subjects with positive blood smear – number/total (%)	Prophylactic success
033	Mefloquine 250 mg	0/153 (0%)	100%
	Arakoda™ 200 mg	0/462 (0%)	100%

Table 4. Prophylactic outcome during the follow-up phase of Study 033¹¹

Treatment	Subjects with positive blood smear number/total (%)
Mefloquine group: 30 mg/day primaquine	1/153 (0.7%)
Arakoda™ group: Placebo	4/462 (0.9%)

The efficacy of post-exposure prophylaxis against malaria relapse by Arakoda™ administered up to the day of exit from the endemic region was nearly identical to that of a standard 14-day regimen of primaquine.⁹

Summary of Arakoda™ (tafenoquine) Efficacy Data

The efficacy data demonstrate the clinical relevance of Arakoda™ as an effective prophylactic to prevent malaria in adults.¹¹

Arakoda™ demonstrates an ability to offer clinically significant protection against malaria while in an endemic region. In addition, it shows an ability to offer post-exposure protection by preventing relapsing malaria. This wide-ranging prophylactic activity demonstrates the potential of Arakoda™ in all malaria-endemic regions.¹¹

Arakoda™, the first approved prophylactic that is active against latent hypnozoites and all blood and liver stages of malaria, shows an ability to offer clinically significant protection against malaria while in an endemic region. Additionally, Arakoda™ demonstrates an ability to offer post-exposure protection in currently asymptomatic individuals by preventing malaria relapse with only one post-exposure dose. This wide-ranging prophylactic activity demonstrates the potential of Arakoda™ in malaria-endemic regions.¹¹

The pivotal data support the use of the recommended 200 mg Arakoda™ dosing regimen: once daily for three days before traveling to a malaria-endemic area, followed by a weekly dose of 200 mg while in a malaria-endemic region, and one dose of 200 mg following exit from an endemic region. This once-a-week dosing schedule and short post-exposure regimen potentially increase a patient's compliance with the full prophylaxis schedule.



Arakoda™ (tafenoquine) - Adverse Reactions

Clinical Trial Experience

The safety of Arakoda™ was studied in clinical trials at various doses and regimens in 3,184 subjects.⁹

The recommended Arakoda™ regimen was evaluated in 825 subjects in 5 controlled clinical trials (Trial 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). Trials 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). 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.⁹

The safety of Arakoda™ was studied in 5 controlled clinical trials at various doses and regimens in 3,184 subjects.⁹

Clinically Significant Adverse Reactions in Trials 1 to 5 (Overall Safety Population)⁹

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

Reversible vortex keratopathy was reported in 21% to 93% of subjects receiving Arakoda™ in the trials which included ophthalmic evaluations.

This 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 $\geq 1\%$ of Subjects Receiving Arakoda™ in Trials 1 to 5⁹

Adverse reactions occurring in $\geq 1\%$ of subjects in the Arakoda™ group in the placebo-controlled pooled Trials 1, 2, 3, and 4 are presented in Table 5.⁹ Adverse reactions occurring in $\geq 1\%$ 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 6.⁹

The most frequently reported adverse events (affecting more than 10% of patients) seen in these 5 trials were headache, back pain, and diarrhea. In addition to these, the following adverse reactions were reported at a rate $\geq 1\%$.

Nervous System Disorders: dizziness

Ear and Labyrinth Disorders: motion sickness

Gastrointestinal Disorders: nausea, vomiting

Investigations: alanine aminotransferase (ALT) increased/abnormal

Psychiatric Disorders: any sleep symptom, insomnia, abnormal dreams, anxiety, depression

Adverse Reactions Reported in $< 1\%$ of Subjects Receiving Arakoda™ in Trials 1 to 5⁹

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

The following adverse events are discussed in greater detail in other sections:

Hemolytic Anemia (*see Warnings and Precautions*)

Methemoglobinemia (*see Warnings and Precautions*)

Psychiatric Effects (*see Warnings and Precautions*)

Hypersensitivity Reactions (*see Warnings and Precautions*)

Table 5. Selected adverse reactions occurring in $\geq 1\%$ of subjects receiving Arakoda™ (tafenoquine) in pooled Trials 1, 2, 4, and 5 (non-deployed subjects)⁹

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

¹ Trials 2 and 4 included a mefloquine arm in addition to placebo

² Arakoda™ 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

Table 6. Selected adverse reactions occurring in $\geq 1\%$ of subjects receiving Arakoda™ in Trial 3 (deployed subjects)⁹

Adverse Reaction	Arakoda™ ¹ (n=492) %	Mefloquine ² (n=162) %
<i>Nervous system disorders</i>	22	27
Headache ³	15	19
Dizziness ⁴	1	1
<i>Ear and labyrinth disorders</i>	7	11
Motion sickness ⁵	5	6
<i>Musculoskeletal and connective tissue disorders</i>	29	30
Back pain	14	15
<i>Gastrointestinal disorders</i>	36	41
Diarrhea	18	20
Nausea	7	9
Vomiting	5	6
<i>Psychiatric disorders</i>	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 and nightmares

