

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210607Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210607
PDUFA Goal Date	August 8, 2018
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Reviewer Name(s)	Naomi Redd, Pharm.D.
Team Leader	Elizabeth Everhart, RN, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 31, 2018
Subject	Evaluation of Need for a REMS
Established Name	tafenoquine
Trade Name	Arakoda
Name of Applicant	60 Degrees Pharmaceuticals LLC
Therapeutic class	8-aminoquinoline antimalarial
Dosage form	100 mg tablets for oral use
Dosage regimen	Loading regimen: For each of the 3 days before travel to a malarious area 200 mg once daily for days; Maintenance regimen while in the malarious area: 200 mg once weekly, start 7 days after the last loading regimen dose; Terminal prophylaxis regimen: in the week following exit from the malarious area 200 mg one time

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Arakoda (tafenoquine) is necessary to ensure the benefits outweigh its risks. 60 Degrees Pharmaceuticals submitted a New Drug Application (NDA 210607) for tafenoquine with the proposed indication for the prevention of malaria in adults for up to 6 months of continuous dosing. This application is under review in the Division of Anti-infective Products (DAIP). The applicant did not submit a proposed REMS or risk management plan with this application. The serious risks associated with tafenoquine include: hemolytic anemia, methemoglobinemia, psychiatric effects, and hypersensitivity reactions.

Based on the available data, DAIP and DRISK agree that a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with tafenoquine use are well documented based on experience with aminoquinolone antimalarial drugs with similar safety profiles.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Arakoda (tafenoquine) is necessary to ensure the benefits outweigh its risks. 60 Degrees Pharmaceuticals submitted a New Drug Application (NDA 210607) for tafenoquine with the proposed indication for the prevention of malaria in adults for up to 6 months of continuous dosing. This application is under review in the Division of Anti-infective Products (DAIP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Tafenoquine is an 8-aminoquinoline antimalarial drug. The mechanism of action is not clearly defined, but is hypothesized to involve redox reactions by killing the developing asexual, exoerythrocytic, and latent hypnozoites of malaria parasites.¹ The Applicant's proposed indication is for the prevention of malaria in adults for up to 6 months of continuous dosing. Tafenoquine is supplied as 100mg tablets with the following dosing regimen^a:

Regimen Name	Timing	Dose
Loading regimen	For each of the 3 days before travel to a malarious area	200mg orally once daily for 3 days
Maintenance regimen	While in the malarious area	200mg orally once weekly – start 7 days after the last loading regimen dose
Terminal prophylaxis regimen	In the week following exit from the malarious area	200mg by mouth at once

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Tafenoquine is not part of a drug class that has a REMS. Tafenoquine is a NME^b and has also been reviewed by the FDA under the trade name Krintafel for the proposed indication of the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years of age and older. Krintafel was approved on July 26, 2018.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210607 relevant to this review:

- 8/21/2017: NDA 210607 tafenoquine submission received
- 03/20/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tafenoquine
- 07/26/2018: An Anti-Infective Drug Advisory Committee was held to discuss the efficacy and safety of NDA 210607 tafenoquine. On the question of whether the Applicant has provided substantial evidence of the effectiveness of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing, the committee voted 11 – yes, 2 – no. On the question of whether the Applicant has provided adequate evidence of the safety of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing, the committee voted 9 – yes, 4 – no.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Malaria is an infection of red blood cells transmitted by *Anopheles* mosquitoes. Five species of the parasite of genus *Plasmodium* (*P.*) cause all malaria infections in humans. These species include: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*; the last which is primarily carried in monkeys in southeast Asia, and transmitted to humans to a lesser extent.² Most infections are caused by either *P. falciparum* or *P. vivax*, and most deaths occur from *P. falciparum*. The first symptoms of malaria are usually non-specific, and may include malaise, headache, fatigue, muscle aches and fever. Untreated malaria can progress to seizures, severe anemia, jaundice and multi-organ failure.^{2,c}

Malaria is transmitted in 108 countries inhabited by approximately 3 billion people², and in 2016, caused an estimated 216 million cases and 455,000 deaths.³ Over 85% of malaria cases and 90% of malaria related deaths occur in sub-Saharan Africa, mainly in young children. The Centers for Disease Control (CDC) and Prevention estimates that there are 1,700 cases of malaria each year in the United

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (F): *Whether the drug is a new molecular entity.*

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

States.³ The vast majority of cases in the United States are in travelers and immigrants returning from countries where malaria transmission occurs, many from sub-Saharan Africa and south Asia.^{3,d}

