CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210607Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research| Office of Surveillance and Epidemiology (OSE)

Feasibility of ARIA to Evaluate the Association between Tafenoquine Use and Neuropsychiatric and Hematologic Adverse Events

Date:	August 3, 2018
Reviewer(s):	Chih-Ying Pratt, Ph.D. Division of Epidemiology II
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Division Director:	David Moeny, R.Ph. M.P.H. Division of Epidemiology II
OPE Deputy Director:	Michael D. Blum, MD, MPH
FDA Sentinel Program Lead:	Michael D. Nguyen, MD
OSE Deputy Director:	Robert Ball MD, MPH, ScM
Subject:	Feasibility of ARIA to Evaluate the Association between Tafenoquine Use and Neuropsychiatric and Hematologic Adverse Events
Drug Name(s):	Arakoda (tafenoquine)
Application Type/Number:	NDA 210607
Applicant/sponsor:	60 Degrees Pharmaceuticals LLC
OSE RCM #:	2018-1054

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

Tafenoquine is an investigational 8-aminoquinoline antimalarial product. It is a primaquine congener which was first reported in 1978. The proposed indication for tafenoquine succinate tablet (NDA 210607) is for the malaria prevention in adults with up to 6 months of continuous dosing. The indication encompasses all species of *Plasmodia* and includes prophylaxis while in the malaria endemic region and post-exposure. The proposed regimen for tafenoquine includes a loading dose of 200 mg (two 100 mg tablets) once daily for 3 days before travel to a malaria endemic area, followed by 200 mg maintenance weekly dose while in the malaria endemic area, followed by a single 200 mg dose in the week following exit from the malaria endemic area.

1.2. Describe the Safety Concern

More than 20 clinical trials were included by the sponsor in the NDA submission, most of which were conducted between 1992-2006. Five comparative trials were most relevant to the evaluation of clinical safety, with four studies including a placebo arm, while two had mefloquine as an active comparator. Mefloquine, a 4-aminoquinoline antimalarial drug, has well-characterized safety regarding neurological and psychiatric adverse reactions with a Boxed Warning for malaria prophylaxis indication. In the pooled analyses of these 5 trials, the safety of tafenoquine with the recommended regimen was evaluated in 825 subjects, but only 529 subjects were exposed to the proposed regimen for greater than or equal to 23 weeks. The total number of subjects is 295 in the placebo arm, and 309 in the mefloquine arm, respectively, in the pooled safety dataset.

In those trials, potential safety signals on neurologic, psychiatric, and hematologic adverse events (AE) were observed with tafenoquine.

Neurological AEs: In the pooled safety data set, the rates of neurologic AEs in tafenoquine group are numerically lower but mostly similar to mefloquine, an agent known to have neurologic effects. The incidence of headache and lethargy was 22% and 3%, respectively, in the tafenoquine group, versus 30% and 4%, respectively, in mefloquine group. The treatment emergent adverse event (TEAE) of dizziness was 3% in the tafenoquine group compared to 6% in the mefloquine group; and vertigo/tinnitus occurred in 5% of the tafenoquine group compared to 7% of the mefloquine group.

The tafenoquine group compared to placebo group had increased neurologic adverse events for myalgia in one clinical study of healthy volunteers (7.4% [6/81 tafenoquine subjects] versus 0% [0/39 placebo subjects]). In four placebo-controlled studies, tafenoquine had a higher rate than placebo for falls, dizziness, or lightheadedness (4.8%, [16/333 tafenoquine subjects] versus 3.7% [11/295 placebo subjects]. In the pooled safety set, there was a higher rate of vertigo and tinnitus for tafenoquine compared to placebo (3% versus 0%).

However, systematic monitoring for neurologic AEs was not conducted in these trials and, therefore, the reported AE rate may significantly underestimate the true incidence of these events in these trials. The safety of tafenoquine in individuals with underlying neurologic conditions cannot be ascertained because these subjects were excluded from the tafenoquine clinical trials.

Psychiatric AEs reported for tafenoquine and mefloquine were similar (3.9% and 3.2%, respectively), higher than the proportion of 0.8% in the placebo group. The psychiatric AEs observed in tafenoquine patients include insomnia (1.2%), abnormal dreams (0.6%), and anxiety (0.2%). There were no deaths due to a psychiatric AE.

Psychiatric TEAEs leading to study discontinuation in the tafenoquine group included suicide attempt and depression, each of which occurred in 1 (0.1%) subject. One subject in the mefloquine group had severe anxiety that led to study discontinuation; no patients had a psychiatric TEAE that led to discontinuation in the placebo group.

Systematic monitoring for psychiatric AEs was not conducted in these trials. Exclusion criteria for psychiatric conditions varied among individual trials. In the studies with a mefloquine control arm, individuals with a history of psychiatric disorder were excluded, consistent with current labeling for mefloquine.[a]

Hematologic AEs: Tafenoquine is associated with decrease in hemoglobin(Hb) levels, hemolytic anemia and methemoglobinemia. Hematologic TEAEs leading to study discontinuation included decreased Hb (3 subjects, 0.4%) and hemolytic anemia (2 subjects, 0.2 %). The percentage of subjects with any Hb decreases ≥ 0.66 g/dL was higher in the tafenoquine group (60.1%) than placebo (41.9%) or mefloquine (46.3%) group. Increase in methemoglobin levels relative to baseline were observe at a higher rate with tafenoquine compared to both the placebo and mefloquine group (Any changes ≥1%: 12.9%, versus 0.8% in placebo and 0% in mefloquine). No dose or duration response was identified with respective to Hb changes or methemoglobinemia in the populations studies. Tafenoquine was not evaluated in individuals with G6PD deficiency, where the risk of hemolytic anemia would be higher.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

During the Advisory Committee Meeting on July 26, 2018, the Sponsor proposed a post-marketing requirement of a health database outcomes study, using a database such as TRICARE to document the rates of diagnosed neuropsychiatric events in travelers, using a local standard of care as a comparator.[b] The Sponsor proposed starting the analysis after sufficient number of ARAKODA prescriptions were recorded. The Division of Anti-infective Drugs (DAIP) consulted the Division of Epidemiology II (DEPI-II) about the feasibility of a post-marketing study to evaluate tafenoquine-associated neurologic and psychiatric adverse events using observational data, focusing on the administrative claims databases in the U.S., including the Sentinel System.

The main goals for such an observational study include:

1) to estimate the incidence of neurologic, psychiatric and hematologic adverse events among patients using tafenoquine for prophylaxis of malaria

[a] The boxed warning on neuropsychiatric adverse event was added to Mefloquine label in July 29, 2013, after the completion of all the tafenoquine clinical trials included in this NDA application.
[b] DEPI's assessment of the feasibility of TRICARE data is addressed in a separate memo to DAIP.

2) to estimate the relative risk of neurologic, psychiatric and hematologic adverse events associated with prophylactic tafenoquine use relative to an active comparator

The DEPI assessment of ARIA sufficiency is documented in this memorandum.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Not Applicable.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population for tafenoquine for malaria prophylaxis in the U.S. will be travelers to malaria-endemic regions.

2.2 Is ARIA sufficient to assess the intended population?

ARIA is not sufficient to assess the intended population. ARIA is unlikely to completely capture the intended population. While non-military travelers are covered under commercial insurance plans, this population cannot be identified for the reasons outlined in Section 3 (Exposures)

3. EXPOSURES

3.1. Treatment Exposure(s)

Tafenoquine for malaria prophylaxis.

3.2. Comparator Exposure(s)

Malaria prophylaxis drug(s). The currently approved drugs for malaria prophylaxis includes atovaquone-proguanil, doxycycline, primaquine and mefloquine.

3.3. Is ARIA sufficient to identify the exposure of interest?

Travel medicines, such as tafenoquine for malaria prophylaxis, are <u>not</u> typically covered by standard health insurance policies. Although travelers can get travel vaccines and chemoprophylactic drugs from their health care providers or travel clinics, the cost is usually out of pocket. Of note, the drugs currently approved for malaria prophylaxis are also used to treat malaria or other non-malarial diseases. While exposure to anti-malarial drug might be captured in administrative claims database, the indication for treatment is not.