⁸ Includes anxiety disorder, panic attack, and stress



Non-Clinical Toxicology Studies

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.⁹

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.⁹

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).⁹



Warnings and Precautions

Hemolytic Anemia

Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing Arakoda™. 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.⁹

In clinical trials, declines in hemoglobin levels were reported in some G6PD-normal patients.⁹

Monitor patients for clinical signs or symptoms of hemolysis. Advise patients to discontinue Arakoda™ and seek medical attention if signs of hemolysis occur.⁹

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.⁹

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 three months after the last dose of Arakoda™.⁹

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.⁹

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.⁹

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 three months after the final dose.⁹

Methemoglobinemia

Asymptomatic elevations in methemoglobin have been observed in the clinical trials of Arakoda™.⁹

Institute appropriate therapy if signs or symptoms of methemoglobinemia occur.⁹

Carefully monitor individuals with nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase deficiency.⁹

Advise patients to discontinue Arakoda™ and seek medical attention if signs of methemoglobinemia occur.⁹

Psychiatric Effects

In the full population of 825 patients receiving Arakoda™ in 5 clinical trials, psychiatric adverse reactions included sleep disturbances (2.5%), depression/depressed mood (0.3%), and anxiety (0.2%).

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.⁹

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 three days) different from the approved Arakoda™ regimen.⁹

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.⁹

Arakoda™ is contraindicated in patients with a history of psychotic disorders or current psychotic symptoms. If psychotic symptoms (hallucinations, delusions, or grossly disorganized thinking or behavior) occur, consider discontinuation of Arakoda™ and seek 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.⁹

Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., angioedema and urticaria) have been observed with administration of tafenoquine.⁹

Hypersensitivity reactions have been reported in clinical trials of Arakoda™.⁹

Discontinue prophylaxis with Arakoda™ and institute appropriate therapy if hypersensitivity reactions occur.⁹

Arakoda™ is contraindicated in patients who develop hypersensitivity to tafenoquine or any component of Arakoda™ or other 8-aminoquinolines.⁹

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.⁹

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.⁹

Advise patients to seek medical attention if signs of hypersensitivity occur.⁹

Drug Interactions

The effect of coadministration of tafenoquine on the pharmacokinetics of Organic Cation Transporter-2 (OCT2) and Multidrug and Toxin Extrusion (MATE) substrates in humans is unknown. However, *in vitro* observations suggest the potential for increased concentrations of these substrates which may increase the risk of toxicity of these drugs.⁹

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.⁹



Use in Specific Populations

Pregnancy

Risk Summary

The use of Arakoda™ during pregnancy may cause hemolytic anemia in a fetus who is G6PD-deficient.⁹

Treatment with Arakoda™ during pregnancy is not recommended.⁹

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.⁹

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.

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.⁹

Treatment with Arakoda™ during pregnancy is not recommended. If a pregnancy is detected, discontinue Arakoda™ as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy.⁹

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.⁹

Arakoda™ is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown.⁹

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.⁹

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 three months after the final dose of Arakoda™.⁹

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.⁹

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating treatment with Arakoda™.⁹

Contraception

Arakoda™ may cause hemolytic anemia in a G6PD-deficient fetus. Advise females of reproductive potential that treatment with Arakoda™ during pregnancy is not recommended and to avoid pregnancy or use effective contraception for three months after the final dose of Arakoda™.⁹

Pediatric Use

Safety and effectiveness of Arakoda™ in pediatric patients have not been established.⁹

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.⁹

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.⁹

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.⁹

Contraindications

Arakoda™ is contraindicated in:

- Patients with G6PD deficiency or unknown G6PD status, due to the risk of hemolytic anemia
- breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if the G6PD status of the infant is unknown
- Patients with a history of psychotic disorders or current psychotic symptoms (i.e., hallucinations, delusions, and/or grossly disorganized behavior)
- Patients with known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of Arakoda™⁹



Dosage and Administration

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™. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with Arakoda™.⁹

Dosage and Administration

Arakoda™ (tafenoquine) can be administered for up to 6 months of continuous dosing in patients 18 years of age and older.⁹

The recommended dosage of Arakoda™ is described in Table 7 below. Arakoda™ administration should be initiated with a loading regimen three days before travel to a malaria-endemic region at a once daily dose of 200 mg (two 100 mg tablets) during these three days. While in the malaria-endemic region, the maintenance regimen of Arakoda™ should be administered once weekly at a dose of 200 mg (two 100 mg tablets) - starting seven days after the last loading regimen dose. In the week following exit from the malaria-endemic region, one

dose of 200 mg (two 100 mg tablets) should be administered for terminal prophylaxis, starting seven days after the last maintenance dose (Table 7).⁹