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Chemoprophylaxis is recommended for travelers during potential exposure to malaria. For drugs that do not have activity against the pre-erythrocytic (liver) stage, chemoprophylaxis is given during exposure and for four weeks thereafter to catch any blood-stage infections that may emerge from the liver.² Recommendations for which drugs to use for chemoprophylaxis are dependent on local patterns of susceptibility to antimalarial drugs and the likelihood of acquiring malaria while in the endemic area. Atovaquone-proguanil, doxycycline, primaquine and mefloquine are the recommended drugs of choice for prevention of malaria, and which drug to use is highly dependent on patient related variables such as pregnancy, age, and co-existing conditions such as neuropsychiatric conditions. The adverse event profiles of these medications vary, and with the exception of mefloquine, the risks of these drugs are addressed in labeling under Warnings and Precautions. Mefloquine was approved in 1989, but due to post marketing cases of suicides and neuropsychiatric events, a Boxed Warning was added in 2013 to communicate these risks. None of these drugs were approved with a REMS.

4 Benefit Assessment¹

The Applicant submitted two randomized comparator-controlled studies to support the efficacy of NDA 210607. Below is a summary of these two trials.

Study 045: This was a randomized comparison of tafenoquine to placebo and to mefloquine for prophylaxis against *P. falciparum* in healthy semi-immune residents of a malarious region in East Africa. After treating existing parasitemia with quinine/doxycycline/primaquine, subjects were randomized into prophylactic groups including tafenoquine 200 mg each dose, mefloquine 250 mg each dose, and placebo. Each group was administered a loading regimen of daily drug for 3 days followed by a maintenance regimen of weekly drug for 10 weeks. For the 3 prophylactic groups, males were 65-72% of the total population. The mean age and weight of males was 37-39 years and 54-56 kg. The mean age and weight of females was 52-54 years and 45-49 kg. The primary efficacy endpoint was first occurrence of a blood smear positive for asexual stage *P. falciparum* parasites. The incidence of parasitemia for the modified intention-to-treat population the 3 prophylactic groups is below:

^d Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Table 1: Incidence of Parasitemia and Protective Efficacy for Study 045

Parasitemia	Placebo	Tafenoquine 200 mg	Mefloquine 250 mg
Total No subjects	94	91	46
No subjects With Positive Smear	86	12	6
% Incidence of positive smear	91.5	13.2	13.0
Protective efficacy (%)	–	85.6	85.7
95% CI for Protective efficacy	–	(76.2%, 91.6%)	(71.9%, 93.3%)

Study 033: This study compared tafenoquine with mefloquine for the prophylaxis of both *P. falciparum* and *P. vivax* malaria in healthy non-immune Australian soldiers deployed to East Timor (now Timor-Leste). The study was divided into 2 phases. The first, or prophylactic phase, consisted of a 26-week period during deployment where subjects received prophylactic study medication (tafenoquine 200 mg or mefloquine 250 mg). At the end of the deployment to the malarious area and once the subjects had returned to barracks in Townsville, Australia, the subjects entered a 24-week relapse follow-up phase. During this follow-up phase, subjects who had been on mefloquine prophylaxis received 14-days of primaquine (15 mg bid) while subjects on tafenoquine prophylaxis received placebo capsules for 14 days. Subjects were almost all male, mostly between 18 and 35 years, and 99% were of the white race.

The primary efficacy endpoint was prophylactic failure which was defined as parasitologic and clinical failure during the 26-week prophylactic phase. The protocol-defined principal efficacy analysis was based on the per-protocol (PP) population, and that all randomized subjects who satisfied inclusion/exclusion criteria and subsequently adhered to the protocol. No subject was a prophylactic failure during the prophylactic phase.

Table 2: Prophylactic Outcome During the Prophylactic Treatment Phase (PP Population) for Study 033

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

5 Risk Assessment & Safe-Use Conditions^{1, e}

The safety of tafenoquine with the recommended regimen was evaluated in 825 subjects in 5 controlled clinical trials (Trials 1, Trial 2, Trial 3, Trial 4 and Trial 5). There were 492 patients that received tafenoquine at some point in these pooled analyses. The mean duration of exposure to tafenoquine in these five clinical trials was 21 weeks (range 10-29 weeks). Adverse events occurring in more than 2% of patients in the tafenoquine group included diarrhea (18%), headache (15%), rash (14%), nausea (7%), vomiting (5%), and vertigo (4%). The adverse events noted below will be communicated via Warnings and Precautions. At this time, review of labeling is still ongoing. There is currently not a Boxed Warning proposed for any of the risks.