So, exposure to tafenoquine or the possible comparator drugs for malaria prophylaxis is unlikely to be captured in administrative claims databases.

4. OUTCOME(S)

4.1. Outcomes of Interest

The outcomes of interest are the key neurologic and psychiatric adverse events identified in the pre-market trials:

- Neurologic:
  headache, lethargy, dizziness, vertigo and tinnitus, and myalgia
- Psychiatric:

Sleep disturbances (e.g. insomnia, abnormal dreams, nightmares, sleep disorder, somnambulism), depression, and suicide attempt

- Hematologic:
  Decrease in hemoglobin, hemolytic anemia, and methemoglobinemia

4.2. Is ARIA sufficient to assess the outcome of interest?

The types of neurologic and psychiatric adverse events listed in Section 4.1 are challenging to capture in claims data using diagnostic codes. Often signs and symptoms and less specific diagnoses, such as the ones listed above, are poorly recorded, so without access to accompanying medical data, it is not possible to adequately study these outcomes.

While administrative claims data sources can capture whether a laboratory test was done, only a subset of Sentinel data partners capture the results of the test to define the hematologic adverse events. While Sentinel Common Data Model captures the laboratory results on hemoglobin level, it does not capture other tests relevant to tafenoquine's hematologic AEs. Anemia (specifically, hemolytic anemia) might be captured by diagnostic codes, but currently, they are not well-validated in administrative claims databases.

Further, the outcomes of interest are likely to occur while the traveler is out of the US healthcare system, and not be recorded in claims data once they return.

5. COVARIATES

5.1. Covariates of Interest

Important covariates of interest include:

Neurologic and psychiatric AEs: history of neuropsychiatric disease, and factors that have impact on mental status, such as stress level.

Hematologic AEs: prior hemoglobin and methemoglobin level, genetic disorder (e.g., G6PD deficiency, Cytochrome b5 reductase deficiency, pyruvate kinase deficiency, etc.), use of various pharmaceutical products (local anesthetic agents, amyl nitrite, chloroquine, nitrates, nitrites, etc.), environmental agents (aromatic amines, arsine, chlorobenzene, chromates, etc.)

During the AC discussions, the committee members discussed the need to better understand if the risk would be modified by BMI or age (e.g. older travelers).

5.2. Is ARIA sufficient to assess the covariates of interest?

While Sentinel system can capture some of the important covariates (age, medications and medical conditions that impact hematologic AEs), other important confounders and/or effect modifiers are unlikely to be captured using administrative claims data.

6. SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1. Surveillance or Study Design

A cohort design is suitable to evaluate the incidence rate of neurologic, psychiatric and hematologic adverse events and relative risk associated with tafenoquine versus another anti-malarial drug used for malaria prevention.

6.2. Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

ARIA is sufficient with respect to analytic tools.

7. NEXT STEPS

DEPI has determined that US administrative claim data sources, including the Sentinel System, are not suitable to examine the neurologic, psychiatric and hematologic adverse events associated with tafenoquine for malaria prophylaxis, mainly due to the challenges in capture of the target exposures and outcomes.

A registry study can be a useful tool for collecting long-term data to assess known and emerging safety concerns. Registry-based prospectively-collected data might offer a better chance to collect data on the neurologic and psychiatric adverse events related to tafenoquine for malaria prophylaxis.

However, to know whether a registry study is feasible as a PMR, the Sponsor would have to:

a. identify and enroll sufficient number of subjects for an adequately powered study, within a reasonable timeline
b. develop or identify the infrastructure for data collection
c. use valid data collection instrument(s) that capture the exposure, the outcomes and important data elements such as potential confounders
d. follow-up the exposed population for at least 6-months after tafenoquine exposure
e. identify potential comparators to evaluate the relative risk of neurologic and psychiatric outcomes associated with tafenoquine
f. capture the information to adjust for baseline differences among tafenoquine exposed and the active comparator

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHIH-YING CHEN
08/03/2018

MONIQUE FALCONER
08/03/2018

DAVID G MOENY
08/03/2018

MICHAEL D BLUM
08/03/2018

MICHAEL D NGUYEN
08/03/2018

ROBERT BALL
08/03/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 2, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210607
Product Name and Strength:	Arakoda (tafenoquine) Tablets, 100 mg
Applicant/Sponsor Name:	60° Pharmaceuticals, LLC
FDA Received Date:	July 30, 2018
OSE RCM #:	2017-1724-4
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label (blister card) and carton labeling for Arakoda (tafenoquine) (Appendix A) to determine if they are acceptable from a medication error perspective. These revisions, to the container label (blister card) and carton labeling, were made by the Applicant to align with the Agency's revision to the product name in the prescribing information (i.e., Arakoda (tafenoquine) tablets, for oral use).

2 CONCLUSION

The container label (blister card) and carton labeling for Arakoda (tafenoquine) are acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 30, 2018

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS
08/02/2018

OTTO L TOWNSEND
08/03/2018

Clinical Inspection Summary

Date	July 16, 2018
From	John Lee, M.D., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Gregory DiBernardo, Regulatory Project Manager Sheral Patel, M.D., Medical Officer Yuliya Yasinskaya, M.D., Clinical Team Leader Sumati Nambiar, M.D., M.P.H., Director Division of Anti-Infective Products (DAIP)
Application	NDA 210607
Applicant	60 Degrees Pharmaceuticals, LLC
Drug	Tafenoquine (proposed, (b) (4)
NME / Original NDA	Yes
Review Status	Priority
Proposed Indication	Prevention of malaria in adults for up to 6 months of continuous dosing
Consultation Date	January 31, 2018
CIS Goal Dates	May 28 (at inspection planning) and July 16 (after inspections), 2018
Action Goal Date	August 8, 2018
PDUFA Due Date	August 8, 2018

I. OVERALL ASSESSMENT OF FINDINGS

Four malaria prophylaxis studies (Studies 33, 43, 45, 49) were audited at good clinical practice (**GCP**) inspections of one foreign clinical investigator (**CI**) site and the sponsor site. Studies 33 and 49 were conducted at the same CI site (Peter Nasveld; Brisbane, Australia), and the study records were audited at this CI site and at the sponsor site. For Studies 43 and 45 conducted in Kenya and Ghana (respectively), the study records were not available at the CI sites and incomplete study records lacking the original source records and case report forms (**CRFs**) were audited only at the sponsor site.

For Studies 33 and 49, a Form FDA 483 was issued to Dr. Peter Nasveld for minor GCP deficiencies unlikely to be significant. A Form FDA 483 was not issued at the sponsor inspection; given the study sponsorship transfers, the NDA applicant was deemed not responsible for the observed recordkeeping deficiencies. For Studies 33 and 49, study conduct appeared adequately GCP-compliant, including sponsor oversight of study conduct. All audited data were acceptably verifiable against source records and CRFs, and the data for Studies 33 and 49 appear reliable as reported in the NDA. For Studies 43 and 45, the lack of the original study records does not allow for the verification of the reliability of the data submitted. The adequacy of monitoring for Studies 43 and 45 cannot be determined in lieu of the missing original study records.

II. BACKGROUND

60 Degrees Pharmaceuticals, LLC (**60P**) proposes tafenoquine (**TQ**) oral tablets (pending, (b) (4) for the prevention of malaria, including infection by Plasmodium falciparum (**Pf**) and Plasmodium vivax (**Pv**) in adults for up to 6 months of treatment.

The United States (**US**) Army has been developing TQ as an anti-malarial agent in collaboration with (among others) the Australian Army Malaria Institute (**AAMI**) and GlaxoSmithKline (**GSK**). The sponsorship for the malaria prophylaxis indication was transferred from GSK to 60P in 2014. For this malaria prophylaxis NDA, the following four foreign studies were identified for on-site audit at good clinical practice (**GCP**) inspections of four clinical investigator (**CI**) sites, one site per study.