Arakoda™ should be administered with food.⁹ Individuals should complete the full course of Arakoda™, including the loading dose and the terminal dose (Table 7).⁹

Missed Doses

How to replace missed doses of Arakoda™ is described in Table 8.⁹

Overdose

There were no reported cases of Arakoda™ overdose.⁹ Hemoglobin decline and methemoglobinemia may be encountered in an overdose with Arakoda™. Treatment of overdose consists of institution of appropriate symptomatic and/or supportive therapy.⁹

Table 7. Recommended dosing regimen for Arakoda™⁹

Regimen Name	Timing	Dose
Loading regimen	For each of the three days before travel to a malaria-endemic area	200 mg (two of the 100 mg tablets) once daily for three days
Maintenance regimen	While in the malaria-endemic area	200 mg (two of the 100 mg tablets) once weekly – start seven days after the last loading regimen dose
Terminal prophylaxis regimen	In the week following exit from the malaria-endemic area	200 mg (two of the 100 mg tablets) one time – administer this dose seven days after the last maintenance dose

Table 8. How to replace missed doses of Arakoda™⁹

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



Patient Counseling Information

Advise the patient to read the FDA-approved patient labeling (Medication Guide).⁹

G6PD Testing and Hemolytic Anemia

Inform patients of the need for testing for G6PD deficiency before starting with Arakoda™.⁹

Advise patients on the symptoms of hemolytic anemia and instruct them to seek medical advice promptly if such symptoms occur. Patients should contact their healthcare provider if they have darker lips or urine as these may be signs of hemolysis or methemoglobinemia.⁹

Important Administration Instructions

Advise patients to take Arakoda™ with food.⁹

Advise patients to swallow the tablet whole and not to break, crush, or chew it.⁹

Advise patients to complete the full course of Arakoda™ including the loading dose, maintenance dose, and terminal dose.⁹

Potential Harm to the Fetus

Advise females of reproductive potential of the potential risk of Arakoda™ to a fetus and to inform their healthcare provider of a known or suspected pregnancy.⁹

Advise females of reproductive potential to avoid pregnancy or use effective contraception during the treatment with Arakoda™ and for three months after the final dose.⁹

Lactation

Advise women with a G6PD-deficient infant, or if they do not know the G6PD status of their infant, not to breastfeed during treatment with Arakoda™ and for three months after the final dose.⁹

Methemoglobinemia

Inform patients that methemoglobinemia has occurred with Arakoda™.⁹

Advise patients on the symptoms of methemoglobinemia and instruct them to seek medical advice promptly if such symptoms occur.⁹

Psychiatric Symptoms

Advise patients who experience hallucinations, delusions, or confused thinking while taking Arakoda™ to seek medical attention as soon as possible.⁹

Other psychiatric symptoms, such as changes in mood, anxiety, insomnia, and nightmares, should be promptly evaluated by a medical professional if they last more than three days or are severe.⁹

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions have occurred with Arakoda™.⁹

Advise patients on the symptoms of hypersensitivity reactions and instruct them to seek medical advice promptly if such symptoms occur.⁹

Dosage Form and Strength, Product Presentation and Storage

Dosage Form and Strength

Arakoda™ tablets are dark pink, film-coated, capsule-shaped tablets debossed with "TQ100" on one side containing 100 mg tafenoquine (equivalent to 125.5 mg of tafenoquine succinate).⁹

Product Presentation

Each blister card contains eight tablets. Each carton contains 16 tablets (two blister cards) housed in a contiguous outer paperboard child-resistant carton component (NDC 71475-257-01) (Figure 7).⁹

Storage and Handling

Store between 20°C and 25°C (68°F to 77°F). Temperature excursions are permitted between 15°C and 30°C (59°F - 86°F).⁹

