CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210795Orig1s000

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	210795
PDUFA Goal Date	July 22, 2018
OSE RCM #	2017-2404
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 18, 2018
Subject	Evaluation of Need for a REMS
Established Name	Tafenoquine
Trade Name	Krintafel
Name of Applicant	GlaxoSmithKline
Therapeutic Class	8-aminoquinolone
Formulation(s)	Tablet for oral use: 150 mg
Dosing Regimen	300 mg by mouth once

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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 Krintafel (tafenoquine) is necessary to ensure the benefits outweigh its risks. GlaxoSmithKline submitted a New Drug Application (NDA) # 210795 for tafenoquine with the proposed indication for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years of age and older. The risks associated with tafenoquine include hemolytic anemia, methemoglobinemia, serious psychiatric adverse reactions and hypersensitivity. The applicant did not submit a REMS with this application but proposed routine pharmacovigilance activities to identify and characterize the safety concerns for tafenoquine.

If approved, the labeling will communicate the risks of tafenoquine with Warning and Precautions specifically highlighting the risks of hemolytic anemia, methemoglobinemia, serious psychiatric adverse reactions and hypersensitivity. The risks are similar to those seen in other approved aminoquinolines (chloroquine, hydroxychloroquine, and primaquine) used in the treatment of malaria. Prescribers are likely to be familiar with the management of adverse reactions associated with aminoquinolines. DRISK and the Division of Anti-Infective Products (DAIP) agree that a REMS is not needed to ensure the benefits of tafenoquine outweigh its risks for the proposed indication: for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years of age and older.

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) Krintafel (tafenoquine) is necessary to ensure the benefits outweigh its risks. GlaxoSmithKline submitted a New Drug Application (NDA) # 210795 for tafenoquine with the proposed indication for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years of age and older. This application is under review in the Division of Anti-Infective Products (DAIP). The applicant did not submit a REMS with this application but proposed routine pharmacovigilance activities to address the risks of hemolytic anemia, methemoglobinemia, serious psychiatric adverse reactions and hypersensitivity.

2 Background

2.1 PRODUCT INFORMATION

Krintafel (tafenoquine), a new molecular entity,[a] is an 8-aminoquinolone proposed for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years of age and older. Tafenoquine, if approved, will be the second drug in the pharmacologic class of 8-aminoquinolones. Tafenoquine is proposed as a 150-mg tablet for oral administration. The recommended dose is 300 mg by mouth once as a single dose with food.[b] Tafenoquine is not currently approved in any jurisdiction.

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

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

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210795 relevant to this review:

- 01/30/2008: IND 101471 submission received for tafenoquine
- 01/15/2013: Orphan drug designation granted for tafenoquine under IND 101471
- 12/18/2013: Breakthrough therapy designation granted for tafenoquine under IND 101471
- 11/22/2017: NDA 210795 submission for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years of age and older
- 03/12/2018: Midcycle telecommunication with the applicant; the FDA stated there were no safety issues that require a REMS for tafenoquine
- 07/12/2018: Meeting of the Antimicrobial Drugs Advisory Committee was convened to discuss the effectiveness and safety of tafenoquine for the radical cure (prevention of relapse) of P. vivax malaria in patients 16 years and older. The committee voted that the applicant provided substantial evidence of effectiveness (voted 13:0) and safety (voted 12:1) based on the data presented.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Malaria, caused by *Plasmodium* parasites, is a life-threatening disease transmitted by infected female *Anopheles* mosquitos.[c1] Malaria can be categorized as either uncomplicated or severe (complicated). The most common symptoms are fever, chills, sweats, head and body aches, nausea and vomiting and general malaise. Severe malaria occurs when organ failure or blood/coagulation abnormalities are present. The World Health Organization (WHO) estimates that in 2016, malaria caused 216 million clinical episodes and 445,000 deaths worldwide.[d] Approximately 1,700 cases of malaria are reported every year in the United States, almost all in recent travelers.[2] Malaria infections due to *Plasmodium vivax* (*P. vivax*) are particularly concerning because *P. vivax* develops dormant liver stages that reactivate at symptomless intervals of up to 2 years.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment of malaria varies and is dependent upon the species of the infecting parasite, geographic location and drug-resistance status, pregnancy, allergies, concomitant medications, and comorbidities. *P. vivax* requires treatment for both the blood stage (asexual erythrocytic parasite) and the dormant liver stage (hypnozoite) that causes relapsing malaria. *P. vivax* malaria treatment usually consists of chloroquine phosphate or hydroxychloroquine for the blood stage plus primaquine phosphate for the liver stage. For chloroquine-resistant locations, quinine sulfate, doxycycline, tetracycline, atovaquone-

[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.*

[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.*

proguanil, mefloquine and primaquine phosphate are used. See table 1 in the appendix for more details.