Study 033: *A randomized, double-blind, comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in nonimmune Australian soldiers deployed to East Timor*

This randomized, double-blind, active-controlled study was conducted from 2000 to 2001 in 654 non-immune Australian soldiers deployed to East Timor. The primary study aim was to evaluate TQ relative to mefloquine (**MQ**), the current first-line agent for malaria prophylaxis despite substantial side effects, mainly gastrointestinal and neuropsychiatric.

- The primary study objective was to compare the safety and tolerability of TQ relative to MQ. The major study objective for efficacy was to compare TQ with MQ in reducing the rate of malaria infection in at-risk subjects exposed to and non-immune for malaria.
- Efficacy results were analyzed for non-inferiority (NI) of TQ relative to MQ, with NI declared if the upper limit of the 95% confidence interval for the difference in prophylaxis failure rates (TQ minus MQ) is $\leq$ 10%.

Healthy malaria-exposed soldiers deployed to East Timor, not pregnant and not having glucose-6-phosphate dehydrogenase deficiency, were randomized to receive either TQ 200 mg or MQ 250 mg oral tablets in 3/1 ratio (TQ/MQ), one tablet daily for 3 days (loading dose) followed by one tablet weekly for 6 months (maintenance treatment).

Subjects were followed for signs and symptoms of malaria with peripheral blood smear (**PBS**) examined as needed to confirm the diagnosis. Polymerase chain reaction (**PCR**) was used for Plasmodium speciation as needed (if inconclusive by light microscopy).

Safety evaluation included adverse event (**AE**) monitoring and laboratory testing at each study visit (Weeks 4, 8, 16, 26). At end of study treatment, those on MQ were given PQ to eradicate any Pv malaria (placebo given to those on TQ to maintain study blind). All subjects were followed for 6 months after returning from East Timor.

Study 043: *Evaluation of Weekly Tafenoquine (SB 252263 / WR 238605) Compared to Placebo for Chemosuppression of Plasmodium falciparum in Western Kenya*

This randomized, double-blind, placebo-controlled, single-center study was conducted between May and September of 1997 in 249 subjects semi-immune to malaria living in Nyanza Province of Kenya, a region holoendemic for malaria where all inhabitants are known to be infected by Pf with varying clinical symptoms.

- The primary study objective was to determine the efficacy of weekly TQ dosing in preventing Pf parasitemia, using prophylaxis failure (**PF**) as the primary endpoint.
- PF was identified by two consecutive PBS showing Plasmodium parasitemia at any time during treatment (two independent microscopists blinded to each other).

Following a 3-day course of (baseline) halofantrine treatment (250 mg daily for 3 days) to eliminate any existing Plasmodium parasitemia, subjects were randomized to four treatment groups, three TQ regimens and placebo:

- TQ load only: 400 mg for 3 days, then placebo for up to 15 weeks
- TQ low dose: 200 mg for 3 days, then 200 mg weekly for 15 weeks
- TQ high dose: 400 mg for 3 days, then 400 mg weekly for 15 weeks
- Placebo: dosing schedule identical to those for the three active groups.

Subjects were evaluated for safety by clinical monitoring and laboratory testing, with weekly PBS examination for efficacy assessment (presence/absence of Plasmodium parasitemia). Subjects were followed for four weeks following treatment completion.

Study 045: *A randomized, double-blind, placebo-controlled evaluation of increasing doses of weekly tafenoquine for chemosuppression of Plasmodium falciparum in semi-immune adults living in the Kassena-Nankana district of Northern Ghana*

This randomized, double-blind, placebo-controlled study was conducted in 1998 in 521 subjects in Ghana semi-immune to malaria. The primary study objectives were to:

- Determine the efficacy of weekly TQ at doses between 25-200 mg in preventing Pf parasitemia relative to placebo and MQ in subjects semi-immune to malaria, and
- Establish the minimum effective prophylactic dose of weekly TQ, and assess the tolerability of treatment at that minimum dose of TQ effective in preventing malaria.

Adult subjects (age 18-60 years if male, age 50-60 years if female) in good general health were treated at study enrollment to eliminate any pre-existing malaria infection, as initial baseline treatment. A loading dose of the study medication was given five days after the completion of the initial baseline treatment, followed by weekly prophylaxis for 12 weeks with follow-up observation for four weeks. PBS was examined weekly during prophylaxis and follow up periods to detect malaria parasitemia.

- Initial baseline treatment regimen, sequential administration of: (1) quinine 10 mg/kg three times daily for four days; (2) doxycycline 100 mg twice daily for seven days; and (3) PQ 30 mg daily for 14 days
- Study treatment, five days after completion of initial baseline treatment: loading dose of TQ (25, 50, 100 or 200 mg), MQ (250 mg), or placebo daily for three days, followed by weekly dosing with the respective study medication for 12 weeks

The primary study endpoint was any (single) positive PBS indicative of the protective efficacy of study medication relative to placebo. Clinical AEs were elicited by field workers (home visits) or by clinic staff (clinic visits) using a standardized symptom evaluation checklist to trigger clinic referral. Routine laboratory tests (chemistry and hematology) were performed at screening and at four clinic visits.

Study 049: *Evaluation of Tafenoquine for the Post-Exposure Prophylaxis of Vivax Malaria (Southwest Pacific Type) in Non-Immune Australian Soldiers*

This open-label randomized study (sponsored by Australian Defense Force) was conducted between 1999 – 2000 in 1534 soldiers stationed in the Southwest Pacific and on daily doxycycline for malaria prophylaxis. Of the 1534 initially enrolled subjects, 1512 were randomized as the intent-to-treat (**ITT**) study population into 3 cohorts:

- AMI 001, Papua New Guinea, 1/1 randomization PQ/TQ
- AMI 002, East Timor, 1/2 randomization PQ/TQ
- AMI 003, East Timor, 1/3 randomization PQ/TQ

Healthy volunteers of age 18-55 years, malaria-free and normal for glucose-6-phosphate dehydrogenase, were randomised to receive one of the following treatment regimens:

- PQ 7.5 mg daily for 14 days
- TQ 400 mg once daily for 3 days (AMI 001 & 002)
- TQ 200 mg twice daily for 3 days (AMI 001 & 002)
- TQ 200 mg once daily for 3 days (AMI 003)

Subjects were followed for 12 months to detect Pv relapse, treated as needed with chloroquine (CQ) for 3 days followed by TQ for 3 days. The primary efficacy endpoint was the proportion of subjects with confirmed parasitemia during the 12 months of follow-up, as detected using PBS preparations for malaria (thick and thin PBS, Giemsa stain).

- PBS was examined routinely at screening and thereafter triggered by clinical symptoms (if symptoms, forwarded to AAMI for confirmation by blinded microscopist).
- Blood samples for other laboratory analysis for safety monitoring were collected at screening and at Day 4. AEs were monitored throughout the study.

III. INSPECTION OUTCOMES

Inspected Entity	Study: Enrollment	Dates	Outcome
Peter Nasveld, M.D. Australian Army Malaria Institute Weary Dunlop Drive Brisbane, Australia	33: 654 subjects 49: 1534 subjects (1512 ITT)	May 21 – June 1, 2018	VAI
60 Degrees Pharmaceuticals, LLC Clinical Network Services USA, Inc. 8403 Colesville Road, Suite 630 Silver Spring, Maryland	33: 654 subjects 49: 1512 subjects 43: 249 subjects 45: 521 subjects	May 29 – June 8, 2018	NAI

CI site selection: foreign sites only (no US studies), high subject enrollment

Compliance Classification of Inspection Outcome

NAI = No Action Indicated, no significant deviations from regulations
VAI = Voluntary Action Indicated, minor deviations from regulations
OAI = Official Action Indicated, major deviations from regulations

1. Peter Nasveld, M.D.

Study 33: 663 subjects were screened, 654 were enrolled, and 640 completed the study. Case records were reviewed in detail for 22 selected or randomly identified subjects.