Protect from moisture.⁹

Dispense only in the original carton.⁹

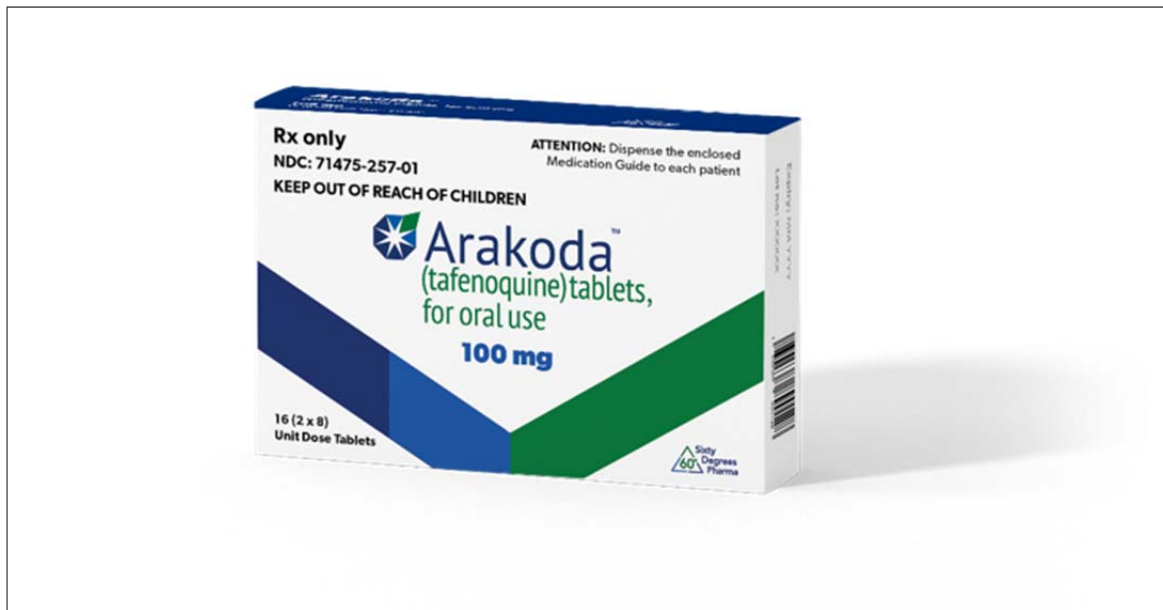


Figure 7. Arakoda™ carton

References

1. World Health Organization, International travel and health: Malaria 2018. Accessible at: <http://www.who.int/ith/diseases/malaria/en/>
2. Mace KE, Arguin PM. Malaria Surveillance - United States, 2014. Morbidity and mortality weekly report Surveillance summaries (Washington, DC: 2002) 2017; 66(12): 1-24
3. Angelo KM, Libman M, Caumes E, et al. Malaria after international travel: a GeoSentinel analysis, 2003-2016. *Malar J* 2017; 16(1): 293
4. Phillips MA, Burrows JN, Manyando C, van Huijsduijnen RH, Van Voorhis WC, Wells TNC. Malaria. *Nat Rev Dis Primers* 2017; 3: 17050
5. Arguin PM, Tan KR. Infectious diseases related to travel. Malaria. In: CDC Yellow Book 2018. <https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/malaria>. Updated June 12, 2017. Accessed September 19, 2018.
6. Chen LH, Wilson ME, Schlagenhauf P. Prevention of malaria in long-term travelers. *JAMA* 2006; 296(18): 2234-44
7. Cunningham J, Horsley J, Patel D, Tunbridge A, Laloo DG. Compliance with long-term malaria prophylaxis in British expatriates. *Travel Med Infect Dis* 2014; 12(4): 341-8
8. 60P. 60 Degrees Pharmaceuticals. 2018. <https://60degreespharma.com/about-us/>
9. Prescribing Information Arakoda™. FDA Approved [12/2018]
10. Novitt-Moreno A, Ransom J, Dow G, Smith B, Read LT, Toovey S. Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis. *Travel Med Infect Dis* 2017; 17: 19-27
11. Nasveld PE, Edstein MD, Reid M, et al. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. *Antimicrob Agents Chemother* 2010; 54(2): 792-8
12. World Health Organization, World Malaria Report 2017. Accessible at: <http://www.who.int/malaria/publications/world-malaria-report-2017/report/en/>
13. Franco-Paredes C, Santos-Preciado JI. Problem pathogens: prevention of malaria in travellers. *Lancet Infect Dis* 2006; 6(3): 139-49
14. Widmer LL, Blank PR, Van Herck K, Hatz C, Schlagenhauf P. Cost-effectiveness analysis of malaria chemoprophylaxis for travellers to West-Africa. *BMC Infect Dis* 2010; 10: 279
15. Massad E, Behrens BC, Coutinho FA, Behrens RH. Cost risk benefit analysis to support chemoprophylaxis policy for travellers to malaria endemic countries. *Malar J* 2011; 10: 130
16. World Health Organization, World Malaria Report 2016. Accessible at: <http://www.who.int/malaria/publications/world-malaria-report-2016/en/>
17. Battle KE, Guerra CA, Golding N, et al. Global database of matched Plasmodium falciparum and P. vivax incidence and prevalence records from 1985-2013. *Sci Data* 2015; 2: 150012

18. Cowman AF, Healer J, Marapana D, Marsh K. Malaria: Biology and Disease. *Cell* 2016; 167(3): 610-24
19. Meibalan E, Marti M. Biology of Malaria Transmission. *Cold Spring Harb Perspect* 2017; 7(3):
20. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. *Lancet* 2014; 383: 723-35
21. Dow GS, Gettayacamin M, Hansukjariya P, et al. Radical curative efficacy of tafenoquine combination regimens in Plasmodium cynomolgi-infected Rhesus monkeys (Macaca mulatta). *Malar J* 2011; 10: 212
22. Li Q, O'Neil M, Xie L, et al. Assessment of the prophylactic activity and pharmacokinetic profile of oral tafenoquine compared to primaquine for inhibition of liver stage malaria infections. *Malar J* 2014; 13: 141
23. Dow GS, McCarthy WF, Reid M, Smith B, Tang D, Shanks GD. A retrospective analysis of the protective efficacy of tafenoquine and mefloquine as prophylactic anti-malarials in non-immune individuals during deployment to a malaria-endemic area. *Malar J* 2014; 13: 49

Arakoda™ (tafenoquine) – Effective Prophylaxis for Malaria

Malaria is one of the most serious, life-threatening infectious diseases.