5.1 HEMOLYTIC ANEMIA

There is a risk of hemolytic anemia in patients with G6PD deficiency, and therefore, G6PD testing must be performed before prescribing. 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 tafenoquine is contraindicated in patients with G6PD deficiency or unknown G6PD status.

5.2 METHEMOGLOBINEMIA

Asymptomatic elevations in methemoglobin have been observed in the clinical trials of tafenoquine. Recommendations are to institute appropriate therapy if signs or symptoms of methemoglobinemia occur, and to carefully monitor individuals with nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase deficiency.

5.3 PSYCHIATRIC EFFECTS

Psychiatric adverse reactions were reported in 3.9% of patients including insomnia (1.2%), abnormal dreams (0.6%), and anxiety (0.2%). Subjects with history of psychiatric disorders were excluded from two out of five tafenoquine clinical trials. Three cases of depression or depressed mood (0.3%) and one case of attempted suicide (0.1%) occurred following tafenoquine use primarily in patients with a history of psychiatric disorders. Additionally, three cases of psychosis were reported in patients with a history of psychiatric illness who received tafenoquine doses different from the approved tafenoquine regimen (350 mg to 500 mg). Safety and effectiveness of tafenoquine have not been established at doses or regimens other than the approved regimen for this indication. Due to the long half-life of tafenoquine (approximately 17 days), signs or symptoms of psychiatric adverse reactions that may occur could be delayed in onset and/or duration. Tafenoquine is contraindicated in patients with active depression, a history of depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.4 HYPERSENSITIVITY REACTIONS

Serious hypersensitivity reactions (e.g., shortness of breath and urticaria) have been observed with administration of tafenoquine. Due to the long half-life of tafenoquine, signs or symptoms of hypersensitivity adverse reactions that may occur could be delayed in onset and/or duration. Tafenoquine is contraindicated in patients who develop hypersensitivity to tafenoquine or any component of tafenoquine or other 8-aminoquinolines.

6 Expected Postmarket Use

Tafenoquine is expected to be prescribed by a wide variety of physicians (general practice, infectious disease providers) to patients in the United States who are traveling to malarious areas, or soldiers who may be deployed to malarious areas.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tafenoquine beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of tafenoquine on the basis of the efficacy and safety information currently available. However, due to what appeared to be a limited data set for this NME, the clinical review team decided to have this application discussed at an Advisory Committee. On the question of whether the Applicant has provided substantial evidence of the effectiveness of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing, the committee voted 11 – yes, 2 – no. On the question of whether the Applicant has provided adequate evidence of the safety of tafenoquine for the prevention of malaria in adults for up to 6 months of continuous dosing, the committee voted 9 – yes, 4 – no. The Committee also voiced concerns on the lack of safety information available in the submitted database. Furthermore, given the psychiatric toxicity found with mefloquine, tafenoquine having a very similar structural activity relationship, and given the small numbers of psychiatric events reported, the committee recommended that the Applicant conduct more studies in this area.

Discussions of a post-marketing requirement for longer term studies of neuropsychiatric events were ongoing at the time of this writing. The review team concluded that that the Applicant will be required to conduct a study, in addition to enhanced pharmacovigilance. Though the numbers were small for neuropsychiatric events, the review team decided that communicating this risk under Warnings and Precautions would be adequate at this time should this NDA be approved. Atovaquone-proguanil, doxycycline, primaquine and mefloquine have been the cornerstones of treatment and chemoprophylaxis of malaria for several years. The adverse event profile of tafenoquine is similar to these drugs and is not new or unusual, so the prescribing community should be aware of its risks. None of the drugs currently approved for the treatment or prevention of malaria are approved with a REMS.

9 Conclusion & Recommendations

Based on the available data, DAIP and DRISK agree that a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with tafenoquine use are well documented based on experience with antimalarial drugs with similar safety profiles. In addition, healthcare providers who will be prescribing tafenoquine for chemoprophylaxis are familiar with the risks and the importance of patient monitoring.

10 References

¹ Arakoda draft prescribing information, July 10, 2018

² Write N, DPhil S, Hien T et al. Malaria. *The Lancet* vol 383 (9918) February 2014, pgs 723-735

³ www.cdc.gov/parasites/malaria/index.html accessed May 14, 2018

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/s/

NAOMI B REDD
07/31/2018

CYNTHIA L LACIVITA
07/31/2018