Study 49: 1559 subjects were screened, 1534 were enrolled, and 1509 completed the study. Case records were reviewed in detail for 20 selected or randomly identified subjects.

Both studies: The inspection included a detailed audit of informed consent, subject selection (inclusion/exclusion criteria), site correspondence with the sponsor, original study records (source records and CRFs), and drug accountability records. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use. A Form FDA 483 was issued for the following two deficiency observations:

- Study 33: For 16 subjects, phone interview at Weeks 18 and 24 (to confirm absence of malaria symptoms) were not performed within the protocol-specified timeframe. These soldier subjects were apparently not available for follow-up during that timeframe, typically out of the country (including at Weeks 18 and 24) after the end of the deployment to *East Timor*.
- Study 49: One subject (apparently isolated) was not evaluated per *Australian Defence Health Policy Directive 215* as specified in the study protocol in that the following laboratory studies were not performed:

- Polymerase chain reaction for malaria speciation or to confirm absence of parasitemia
- Study medication drug level assays
- Light microscopy of serial PBS slides for parasite detection and malaria speciation.

Note: This case of malaria apparently was not reported to the authorities and therefore not included in final study report. However, per follow up documentation, the subject was later treated adequately by non-study health authorities.

The cited deficiency observations (one per study, as noted above) appeared unlikely to be significant to the study outcome. Study conduct otherwise appeared GCP-compliant, including adequate recordkeeping and acceptable sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

2. 60 Degrees Pharmaceuticals, LLC

This inspection was complicated by the involvement of many sponsors and contract research organizations (**CROs**), old (legacy) studies conducted per early (~20 years ago) GCP standards, and missing original source records for Studies 43 and 45. The audit included a general evaluation of GCP compliance of the previous study sponsors and 60P as the current NDA applicant, and:

- CI financial disclosure, site training, and site monitoring of study conduct
- Data flow from the CI sites to the study sponsors
- Relationships among sponsors and contract research organizations (**CROs**)

Study 49 was co-sponsored (not under IND) by AAMI and GSK, and the sponsorship was transferred to 60P as the NDA applicant. The US Army sponsored (under IND) the remaining three Studies 033, 043, and 045, and the US Army partnered with 60P as the NDA sponsor under a Cooperative Research and Development Agreement.

- 60P hired (b) (4) to prepare the NDA, which in turn hired other CROs including (b) (4) as the registered agent for the NDA.
- Study conduct was monitored by the US Army (Studies 33, 43, and 45) and by GSK (Study 33 indirectly through CRO, Study 49 directly).

The source records and CRFs for Studies 43 and 45 were not available for review (apparently destroyed, lost, or missing). 60P was deemed not responsible and a Form FDA 483 was not issued. The following deficiency observations were verbally discussed:

- The original records (source, CRFs, drug accountability) for Studies 43 and 45 were missing. Drug accountability records for Study 33 were inadequate.
- The informed consent forms for Studies 43 and 45 did not describe the risks and benefits of the investigational medication relative to the alternative standard agents for malaria prophylaxis (MQ and doxycycline).
- The CIs for Studies 33 and 45 completed GCP training prior to study conduct. GCP training was not documented for the CIs for Studies 43 and 49.
- Nine site monitors covered the four malaria prophylaxis studies; qualifications of study monitors were not well documented.

- Documentation of serious AEs (**SAEs**) often appeared inadequate and typically no more rigorous or detailed than non-serious AEs, particularly for Study 45.

The findings for Studies 33 and 49 were consistent with those observed at the CI sites (where the studies were conducted) and appeared to be adequately GCP-compliant for the NDA data to be considered reliable. For Studies 43 and 45, the lack of the original study records does not allow evaluation of the accuracy, consistency, and the overall quality of the study data.

Note: The sponsor amended the NDA to include site monitoring reports for Studies 43 and 45, which consisted of the general standard operating procedures (**SOPs**) and high-level audit findings summarized as pre-study, mid-study, and close-out reports.

- Study 43 (Western Kenya, February 1997 – June 1998) appeared to have been adequately monitored to assure GCP-compliant study conduct (per standards ~20 years ago) despite the limited resources available at the study site at that time.
- Study 45 (Northern Ghana, February 1997 – February 1999) appeared GCP-compliant (current standards), including GCP-compliant recordkeeping and study monitoring.

For both studies, the monitoring reports lacked a specific site-study monitoring plan, described general audit findings, and did not incorporate key original study records (source records and CRFs) as exhibits or appendices. Although informative, the monitoring records appear inadequate to support study data reliability in lieu of the missing original study records.

{See appended electronic signature page}

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Office of Scientific Investigations

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Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Document Room / NDA 210607
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DAIP / Clinical Team Leader / Yuliya Yasinskaya
DAIP / Medical Officer / Sheral Patel
DAIP / Regulatory Project Manager / Gregory DiBernardo

OSI / Office Director / David Burrow
OSI / DCCE / Division Director / Ni Khin
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OSI / DCCE / GCPAB / Team Leader / Janice Pohlman
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OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

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/s/

JONG HOON LEE
07/15/2018

JANICE K POHLMAN
07/16/2018

KASSA AYALEW
07/16/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 11, 2018
To:	Sumathi Nambiar, MD, MPH Director **Division of Anti-Infective Products (DAIP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** David Foss, Pharm. D., MPH, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ARAKODA (tafenoquine succinate)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 210607
Applicant:	Sixty Degrees Pharmaceuticals, LLC

1 INTRODUCTION

On August 21, 2017, Sixty Degrees Pharmaceuticals, LLC submitted for the Agency's review a 505(b)(1) original New Drug Application (NDA) 208251 for ARAKODA (tafenoquine) tablets, for oral use. The proposed indication for ARAKODA (tafenoquine) tablets, for oral use is for the prophylaxis of malaria in patients aged 18 years and older.

On June 28, 2018 the Applicant submitted a Medication Guide (MG) in response to the Agency's Late-Cycle Meeting (LCM) Background Package dated June 1, 2018, which included a request for submission of a MG which will become a part of the approved product labeling.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infective Products (DAIP) on June 12, 2018 and March 6, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed MG for ARAKODA (tafenoquine) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft ARAKODA (tafenoquine) tablets, for oral use MG received on June 28, 2018 and received by DMPP on June 28, 2018.
- Draft ARAKODA (tafenoquine) tablets, for oral use MG received on June 28, 2018 and received by OPDP on June 28, 2018.
- Draft ARAKODA (tafenoquine) tablets, for oral use Prescribing Information (PI) received on August 21, 2017, revised by the review division throughout the review cycle, and received by DMPP on June 12, 2018.
- Draft ARAKODA (tafenoquine) tablets, for oral use Prescribing Information (PI) received on August 21, 2017, revised by the review division throughout the review cycle, and received by DMPP on June 22, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
07/11/2018

DAVID F FOSS
07/11/2018

MARCIA B WILLIAMS
07/11/2018

LASHAWN M GRIFFITHS
07/11/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 5, 2018

To: Sheral Patel, M.D.
Division of Anti-Infective Products (DAIP)

Gregory DiBernardo, Regulatory Project Manager, (DAIP)

Abimbola Adebowale, Associate Director for Labeling, (DAIP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME™ (tafenoquine tablets) for oral use

NDA: 210607

In response to DAIP's consult request dated March 6, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for TRADENAME™ (tafenoquine tablets) for oral use.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAIP on June 22, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAIP on June 29, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
07/05/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 20, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210607
Product Name and Strength:	Arakoda (tafenoquine) Tablets, 100 mg
Applicant/Sponsor Name:	60° Pharmaceuticals, LLC
FDA Received Date:	June 18, 2018
OSE RCM #:	2017-1724-3
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label (blister card) and carton labeling for Arakoda (tafenoquine) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label (blister card) and carton labeling for Arakoda are acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Myers, D. Label and Labeling Memo Review for Arakoda (tafenoquine) (NDA 210607). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 11. RCM No.: 2017-1724-2.