Arakoda™ is the first antimalarial chemoprophylaxis that is specifically developed for use during travel to any malaria-endemic region.

Arakoda™ has demonstrated an ability to offer an effective prophylactic option to prevent malaria.

Arakoda™ tablets are indicated for the prophylaxis of malaria in patients aged 18 years and older for up to 6 months of continuous dosing.

**see Malaria and Arakoda™ Clinical Studies*



Arakoda[™]
(tafenoquine) tablets,
for oral use



Manufactured by: Piramal Enterprises, Plot # 67-70 Sector II Pithampur District Dhar,
Madyha Pradesh 454 775, India

Manufactured for: 60 Degrees Pharmaceuticals LLC, 1025 Connecticut Avenue NW,
Suite 1000, Washington DC 20036, USA

The information presented in this publication was prepared in 2018 based on
the Arakoda[™] Prescribing Information, FDA approved [12/2018].

Please consult full Prescribing Information before prescribing. Visit our website at www.60Degreespharma.com.

ARA-09-1120 A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARAKODA™ safely and effectively. See full prescribing information for ARAKODA™.

ARAKODA™ (tafenoquine) tablets, for oral use

Initial U.S. Approval: 2018

INDICATIONS AND USAGE

ARAKODA is an antimalarial indicated for the prophylaxis of malaria in patients aged 18 years and older. (1)

DOSAGE AND ADMINISTRATION

- All patients must be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to prescribing ARAKODA. (2.1)
- Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with ARAKODA. (2.1)

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 <u>daily</u> for 3 days
Maintenance regimen	While in the malarious area	200 mg (2 of the 100 mg tablets) once <u>weekly</u> – 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) one-time 7 days after the last maintenance dose

- Administer ARAKODA with food. (2.2)
- See full prescribing information for instructions on how to replace missed doses. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg of tafenoquine (3)

CONTRAINDICATIONS

- G6PD deficiency or unknown G6PD status (4)
- Breastfeeding by a lactating woman when the infant is found to be G6PD deficient or if G6PD status is unknown (4, 8.2)
- Patients with a history of psychotic disorders or current psychotic symptoms (4, 5.4)
- Known hypersensitivity reactions to tafenoquine, other 8-aminoquinolines, or any component of ARAKODA. (4)

WARNINGS AND PRECAUTIONS

- Hemolytic Anemia:** G6PD testing must be performed before prescribing ARAKODA due to the risk of hemolytic anemia. Monitor patients for signs or symptoms of hemolysis. (5.1)

- G6PD Deficiency in Pregnancy or Lactation:** ARAKODA may cause fetal harm when administered to a pregnant woman with a G6PD-deficient fetus. ARAKODA is not recommended during pregnancy. A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Check infant's G6PD status before breastfeeding begins. (5.2, 8.1, 8.2)
- Methemoglobinemia:** Asymptomatic elevations in blood methemoglobin have been observed. Initiate appropriate therapy if signs or symptoms of methemoglobinemia occur. (5.3)
- Psychiatric Effects:** Serious psychotic adverse reactions have been observed in patients with a history of psychosis or schizophrenia, at doses different from the approved dose. If psychotic symptoms (hallucinations, delusions, or grossly disorganized thinking or behavior) occur, consider discontinuation of ARAKODA therapy and, evaluation by a mental health professional as soon as possible. (5.4)
- Hypersensitivity Reactions:** Serious hypersensitivity reactions have been observed with administration of ARAKODA. If hypersensitivity reactions occur, institute appropriate therapy. (5.5)
- Delayed Adverse Reactions:** Due to the long half-life of ARAKODA (approximately 17 days), psychiatric effects, hemolytic anemia, methemoglobinemia, and hypersensitivity reactions may be delayed in onset and/or duration. (5.6, 12.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 1\%$) were: headache, dizziness, back pain, diarrhea, nausea, vomiting, increased alanine aminotransferase (ALT), motion sickness, insomnia, depression, abnormal dreams, anxiety. (6.1)

