

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: 09/2024

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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)].

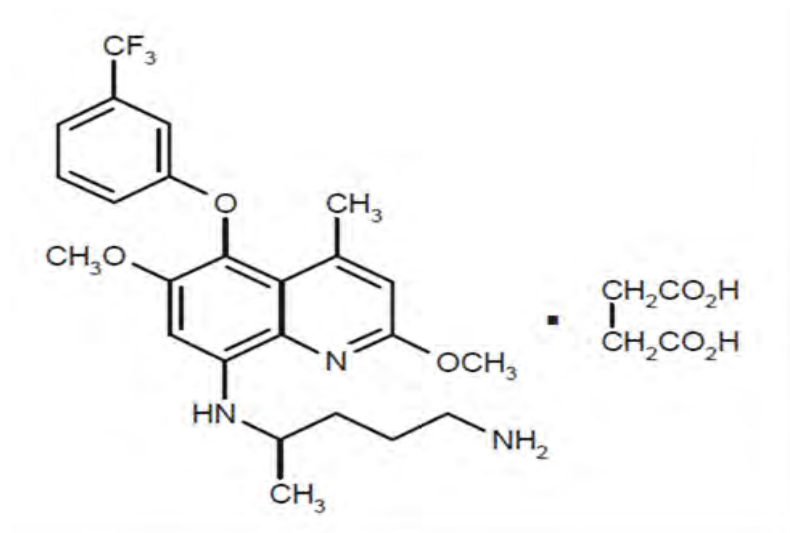
10 OVERDOSAGE

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	ARAKODA¹
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 blister packs or bottles.

For the blister pack presentation, ARAKODA tablets are packed in polyamide aluminum and PVC formable laminate backed blisters with a polyethylene terephthalate aluminum foil cover. Each blister card contains 8 tablets. Each package contains 2 blister cards (16 tablets) housed in a contiguous outer paperboard child-resistant carton component (NDC 71475-257-01).

For the bottle presentation, ARAKODA tablets are packed in 40 cc, 33 mm white high-density polyethylene bottles with a 33 mm polypropylene screw-top child resistant cap with an induction seal liner. Each bottle contains 8 tablets (NDC 71475-257-02).

Storage

Store at less than 30°C (86°F). Protect from moisture. Dispense only in the original carton or bottle.

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)*].

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