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/s/

DEBORAH E MYERS
06/20/2018

OTTO L TOWNSEND
06/20/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 11, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210607
Product Name and Strength:	Arakoda (tafenoquine) Tablets, 100 mg
Applicant/Sponsor Name:	60° Pharmaceuticals, LLC
FDA Received Date:	June 7, 2018
OSE RCM #:	2017-1724-2
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label (blister card) and carton labeling for Arakoda (tafenoquine) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label (blister card) and carton labeling are unacceptable from a medication error perspective. See Section 3 for details and recommendations to be conveyed to the Applicant.

3 RECOMMENDATIONS FOR 60° PHARMACEUTICALS, LLC

Please address the following issues:

Container Label (blister card) and Carton Labeling

[a] Myers, D. Label and Labeling Review Memo for Tafenoquine (NDA 210607). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 21. RCM No.: 2017-1724-1.

IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
As currently presented the expiration date is notated as XX/XXXX on the container label (blister card) and MM/YYYY on the carton labeling.	There is a risk for deteriorated drug medication errors if the expiration date is misinterpreted.	To provide clarity, minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend using a format like either: DDMMMYYYY (e.g., 31JAN2013) MMMYYYY (e.g., JAN2013) YYYY-MMM-DD (e.g., 2013-JAN-31) YYYY-MM-DD (e.g., 2013-01-31)
Carton Labeling		
We note that you submitted a proposed Medication Guide. However, as currently presented there is no statement displayed on the principal display panel (PDP) instructing the dispenser to provide the Medication Guide to each patient to whom the drug product is dispensed.	Per 21 CFR 208.24(d).	Add the statement "ATTENTION: Dispense the enclosed Medication Guide to each patient" prominently and in a conspicuous manner on the PDP of the carton labeling.

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/s/

DEBORAH E MYERS
06/11/2018

OTTO L TOWNSEND
06/11/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: May 22, 2018 **Date consulted:** January 30, 2018

From: Jane Liedtka M.D., Medical Officer (MO), Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Sheral S. Patel, M.D., MO,
Office of Antimicrobial Products (OAP),
Division of Anti-Infective Products (DAIP)

Drug: Tafenoquine

NDA: 210607

Applicant: 60 Degrees Pharmaceuticals

Subject: Pregnancy and Lactation Labeling [new NDA, priority review, resubmission after refuse to file (RTF)]

Proposed Indication: Tafenoquine is an antimalarial indicated for the prevention of malaria in adults for up to 6 months of continuous dosing.

Materials Reviewed:

- Applicant's submitted background package for NDA 210607, resubmitted on December 8, 2017 (Original submitted on August 21, 2017 –RTF)

- DPMH review of KRINTAFEL (tafenoquine), NDA 210795. Jane Liedtka, MD. May 21, 2018. DARRTS Reference ID 4266131.

INTRODUCTION AND BACKGROUND

On December 8, 2017, the applicant (60 Degrees Pharmaceuticals) resubmitted an original 505 (b) (1) new drug application (NDA) for tafenoquine, NDA 210607. DAIP consulted DPMH on January 30, 2018, to assist with the Pregnancy and Lactation subsections of labeling.

- Tafenoquine (TQ) is an 8-aminoquinolone anti-malarial indicated for the radical cure (prevention of relapse) of Plasmodium vivax (PV) malaria.
- Same pharmacologic class as Primaquine (NDA 8316), approved on January 23, 1952.

REVIEW
PREGNANCY

Malaria and Pregnancy

- Malaria infection during pregnancy is a major public health problem worldwide, with 50 million pregnancies exposed to the infection every year[1].
- Approximately 25,000 maternal deaths and between 75,000 and 200,000 infant deaths could be prevented each year by effective malaria control in pregnancy[2].
- According to the Center for Disease Control (CDC)[3], malaria infection in pregnant women can be more severe than in non-pregnant women. Malaria increases the risk for adverse pregnancy outcomes, including prematurity, spontaneous abortion, and stillbirth. For these reasons, and because no chemoprophylaxis regimen is completely effective, women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible. If travel to a malarious area cannot be deferred, use of an effective chemoprophylaxis regimen is essential.
- Current World Health Organization (WHO) recommendations for the control of Malaria in Pregnancy (MIP) in areas of stable [high] transmission include intermittent preventive treatment (IPT) with at least two treatment doses of sulfadoxine—pyrimethamine (SP).
- Non-infected pregnant women traveling to areas where chloroquine-resistant P. falciparum has not been reported may take chloroquine prophylaxis. For travel to areas where chloroquine resistance is present, mefloquine is the only medication recommended for malaria chemoprophylaxis during pregnancy. In 2011, the FDA reviewed available data for mefloquine use during pregnancy and reclassified it from category C to category B.
- Current recommendations from the WHO for the control of MIP based on region are displayed below in Table1.

[1] WHO. A strategic framework for malaria prevention and control during pregnancy in the African region. WHO, Geneva 2004, 2004: AFR/MAL
[2] van Geertruyden JP *et al*. The contribution of malaria in pregnancy to perinatal mortality. Am J Trop Med Hyg. 2004; 71:35-40
[3] CDC- Chemoprophylaxis during pregnancy and breastfeeding. Accessed 4/10/18. https://wwwnc.cdc.gov/travel/yellowbook/2018/advising-travelers-with-specific-needs/pregnant-travelers.

Table 1: Currently recommended drugs for treatment and Prevention of Malaria in Pregnancy by WHO region

Region	*P. falciparum*				*P.vivax*	
	Treatment				Prevention Treatment	
	Uncomplicated		Severe			
	1st Trimester (T)	2 – 3rd T	1st T	2 – 3rd T		
Africa	QN + clindamycin*	ACT[Y]	QN/AS	AS	IPTp–SP[♪]	CQ[#]
Americas	QN + clindamycin* (or CQ**)	ACT or MQ		or	NA	CQ[zz]
Eastern Mediterranean	QN + clindamycin*	ACT[§§]		AM	NA[♪♪]	
Europe	-			or	NA	
South-east Asia	QN + clindamycin* (or CQ**)	Act		QN[§]	NA	
Western Pacific	QN + clindamycin*	ACT			CQ weekly[##]	

WHO World Malaria report 2008 and WHO Malaria treatment guidelines 2006.

ACT: Artemisinin-based combination therapy; AM: Artemether; AS: Artesunate; CQ: Chloroquine; IPTp: Intermittent preventive treatment in pregnancy; MQ: Mefloquine; NA: Not adopted; QN: Quinine; SP: Sulfadoxine--pyrimethamine; T: Trimester. *If clindamycin is unavailable or unaffordable, then QN monotherapy should be given.

[Y]ACTs being adopted in the African region are artemether–lumefantrine (Angola, Benin, Bostwana, Burkina Faso, Central African Republic, Comoros, Ethiopia, Gambia, Guinea-Bissau, Kenya, Malawi, Mozambique, Namibia, Niger, Nigeria, Rwanda, South Africa, Tanzania, Togo, Uganda, Zambia, Zimbabwe) and artesunate + amodiaquine (Burundi, Cameroon, Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Ghana, Guinea, Liberia, Madagascar, Mauritania, Sao Tome and Principe, Senegal, Sierra Leone). CQ is used in Cape Verde and Swaziland, CQ + SP in Eritrea. Some of these countries have not yet implemented these current policies.

[§]Parenteral administration. Where available, AS is the first, and AM the second option for treating severe malaria during pregnancy in the second and third trimesters.

[♪]Chloroquine + proguanil is given in Bostwana, South Africa and Swaziland instead of IPTp with SP. In Cape Verde, CQ weekly is policy for preventing malaria in pregnancy.

[#]CQ is recommended in Algeria, Ethiopia and Mauritius, where the malaria parasite is CQ sensitive.