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

DRUG INTERACTIONS

Avoid co-administration with drugs that are substrates of organic cation transporter-2 (OCT2) or multidrug and toxin extrusion (MATE) transporters (7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed a G6PD-deficient infant or infant with unknown G6PD status during treatment and for 3 months after the last dose of ARAKODA. (5.2, 8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Tests to be Performed Prior to ARAKODA Dose Initiation
- 2.2 Recommended Dosage and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Hemolytic Anemia
- 5.2 G6PD Deficiency in Pregnancy or lactation
- 5.3 Methemoglobinemia
- 5.4 Psychiatric Effects
- 5.5 Hypersensitivity Reactions
- 5.6 Delayed Adverse Reactions, Including Hemolytic Anemia, Methemoglobinemia, Psychiatric Effects, and Hypersensitivity Reactions

6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience

7 DRUG INTERACTIONS

- 7.1 Effect of ARAKODA on OCT2 and MATE Substrates

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ARAKODA is indicated for the prophylaxis of malaria in patients aged 18 years and older.

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)*].

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.

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 <u>daily</u> for 3 days
Maintenance regimen	While in the malarious area	200 mg (2 of the 100 mg tablets) once <u>weekly</u> – 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 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.

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.

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)*].

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.

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)*].

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)*].

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.

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)*].

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)*].

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)*].

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)*]

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 $\geq 1\%$ 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 $\geq 1\%$ of Subjects Receiving ARAKODA in Pooled Trials 1, 2, 4, and 5 (Non-Deployed Subjects)

Adverse Reaction	ARAKODA ¹	Placebo	Mefloquine ²
	(n=333) %	(n=295) %	(n=147) %
<i>Nervous system Disorders</i>	35	34	47
Headache ³	32	32	44
Dizziness ⁴	5	3	10
<i>Musculoskeletal and connective tissue disorders</i>	27	26	37
Back pain	14	9	11
<i>Gastrointestinal disorders</i>	31	33	46
Diarrhea	5	3	1
Nausea	5	2	2
Vomiting	2	2	1
<i>Investigations</i>	8	7	11
Alanine Aminotransferase (ALT) increased/abnormal	4	2	3
<i>Psychiatric disorders</i>	2	1	2
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 $\geq 1\%$ 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	ARAKODA¹ (n=492) %	Mefloquine² (n=162) %
<i>Nervous system Disorders</i>	22	27
Headache ³	15	19
Dizziness ⁴	1	1
<i>Ear and labyrinth Disorders</i>	7	11
Motion sickness ⁵	5	6
<i>Musculoskeletal and connective tissue disorders</i>	29	30
Back pain	14	15
<i>Gastrointestinal disorders</i>	36	41
Diarrhea	18	20
Nausea	7	9
Vomiting	5	6
<i>Psychiatric disorders</i>	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.

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.

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.

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.

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.

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.

8.4 Pediatric Use

Safety and effectiveness of ARAKODA in pediatric patients 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)*].

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)].

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)].

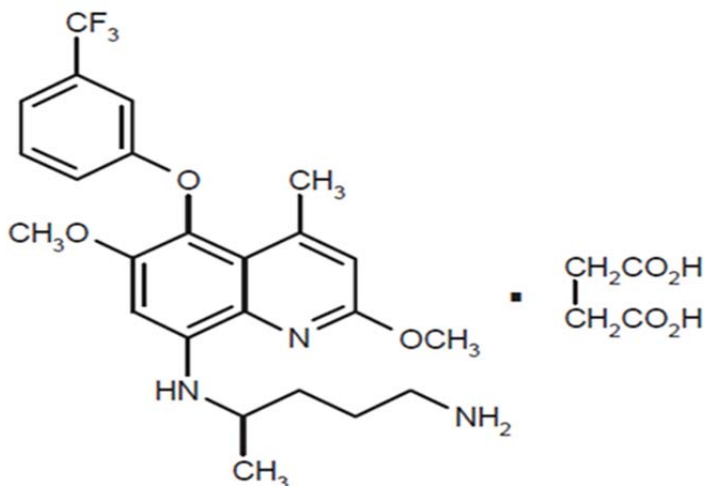
10 OVERDOSAGE

There were no reported cases of ARAKODA overdose. Hemoglobin decline and methemoglobinemia may be encountered in an overdose with ARAKODA. Treatment of overdose consists of institution of appropriate symptomatic and/or supportive therapy.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tafenoquine is an 8-aminoquinoline antimalarial drug [see *Microbiology (12.4)*].

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.

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_{max} 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.

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.

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.

Excretion

The full excretion profile of tafenoquine in humans is unknown.

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.

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.

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 hemozoin 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.

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.

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.

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).

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).

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 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).

Storage

Store at 20°C to 25°C (68°F to 77°F). Temperature excursions are permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture. Dispense only in the original carton.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

G6PD Testing and Hemolytic Anemia

Inform patients of the need for testing for G6PD deficiency before starting ARAKODA. Advise patients on the symptoms of hemolytic anemia and instruct them to seek medical advice promptly if such symptoms occur. Patients should contact their health care provider if they have darker lips or urine as these may be signs of hemolysis or methemoglobinemia [see *Warnings and Precautions (5.1)*].