- Chloroquine-Sensitive Regimen:
    - Chloroquine phosphate plus Primaquine phosphate
    - Hydroxychloroquine plus Primaquine phosphate
- Chloroquine-Resistant Regimen:
    - Quinine sulfate plus either Doxycycline or Tetracycline plus Primaquine phosphate
    - Atovaquone-proguanil plus Primaquine phosphate
    - Mefloquine plus Primaquine phosphate

4 Benefit Assessment[e]

The efficacy and safety of tafenoquine for the radical cure (prevention of relapse) of *P. vivax* malaria was demonstrated in the pivotal study, TAF 112582 part 2. The pivotal study was a phase 3, randomized, double-blind, double-dummy, parallel group, placebo- and active control study that determined the efficacy of tafenoquine relative to a chloroquine-only control.[3] The study enrolled 522 patients 16 years and older with confirmed *P. vivax* infection (positive blood smear) and 70% or greater normal glucose-6-phosphate-dehydrogenase deficiency (G6PD) levels. The primary efficacy endpoints were time to recurrence over the first 6 months and recurrence-free efficacy 6 months post-dosing.

Exploratory non-inferiority analysis was conducted to test the hypothesis that tafenoquine is non-inferior to primaquine for the prevention of recurrence over the 6-month post-dosing period. Therefore, the 522 enrolled patients were randomized to the following 3 dosing regimens:

Chloroquine 600 mg by mouth once daily for 2 days then 300 mg by mouth once daily for 1 day PLUS

1. Tafenoquine 300 mg by mouth for one dose (n = 260) OR
2. Primaquine 15 mg by mouth once daily for 14 days (n = 129) OR
3. No additional treatment (n = 133)

Results showed a statistically significant risk reduction of recurrence at any time point over 6 months of 70.1% (95% CI: 59.6%, 77.8%; p<0.001) compared to chloroquine alone. The estimated recurrence-free efficacy rate at 6 months was 62.4% in the tafenoquine plus chloroquine group compared with 27.7% in the chloroquine-only group and 69.6% in the primaquine plus chloroquine group. Non-inferiority of tafenoquine versus primaquine was not demonstrated. See table 2 below for more details. The FDA's review confirmed the applicant's efficacy results.[4]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Table 2[3]: Study TAF 112582 Part 2: Analysis of Recurrence-Free Efficacy over 6 months

	CQ alone (N=133)	TQ+CQ (N=260)	PQ+CQ (N=129)
Number of subjects, n (%)			
Recurrence-free at 6 months	35 (26)	155 (60)	83 (64)
Recurrence-free efficacy rate at 6 months			
Estimate (95% CI)	27.7% (19.6,36.3)	62.4% (54.9,69.0)	69.6% (60.2,77.1)

CQ = Chloroquine; TQ = Tafenoquine; PQ = Primaquine

5 Risk Assessment & Safe-Use Conditions[f]

The safety profile of tafenoquine is derived from the following 3 randomized, double-blind studies: TAF112582 Part 1 (Phase 2b), TAF112582 Part 2 (pivotal Phase 3) and TAF116564 (Phase 3).[5] These studies are referred to as the all primary study dataset (AP studies). A total of 483 patients with *P. vivax* malaria were exposed to tafenoquine plus chloroquine in these 3 studies. The serious adverse events (referred to as risks) determined to be associated with tafenoquine are hemolytic anemia, methemoglobinemia, serious psychiatric adverse reactions and hypersensitivity.[g] The Warnings and Precautions section of the tafenoquine proposed label includes these risks and are discussed below.

5.1 Hemoglobin-associated Adverse Events of Special Interest (AESI)

Because tafenoquine is an 8-aminoquinolone with the potential to cause drug-induced hemolysis, hemoglobin-associated AESI were assessed. Overall, hemoglobin-associated adverse events of all grades were reported in 29/483 patients (6%). The most common hemoglobin-associated AESI was hemoglobin decreased (n = 19; 4%). One CTCAE (Common Terminology Criteria for Adverse Events) Grade 3 event of increased bilirubin following *P. vivax* recurrence occurred.