**CQ is indicated for the treatment of *P. falciparum* infections in areas where the parasite is CQ sensitive (e.g. Guatemala, Myanmar).

[zz]CQ is given for treatment and then weekly until delivery; primaquine is contraindicated in pregnancy and is administered only after delivery. [§§]AS + SP is given in Dijibouti, Pakistan, Somalia, Sudan and Yemen; CQ + SP is indicated in Afghanistan [♪♪] IPTp with SP is the policy in Somalia and Sudan.

[##]Weekly prophylaxis with CQ is recommended drug policy for prevention of malaria in pregnancy in Malaysia, Papua New Guinea, Philippines, Vanuatuand Vietnam.

Source: Sevene *et al*[4]pg. 1287

Nonclinical Experience

There were increased abortions, with and without maternal toxicity when TQ 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. 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) at the high-dose. There was no evidence of malformations in either species. The reader is referred to the full Pharmacology/Toxicology review by Owen McMaster, PhD.

[4] Sevene E *et al.* Current knowledge and challenges of antimalarial drugs for treatment and prevention in pregnancy. 2010. Expert Opinion on Pharmacotherapy, 11:8, 1277-1293.

Review of Pharmacovigilance Database

No review of the pharmacovigilance database was performed by the Applicant. The Integrated Summary of Safety for the development program for TQ notes that

> As of October 2014, there had been a total of 25 pregnancies reported in association with tafenoquine clinical studies, 18 of which were in subjects who had received tafenoquine. Outcomes of these 18 were as follows:
>
> - Four had uncomplicated pregnancies, with uncomplicated deliveries of healthy offspring. All of these subjects had first trimester tafenoquine exposure.
> - Two had spontaneous abortions (SABs) that occurred in the first trimester and both were considered unrelated to tafenoquine. The first subject developed menorrhagia 11 days after a positive pregnancy test, and a subsequent ultrasound revealed no fetus. Similarly, the second subject also experienced vaginal bleeding (a "menstrual period") at 8 weeks' gestation, and a subsequent pregnancy test was negative.
> - Six pregnancies ended in elective abortions (TABs).
> - One pregnant subject was lost to follow-up.
> - Five reported suspected pregnancies were not confirmed by subsequent laboratory tests. These were considered probable false positive results.

Applicant's Review of Literature

The applicant did not provide a review of the literature.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase on April 9, 2018 using the search terms "tafenoquine and pregnancy," "tafenoquine and pregnant women," "tafenoquine and pregnancy and birth defects," "tafenoquine and pregnancy and congenital malformations," "tafenoquine and pregnancy and stillbirth," "tafenoquine and spontaneous abortion" and "tafenoquine and pregnancy and miscarriage." No reports of adequate and well-controlled studies of tafenoquine use in pregnant women were found. No published case reports involving pregnancy in tafenoquine patients were identified. A few general articles on the treatment of malaria during pregnancy were identified and were cited earlier in this review in the section entitled "Malaria and Pregnancy".

Tafenoquine is referenced in MicroMedex[5] under investigational products, the authors' state

> Tafenoquine is an 8-aminoquinoline antimalarial and more lipophilic derivative of primaquine. It acts as a tissue schizontocide and is under investigation as the succinate for the radical cure and prevention of relapse in vivax malaria. It may also have a role in the prophylaxis of falciparum malaria. Although it has been suggested to be better tolerated than primaquine, tafenoquine still carries a risk of hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients.

[5] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 4/9/18.

Reviewer comment:
The Applicant notes that they have modeled their proposed labeling after primaquine labeling due to the fact that their product is closely related in structure and is expected to have similar effects. Therefore, I have accessed the relevant information on primaquine in several sources.

In the MicroMedex[5] statement for primaquine, the authors note "fetal risk has been demonstrated" and state

> The CDC recommend that primaquine not be administered during pregnancy because of the possibility the fetus may be G6PD-deficient, especially in pregnant patients at risk for this disorder[6]. Perform a pregnancy test prior to therapy initiation in women of reproductive potential. Advise women to avoid pregnancy during administration of primaquine. Advise sexually-active women to use effective contraception during and until after stopping treatment until completion of an ongoing ovulatory cycle (e.g., up to next menses). Advise men to avoid fathering a child and to use condoms during and for 3 months after completing treatment[7].

Similarly, in *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk,*[8] the authors' state

> No reports describing the use of primaquine in human pregnancy have been located. Primaquine may cause hemolytic anemia in patients with G6PD deficiency… Because the fetus is relatively G6PD-deficient, the drug should not be used in pregnancy regardless of the mother's status[9,10,11].

Reviewers comment:
Like primaquine, tafenoquine may cause hemolytic anemia if taken by a person with G6PD deficiency. Current labeling for primaquine (b) (4) *contraindicates the use of these products during pregnancy due to the potential for hemolytic anemia in the event that the fetus has G6PD deficiency.*

The embryologic development of the circulatory system begins early; the heart has developed enough by day 21 post-fertilization to begin beating. Circulation patterns are clearly established by the fourth week of embryonic life. [12]The possibility of an inadvertent exposure early in pregnancy (during the window before a pregnancy test becomes positive or in the event of a false

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[6] Arguin PM and Tan KR: Malaria. In: Centers for Disease Control and Prevention (CDC), Brunette GW, eds. CDC Health Information for International Travel 2018 Yellow Book, Oxford University Press, New York, NY, 2017.
[7] Product Information: primaquine phosphate oral tablets, primaquine phosphate oral tablets. Sanofi-Aventis US LLC (per FDA), Bridgewater, NJ, 2017.
[8] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[9] Phillips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. Drug Saf 1996; 14:131-45.
[10] Nosten F *et al.* Antimalarial drugs in pregnancy: a review. Curr Drug Saf 2006; 1:1-15.
[11] Irvine MH, Einarson A, Bozzo P. Prophylactic use of antimalarials during pregnancy. Can Fam Physician 2011; 57:1279-81.
[12] https://courses.lumenlearning.com/suny-ap2/chapter/development-of-blood-vessels-and-fetal-circulation/

negative pregnancy test) still exists. Given the lack of teratogenicity in animal studies and the time that is takes for the development of a circulatory system with red blood cells that may be affected by hemolysis, DPMH recommends a Warning and Precaution for Embryofetal Toxicity (b) (4)

LACTATION

Nonclinical Experience
No preclinical studies have been conducted to determine if tafenoquine or any of its metabolites are excreted in breast milk.

Applicant's Review of Literature
The applicant did not provide a review of the literature.

DPMH's Review of Literature
DPMH conducted a search of *Medications and Mother's Milk*[13], Micromedex[5], LactMed[14] and of published literature in PubMed and Embase using the search terms "tafenoquine and lactation" and "tafenoquine and breastfeeding." No relevant data were found.

According to the proposed label, the molecular weight of tafenoquine is ≈ 582 Daltons as the succinate salt and ≈ 464 Daltons as the free base and is highly protein bound (> 99.5%). The average terminal half-life is ≈ 15 days. Common adverse reactions (≥5%) were dizziness, nausea, vomiting, headache, and decreased hemoglobin. Proposed Warnings for the label for tafenoquine include hemolytic anemia, methemoglobinemia, serious psychiatric reactions and serious hypersensitivity reactions and G6PD testing is mandatory before administration.

Pharmacokinetic information for primaquine (a closely related medication) includes a molecular weight of ≈ 259, a half-life of 6 hours, bioavailability of 96% and protein binding of 20%.