Important Administration Instructions

- Advise patients to take ARAKODA with food.
- Advise patients to swallow the tablet whole and not to break, crush or chew it.
- Advise patients to complete the full course of ARAKODA including the loading dose, maintenance dose and terminal dose.

Potential Harm to the Fetus

Advise females of reproductive potential of the potential risk of ARAKODA to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.1)*].

Advise females of reproductive potential to avoid pregnancy or use effective contraception during treatment with ARAKODA and for 3 months after the final dose [see *Use in Specific Populations (8.3)*].

Lactation

Advise women with a G6PD-deficient infant, or if they do not know the G6PD status of their infant, not to breastfeed during treatment with ARAKODA and for 3 months after the final dose [see *Contraindication (4), Warnings and Precautions (5.2), Use in Specific Populations (8.2)*].

Methemoglobinemia

Inform patients that methemoglobinemia has occurred with ARAKODA. Advise patients on the symptoms of methemoglobinemia and instruct them to seek medical advice promptly if such symptoms occur [see *Warnings and Precautions (5.3)*].

Psychiatric Symptoms

Advise patients who experience hallucinations, delusions, or confused thinking while taking ARAKODA to seek medical attention 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 last more than three days or severe [see *Warnings and Precautions (5.4)*].

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions have occurred with ARAKODA. Advise patients on the symptoms of hypersensitivity reactions and instruct them to seek medical advice promptly if such symptoms occur [see *Warnings and Precautions (5.5)*].

Manufactured For:

60 Degrees Pharmaceuticals LLC,
1025 Connecticut Avenue NW, Suite 1000,
Washington DC 20036

1217a

Medication Guide

MEDICATION GUIDE
ARAKODA (AIR-uh-KOH-duh)
(tafenoquine)
tablets, for oral use

What is the most important information I should know about ARAKODA?

ARAKODA can cause serious side effects including:

- **Breakdown of red blood cells (hemolytic anemia).** See “**Do not take ARAKODA if you:**”

ARAKODA can cause a breakdown of red blood cells (hemolysis) in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Your healthcare provider will test you for G6PD deficiency before you start taking ARAKODA. Signs of hemolytic anemia may not happen right away (delayed reaction). Tell your healthcare provider or get emergency medical help right away if you develop signs of hemolytic anemia which include darkening of the urine, dizziness, confusion, feeling tired, light-headedness, or shortness of breath, pale skin or yellowing of the skin and whites of the eyes.

- **Decrease of oxygen in your blood caused by a certain type of abnormal red blood cell (methemoglobinemia).** Signs and symptoms of methemoglobinemia may not happen right away (delayed reaction). Get medical help right away if you have bluish coloring of the lips or skin, headache, fatigue, shortness of breath, or lack of energy.

- **Mental health (psychiatric) symptoms.** See “**Do not take ARAKODA if you:**” Sleep problems, depression, anxiety and psychosis have happened while taking ARAKODA. Psychiatric symptoms may not happen right away (delayed reaction). Get emergency medical help right away if you develop hallucinations (seeing or hearing things that are really not there), delusions (false or strange thoughts or beliefs), or if you get confused or have problems thinking while taking ARAKODA. Call your healthcare provider if you develop changes in your mood, anxiety, trouble sleeping (insomnia), or nightmares for 3 days or longer while taking ARAKODA.

ARAKODA can have other serious side effects. See “**What are the possible side effects of ARAKODA?**”

What is ARAKODA?

- ARAKODA is a prescription medicine used to help prevent malaria in people 18 years of age and older.
- Malaria is a serious disease of the blood that is spread by infected mosquitos. It is not known if ARAKODA is safe and effective in children.

Do not take ARAKODA if you:

- have G6PD deficiency.
- are breastfeeding a child known to have G6PD deficiency or breastfeeding a child that has not been tested for G6PD deficiency.
- have a history of psychotic disorders, or you currently have psychotic symptoms including hallucinations (seeing or hearing things that are not really there), delusions (false or strange thoughts or beliefs), or disorganized thinking or behavior.

•are allergic to tafenoquine, other 8-aminoquinolines, or any of the ingredients in ARAKODA. See the end of this Medication Guide for a complete list of ingredients in ARAKODA.

Before taking ARAKODA, tell your health care provider about all your medical conditions, including if you:

- have nicotinamide adenine dinucleotide (NADH) reductase deficiency. People with NADH reductase deficiency have a higher risk for methemoglobinemia if they take ARAKODA.
- have or have had mental health problems.
- are pregnant or plan to become pregnant. ARAKODA can harm an unborn baby who has G6PD deficiency.
 - You should not become pregnant during treatment with ARAKODA.
 - Females who are able to become pregnant should use effective birth control (contraception) during treatment with ARAKODA. Talk with your healthcare provider about birth control methods that may be right for you.
 - Your healthcare provider may suggest you take a pregnancy test before you start taking ARAKODA. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with ARAKODA.
 - are breastfeeding or plan to breastfeed. It is not known if ARAKODA passes into breast milk. See “**Do not take ARAKODA if you:**”
 - Your healthcare provider should check your child for G6PD deficiency before you start breastfeeding.
 - If you know your child has G6PD deficiency, do not breastfeed during treatment with ARAKODA and for 3 months after your last dose of ARAKODA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ARAKODA and other medicines may affect each other causing side effects.