5.1.1 Hemolytic Anemia due to G6PD Deficiency

There were no events of tafenoquine-induced hemolysis due to G6PD deficiency reported in the AP studies. One patient in the pivotal study, who received tafenoquine plus chloroquine, was identified as having a Viangchan G6PD mutation and experienced hemoglobin decreases along with increases in bilirubin and reticulocytes. Medical intervention was not required but the applicant stated drug-induced hemolysis could not be excluded. One patient in study TAF112582, who received tafenoquine plus chloroquine, was identified as heterozygous for the Mahidol known G6PD-deficient variants. No adverse events of hemolysis or decreased hemoglobin were reported in this patient.

[f] 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.*

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The proposed label includes a contraindication for G6PD deficiency, a statement in Warnings and Precautions that G6PD testing must be performed before prescribing Krintafel due to the risk of hemolytic anemia, and a recommendation to monitor patients for signs and symptoms of hemolysis. Other FDA-approved drugs with the same risk of hemolytic anemia due to G6PD deficiency are managed in labeling under the different sections including: Boxed Warning, Precautions, Warnings, Warnings and Precautions, Contraindications, Adverse Reactions, Overdosage, Patient Counseling Information, Clinical Pharmacology, Clinical Studies, and Use in Specific Populations. The two drugs with Boxed Warnings are pegloticase and rasburicase. Both drugs are urate-oxidase enzymes with Boxed Warnings for hemolysis and methemoglobinemia.

5.1.2 Methemoglobinemia

In study TAF112582 (parts 1 and 2), in patients treated with tafenoquine and chloroquine, a 2.4% and 2.1% median increase in methemoglobin occurred in female and male patients respectively. The proposed label advises to initiate appropriate therapy if signs or symptoms of methemoglobinemia occur.

5.2 PSYCHIATRIC ADVERSE REACTIONS

Overall, 15/483 (3%) patients experienced a psychiatric adverse event in the AP studies. Insomnia occurred in 15/483 (3%) patients and anxiety occurred in 2/483 (less than 1%) patients. No severe adverse events (CTCAE Grade 3 or higher) occurred. The proposed label advises to use caution in patients with a history of serious psychiatric conditions.

5.3 HYPERSENSITIVITY

There were no events of hypersensitivity in the AP studies. The proposed label includes a contraindication for known serious hypersensitivity reactions (e.g. angioedema) to tafenoquine, other 8-aminoquinolones, or any component of the formulation and advises if hypersensitivity occurs, institute appropriate therapy.

6 Expected Postmarket Use

Tafenoquine will be primarily prescribed in the outpatient setting and the likely prescribers will be primacy care physicians and physicians specializing in infectious diseases. The risks are similar to the approved aminoquinolines (chloroquine, hydroxychloroquine, and primaquine) used in the treatment of malaria. Prescribers are likely to be familiar with the management of adverse reactions associated with aminoquinolines. The proposed label currently addresses the associated risks and management of hemolytic anemia, methemoglobinemia, serious psychiatric adverse reactions and hypersensitivity.

7 Risk Management Activities Proposed by the Applicant

The applicant did not submit a REMS with this application but proposed routine pharmacovigilance activities to identify and characterize the safety concerns for tafenoquine.

8 Discussion of Need for a REMS

The FDA's review confirms the applicant's statement of efficacy. Malaria due to *Plasmodium* parasites is a life-threatening infection with the WHO estimating in 2016, malaria caused 216 million clinical episodes and 445,000 deaths worldwide. The standard treatment depends on the species of the infecting parasite, geographic location and drug-resistance status, pregnancy, allergies, concomitant medications, and comorbidities. Treatment with tafenoquine provides an effective alternative to primaquine phosphate with a shorter duration of therapy (one time dose of tafenoquine versus 14 days of primaquine) for the liver stage of *P. vivax* malaria infections. On July 12, 2018, the effectiveness and safety of tafenoquine for the radical cure (prevention of relapse) of *P. vivax* malaria in patients 16 years and older was discussed at the Antimicrobial Drugs Advisory Committee meeting. The committee voted that the applicant provided substantial evidence of effectiveness (voted 13:0) and safety (voted 12:1) based on the data presented.