The relevant "Summary of Use" information on primaquine in LactMed[13] states

> Primaquine is poorly excreted into breastmilk of nursing mothers and undetectable in the serum of their breastfed infants. Breastfed infants beyond the neonatal period have shown no evidence of hemolysis, but neonates and those with glucose-6-phosphate dehydrogenase (G6PD) deficiency have not been studied. If primaquine is required, the mother and infant should be tested for G6PD deficiency before primaquine is given to a nursing mother.
>
> United Kingdom malaria treatment guidelines recommend that primaquine be avoided in nursing mothers with malaria and that weekly chloroquine 500 mg be

[13] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.
[14]http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 4/9/18.

given until breastfeeding is completed[15]. However, these guidelines were developed before information on the excretion of primaquine into breastmilk and safety in breastfed infants was published. The Centers for Disease Control and Prevention guidelines state that primaquine may be used in breastfeeding mothers and infants with normal G6PD levels[16,17]. Because the small amounts of primaquine transferred in breast milk are insufficient to provide adequate protection or treatment of malaria, infants who require chemoprophylaxis or therapy must receive the recommended dosages of primaquine.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In a rat fertility study, tafenoquine was given orally at 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 in the presence of maternal toxicity (mortality, piloerection, rough coat, and reduced body weight). The reader is referred to the full Pharmacology/Toxicology review by Owen McMaster, PhD.

DPMH's Review of the Literature

DPMH conducted a search of published literature in PubMed and Embase regarding tafenoquine and its effects on fertility and found no relevant literature. However, the Applicant proposes pregnancy testing and contraception recommendations to be included in Section 8.3. DPMH agrees with this proposal. See DPMH proposed labeling for details.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are very little data on human exposure to tafenoquine during pregnancy (thirteen exposures, four live births, two SABs, 6 TABs, one lost to follow-up). Teratogenicity was not seen in animal studies but increased abortions (mostly in the presence of maternal toxicity-there was only one abortion below maternally toxic doses) were seen at doses below human equivalents.

The major issue of concern is the potential for hemolysis in a G6PD-deficient fetus (which theoretically can occur even in the presence of a G6PD normal mother). The currently proposed labeling from the Applicant (b) (4) recommends the following:

[15] Lalloo DG *et al*. UK Malaria Treatment Guidelines 2016. J Infect. 2016; 72:635-49.
[16] CDC Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press. 2017.
[17] Gilder ME *et al*. Primaquine pharmacokinetics in lactating women and breastfed infant exposures. Clin Infect Dis. 2018.

1. A Warning for embryofetal toxicity
2. A recommendation for pregnancy testing prior to administration of tafenoquine
3. A recommendation for contraception use in females of reproductive potential during administration of tafenoquine.

Lactation

There is no information available regarding the presence of tafenoquine in human or animal milk. Only recently (in 2018) results of studies on primaquine in human milk were published which document that primaquine is very poorly excreted into human milk and levels were undetectable in infants[15, 16]. Tafenoquine is a larger molecule than primaquine (464 vs 259) and has very high protein binding (>99%) which would suggest it is even less likely to be excreted in significant amounts into human milk. However, if it is present even in small amounts, the very long half-life (15 days) raises the possibility of tafenoquine accumulating in the infant's plasma.

With regard to breastfeeding, if the full-term infant has normal levels of G6PD upon testing, breastfeeding can be considered, keeping in mind that with the long half-life of tafenoquine means whatever exposure does occur will not be resolved for almost 3 months even with a one-time exposure. If G6PD levels for the infant are unavailable, or if the infant is premature or G6PD-deficient, breastfeeding is not recommended unless long term serial laboratory monitoring of the infant's blood parameters can be performed.

Females and Males of Reproductive Potential

Animal studies demonstrated "slight" changes in viable fetuses (decreased by 15% per PT reviewer) but these were seen in the context of maternal toxicity and are unlikely to be relevant to humans. There are no human data regarding the effect of tafenoquine on fertility.

Because of concerns about embryofetal toxicity due to a G6PD-deficiency in the fetus, DPMH is recommending pregnancy testing prior to administration for section 8.3. Contraception for women during treatment is recommended for the same reason.

LABELING RECOMMENDATIONS

DPMH revised the HPI, sections 4, 5, 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Tafenoquine Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------CONTRAINDICATIONS----------

- Breastfeeding by a lactating woman when her infant is found to be G6PD deficient (4, 5.x, 8.2)

----------WARNINGS AND PRECAUTIONS----------

•Embryo-fetal Toxicity: TAFENOQUINE may cause fetal harm when administered to a pregnant woman with a G6PD-deficient fetus. Advise of the potential risk to a fetus. (5.X, 8 1, 8.3).

----------USE IN SPECIFIC POPULATIONS----------

- Lactation*:* Advise not to breastfeed a G6PD-deficient infant (4, 5.x, 8.2).

FULL PRESCRIBING INFORMATION

4 Contraindications

Breastfeeding by a lactating woman when her infant is found to be G6PD deficient [*see Warnings and Precautions (5.x) and Use in Specific Populations (8.2)]*.

WARNINGS AND PRECAUTIONS

5.X G6PD Deficiency

Potential Harm to the Fetus

The use of TAFENOQUINE during pregnancy may cause hemolytic anemia in a fetus who is G6PD deficient. Even if a pregnant woman has normal levels of G6PD, the fetus may have deficient levels of G6PD. Advise females of reproductive potential that TAFENOQUINE treatment during pregnancy is not recommended because there are other drug options available to treat malaria and to use effective contraception during treatment with TAFENOQUINE. If a pregnancy is detected during TAFENOQUINE use, discontinue TAFENOQUINE as soon as possible and switch to a preferred treatment for malaria during pregnancy [*see Use in Specific Populations (8.1 and 8.3)*].

Potential Harm to the Breastfeeding Infant

An infant with G6PD deficiency may be at risk for hemolytic anemia from TAFENOQUINE exposure through breast milk. Infant G6PD levels should be checked before lactation begins. Advise the woman with an infant who has G6PD deficiency not to breastfeed during treatment with TAFENOQUINE and for 3 months after the final dose *[see Contraindications (4), Use in Specific Populations (8.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The use of TAFENOQUINE during pregnancy may cause hemolytic anemia in a fetus who is G6PD deficient. TAFENOQUINE treatment during pregnancy is not recommended because there are other drugs options available to treat malaria. If a pregnancy is detected, discontinue TAFENOQUINE as soon as possible and switch to a preferred treatment for malaria during pregnancy *[see Warnings and Precautions (5.X)]*. Available data with TAFENOQUINE use 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.

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 (GD 6 to 18), at doses 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) at the high-dose. 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 TAFENOQUINE exposure. Infant G6PD status should be checked before lactation begins. An infant with G6PD deficiency should not be breastfed during maternal use of TAFENOQUINE *[see Contraindications (4), Warnings and Precautions (5.x) and Clinical Considerations]*. There is no information regarding the presence of TAFENOQUINE 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 TAFENOQUINE and any potential effects on the breastfed infant from TAFENOQUINE or from the underlying maternal condition.

Clinical Considerations

Check the infant's G6PD status before maternal breastfeeding commences. If an infant has G6PD deficiency, exposure to TAFENOQUINE during breastfeeding may result in hemolytic anemia in the infant; therefore, advise the woman with an infant who has G6PD deficiency not to breastfeed during treatment with TAFENOQUINE and for 3 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating treatment with TAFENOQUINE. *[see Dosage and Administration (2.x), Warnings and Precautions, (5.x), and Use in Specific Populations (8.1)]*.

Contraception

TAFENOQUINE may cause hemolytic anemia in a G6PD deficient fetus *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential that TAFENOQUINE treatment during pregnancy is not recommended because there are other drug options available to treat malaria and to use effective contraception during treatment with TAFENOQUINE. If a pregnancy is detected during TAFENOQUINE use, discontinue TAFENOQUINE as soon as possible and switch to a preferred treatment for malaria during pregnancy.

17 PATIENT COUNSELING INFORMATION

Embryofetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.x) and Use in Specific Populations 8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with TAFENOQUINE *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women with a G6PD-deficient infant not to breastfeed during treatment with TAFENOQUINE and for 3 months after the final dose *[see Contraindication (4), Warnings and Precautions 5.x, Use in Specific Populations (8.2)]*.