How should I take ARAKODA?

- Take ARAKODA exactly as your healthcare provider tells you to take it.
- ARAKODA is given as 2 tablets that you will take together as a single dose. Each ARAKODA tablet has 100 mg of tafenoquine.
- You will start taking ARAKODA 3 days before you travel to a malaria area.
 - Take 2 tablets, 1 time **each day for 3 days**.
- You will **continue to take ARAKODA** while you are in the malaria area.
 - Take 2 tablets, 1 time **each week**.
 - Start taking this dose of ARAKODA **7 days after the last dose of ARAKODA** that you took before your travel to the malaria area.
- You will **take your last dose of ARAKODA** after you leave the malaria area.
 - Take 2 tablets.
 - Take this dose of ARAKODA **7 days after the last dose of ARAKODA** that you took while you were in the malaria area.
- Take ARAKODA tablets whole. **Do not** break, crush, or chew the tablets before swallowing.
- Take ARAKODA with food.

- **It is important that you take the full course of treatment with ARAKODA. Do not** stop taking ARAKODA without first talking to your healthcare provider because the medicine may not work as well to prevent malaria.
- If you miss 1 or 2 daily doses of ARAKODA before your travel to the malaria area:
 - **1 daily dose:** take 2 tablets (missed dose), and then continue to take your daily dose of ARAKODA until you have taken a total of 3 daily doses before your travel to the malaria area. Start taking your weekly doses or ARAKODA 1 week after your last daily dose.
 - **2 daily doses:** take 2 tablets (missed dose), 1 time **each day for 2 days in a row (consecutive days)** so that you have taken a total of 3 daily doses before your travel to the malaria area. Start taking your weekly doses of ARAKODA 1 week after your last daily dose.
- If you miss any weekly doses of ARAKODA while you are in the malaria area:
 - **1 weekly dose:** take 2 tablets, 1 time on any day up to the time of your next scheduled weekly dose.
 - **2 weekly doses:** take 2 tablets, 1 time on any day before your next scheduled weekly dose.
 - **3 or more weekly doses:** take 2 tablets, 1 time **each day for 2 days** up to the time of your next scheduled weekly dose.
- If you miss taking your last dose of ARAKODA 7 days after the last dose of ARAKODA you took while you were in the malaria area, take this last dose of ARAKODA as soon as you remember.

What are the possible side effects of ARAKODA?

ARAKODA may cause serious side effects, including:

- See “**What is the most important information I should know about ARAKODA?**”
- **Allergic (hypersensitivity) reactions.** See “**Do not take ARAKODA if you:**” Allergic reactions can happen after you take ARAKODA. Signs and symptoms of an allergic reaction may not happen right away (delayed reaction). Get medical help right away if you have any signs or symptoms of an allergic reaction including:
 - swelling of the face, lips, tongue or throat
 - itching
 - trouble breathing or wheezing
 - vomiting
 - fainting and feeling lightheaded
 - rash
 - hives

The most common side effects of ARAKODA include: diarrhea, headache, back pain, nausea, vomiting, dizziness, increased liver enzyme levels in your blood, motion sickness, insomnia, depression, abnormal dreams and anxiety.

Other side effects of ARAKODA include eye problems. Some people who take ARAKODA can have a problem with the cornea of the eye called vortex keratopathy. This problem can be seen during an eye exam. Vortex keratopathy does not cause vision problems and will usually go away after you stop taking ARAKODA.

These are not all the possible side effects of ARAKODA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Sixty Degrees Pharmaceuticals, LLC at 1-888-834-0225.

How should I store ARAKODA?

- Store ARAKODA at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect tablets from moisture.

Keep ARAKODA and all medicines out of the reach of children.

General information about the safe and effective use of ARAKODA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ARAKODA for a condition for which it was not prescribed. Do not give ARAKODA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about ARAKODA that is written for health professionals.

What are the ingredients in ARAKODA?

Active ingredient: tafenoquine succinate

Inactive ingredients: microcrystalline cellulose, mannitol, and magnesium stearate. The tablet film-coating contains the following inactive ingredients: hypromellose, iron oxide red, titanium dioxide, and macrogol/polyethylene glycol.

Manufactured for:



Sixty Degrees Pharmaceuticals, LLC

Washington, DC 20036

For more information, go to <https://60degreespharma.com> or call 1-888-834-0225.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: August 2018