The serious risks associated with tafenoquine include hemolytic anemia, methemoglobinemia, serious psychiatric adverse reactions and hypersensitivity. These risks are addressed in the proposed label under Contraindications and Warnings and Precautions. Primary care physicians and physicians specializing in infectious diseases are the likely prescribers and should be familiar with managing these risks. The risks are common to the aminoquinoline class of drugs and are included in the respective labels. DRISK recommends that, should tafenoquine be approved, a REMS is not necessary to ensure its benefits outweigh its risks for the radical cure (prevention of relapse) of *P. vivax* malaria in patients aged 16 years of age and older.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable for the treatment of *P. vivax* malaria and therefore, a REMS is not necessary for tafenoquine to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

1. Malaria Fact Sheet. World Health Organization. Available at: http://www.who.int/mediacentre/factsheets/fs094/en/. Accessed March 19, 2018.
2. Malaria Fast Facts. Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/malaria/about/facts.html. Accessed March 19, 2018.
3. GlaxoSmithKline. Krintafel (tafenoquine), Module 2.7.3 - Summary of Clinical Efficacy. November 22, 2017.
4. FDA Briefing Document for Tafenoquine (150 mg tablets). Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC). July 12, 2018.
5. GlaxoSmithKline. Krintafel (tafenoquine), Module 2.7.4 - Summary of Clinical Safety. November 22, 2017.

6. Drugs@FDA: FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed March 29, 2018.
7. Guidelines for Treatment of Malaria in the United States (Updated July 1, 2013). Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf. Accessed March 21, 2018.

10.2 TABLE 1[6,7]: TREATMENT OF *PLASMODIUM VIVAX* MALARIA

Product Trade Name (Generic) Year Approved	Dosing and Administration	Important Safety and Tolerability Issues	Risk Management Approaches
Chloroquine phosphate 1949 Aminoquinoline	1000 mg (600 mg base) PO then 500 mg (300 mg base) at 6-, 24-, and 48 hrs after the 1st dose.	Hypoglycemia, Extrapyramidal effects, Neuromuscular effects, Psoriasis, Porphyria, Retinal toxicity, Hematologic effects, Hemolytic anemia due to G6PD deficiency, Auditory damage, and Cardiomyopathy	Labeling – Warning and Precautions
Primaquine sulfate 1952 8-aminoquinolone	30 mg (base) PO daily x 14 days	Hemolytic anemia, Hematologic effects, G6PD deficiency, NADH methemoglobin reductase deficiency, and Cardiovascular effects	Labeling – Warning and Precautions
Plaquenil (Hydroxychloroquine sulfate) 1955 Aminoquinoline	800 mg (620 mg base) PO then 400 (310 mg base) mg at 6-, 24-, and 48 hrs after the 1st dose.	Retinal toxicity, Cardiovascular effects, Psoriasis, Porphyria, Neuromuscular effects, Psychiatric effects, Hypoglycemia, Hematologic effects, G6PD deficiency, Dermatologic effects, and GI disorders	Labeling – Warning and Precautions
Quinine sulfate 1950 Antiarrhythmic/antimalarial	648 mg (salt) PO TID x 3 or 7 days Plus doxycycline or tetracycline	Treatment of nocturnal leg cramps with quinine sulfate may result in serious, life-threatening hematologic reactions, renal impairment, and thrombotic thrombocytopenic purpura	Labeling - Boxed Warning
		Nocturnal leg cramps, Hematologic effects, Cardiovascular effects, G6PD deficiency, Myasthenia gravis, Optic neuritis, and Hypoglycemia	Labeling – Warning and Precautions
Malarone (Atovaquone/Proguanil 250/100 mg) Antimalarial	4 tabs PO daily x 3 days	Diarrhea/Vomiting, Obesity, Hepatotoxicity, and Malaria	Labeling – Warning and Precautions
Mefloquine 1989 Quinolone antimalarial	750 mg PO then 500 mg 6-12 hrs after the 1st dose	Neuropsychiatric disorders and effects	Labeling – Boxed Warning
		Life-threatening P. falciparum infections, CNS effects, Ophthalmic effects, Cardiac effects, Drug-resistance and cross-resistance, Hematologic effects	Labeling – Warning and Precautions
Doxycycline 1967 Tetracycline derivative	100 mg PO TID x 7 days	Intracranial hypertension, GI inflammation/ulceration, Increased blood urea nitrogen (BUN), Oracea, Hepatotoxicity, Tissue hyperpigmentation, and Oral candidiasis	Labeling – Warning and Precautions
Tetracycline	250 mg PO QID x 7 days	Intracranial hypertension and Increased blood urea nitrogen	Labeling – Warning and Precautions

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/s/

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I concur

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