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/s/

JANE E LIEDTKA
05/23/2018

MIRIAM C DINATALE
05/23/2018

LYNNE P YAO
05/23/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	May 21, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210607
Product Name and Strength:	Arakoda (tafenoquine) Tablets, 100 mg
Applicant/Sponsor Name:	60° Pharmaceuticals, LLC
FDA Received Date:	May 18, 2018
OSE RCM #:	2017-1724-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label (blister card) and carton labeling for Arakoda (tafenoquine) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label (blister card) and carton labeling for Arakoda (tafenoquine) are unacceptable. See section 3 for details and recommendations to be conveyed to the Applicant.

3 RECOMMENDATIONS FOR 60° PHARMACEUTICALS, LLC

Please address the following issues:

Container Label (blister card) and Carton Labeling

[a] Myers, D. Label and Labeling Review for Tafenoquine (NDA 210607). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 23. RCM No.: 2017-1724.

IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
The placeholder "Tradename" is included on the container label (blister card) and carton labeling.	We reference our MAY 21, 2018 letter informing you that the proprietary name, "Arakoda," was found conditionally acceptable.	Remove all references to "Tradename" and replace with the conditionally acceptable proprietary name "Arakoda" and submit for our review.
Container Label (blister card)		
Our Labeling comments dated May 8, 2018 recommend that "you decrease the prominence, font size (height) of the letters within your graphic design for "Sixty Degrees Pharma," as well as decreasing the size and prominence of the numeral "60" within your graphic design." However, we note that (b) (4)	Container labels (e.g., vials, blisters) must contain the specified minimum amount of information including "the name of manufacturer, packer, or distributer of the drug" as required by 21 CFR 201.10(i)(1)(iv).	Add the name of manufacturer, packer, or distributer of the drug to each individual blister and submit for our review.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBORAH E MYERS
05/21/2018

OTTO L TOWNSEND
05/22/2018

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	NDA 210607
Brand Name	(b) (4)
Generic Name	Tafenoquine (SB-252263)
Sponsor	60 Degrees Pharmaceuticals, Inc.
Indication	(b) (4) (tafenoquine) tablets are indicated for the prevention of malaria in adults for up to 6 months of continuous dosing.
Dosage Form	Tablet
Drug Class	Antimalarial
Therapeutic Dosing Regimen	Loading (3 days): 200 mg qd Maintenance (7 days post loading): 200 mg q7d Terminal prophylaxis: 200 mg once
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Unknown
Submission Number and Date	SDN 001; 22 Feb 2018
Review Division	DAIP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large mean increase (i.e., >20 ms) in the QTc interval is anticipated for tafenoquine (SB-252263) 400 mg. This conclusion is based on by-time analysis for bioequivalence study 014 (Table 1). The largest upper bounds of the 2-sided 90% CI for the mean difference for tafenoquine 400 mg was < 20 ms and the mean changes were <10 ms. Additionally, no significant relationship between tafenoquine concentration and changes in the QTc interval was observed (section 5.3). These findings are further supported by the available preclinical information (hERG assay, isolated dog Purkinje fiber, dog CV safety studies) (section 3.3).

In this randomized, open-label, parallel group bioequivalence study, 58 healthy subjects were randomized to receive single dose of tafenoquine 400 mg Phase 2 capsule (existing formulation), tafenoquine 400 mg Phase 3 capsule (novel formulation), and SB-252263 400 mg Phase 3 tablet (novel formulation) on 3 consecutive days. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Tafenoquine 400 mg (FDA Analysis)

Treatment	Time (hour)	ΔQTcF (ms)	90% CI (ms)
SB-252263 400 mg Phase 2 capsule	Day 2, Predose	8.5	(4.3, 12.7)
SB-252263 400 mg Phase 3 capsule	Day 2, 14 h	4.5	(-11.4, 4.2)
SB-252263 400 mg Phase 3 tablet	Day 3, Predose	9.9	(6.2, 13.6)

The doses evaluated in this study produces a mean C_{max} that is ~2.4-fold higher than the anticipated $C_{max,ss.}$ These concentrations are above the currently known worst-case exposure scenario, concomitant administration with chloroquine (38% increase in C_{max}) (section 4.2.6.2). Of note, the sponsor has not provided information about the changes in tafenoquine pharmacokinetics for patients with renal or hepatic impairment.

1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

Division: Alternatively, DAIP may request the Applicant to submit a protocol amendment for their ongoing ophthalmologic safety study in healthy volunteers (Study 60PH04, \\CDSESUB1\evsprod\IND129656) to include a sub-study to obtain information on tafenoquine QT prolongation potential. Please provide an outline of additional information needed to assess QT prolongation in such a sub-study, based on your review of the data submitted by the Applicant.

QT-IRT's Response: We have reviewed the available ECG data included in the NDA submission, mainly focusing on study 014 as the study included three dose groups of subjects receiving 400 mg qd as well as ECG sampling on multiple occasions including a sample near T_{max} after the last dose on day 3. Based on our review of the data, we consider this study to be adequate to exclude large mean changes in the QTc interval (i.e. 20 ms). If the Division wants to exclude small mean changes, the sponsor will likely need to conduct a thorough QT study.

2 PROPOSED LABEL

The following are the sponsor's proposed labeling language related to QT:

12.2 Pharmacodynamics

(b) (4)

The following is QT-IRT's proposed labeling language, which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology:

The effects of tafenoquine on the QT interval was evaluated in a relative bioequivalence study. In this study, subjects were randomized to 400 mg qd for 3 days (3 different formulations). The results of this study suggest that the mean increase in the QTcF interval for tafenoquine is less than 20 ms.

3 BACKGROUND

3.1 Product Information

Tafenoquine (8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline succinate) (other codes SB-252263-AX [succinate salt], SB-252263-AAB [free base], [redacted] (b) (4) is an 8-aminoquinoline, formulated for clinical use as an oral tablet. Tafenoquine is a synthetic analogue of primaquine, but has a longer elimination half-life than primaquine (Gutteridge-1989; Milhous-2001; Franklin-2011; Brueckner-1998b).

3.2 Market approval status

Tafenoquine is not approved for marketing in any country.

3.3 Preclinical Information

The in vitro IC50 value for inhibition of hERG tail current was determined to be 0.51 µg/mL, a relatively low value which approximates to the plasma concentration seen following a clinical dose of 600 mg. However, there were no adverse effects observed in the ECG evaluations (including QTc interval) conducted in the in vivo oral and intravenous cardiovascular and pulmonary safety pharmacology studies in dogs or in repeat dose oral toxicity studies in dogs of up to 52 weeks in duration. Plasma tafenoquine concentrations reached an average (sexes combined) 1.841µg/mL following repeated administration of the high dose of 4 mg/kg to the dog, which was approximately 3.5 times higher than the IC50 in the hERG assay. Nor were there any clinical QTcF effects at doses up to 1200 mg. Therefore, tafenoquine is considered to have no or low potential for QTc prolongation at a clinical dose.

Reviewer's Comment: The results of the hERG assay suggests a hERG safety margin of ~168x (for the anticipated $C_{max,ss}$: ~300 ng/mL) assuming plasma protein binding of 1%, which suggests a low risk for hERG mediated QTc prolongation consistent with the lack of observed QTc prolongation in the CV and pulmonary safety studies in dogs or repeat dose toxicology study in dogs as summarized above. Lastly, the sponsor also evaluated the effects of tafenoquine in isolated dog Purkinje fibers and did not observe any changes on action potential duration.

3.4 Clinical Experience

Among human subjects who received the Tafenoquine ACR (n=825) in 5 pooled clinical trials (Studies 030, 033, 043, 045, 057), there were no reported cardiac SAEs (ISS Table 14.3.1.1.4.5.1a) and no study discontinuations due to cardiac AEs (ISS Table

14.3.1.1.6.5.1a). Furthermore, no cardiac AEs occurred at an incidence ≥1% in subjects who received the Tafenoquine ACR(ISS Table 14.3.1.1.9.5.1a).

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of tafenoquine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. In our previous consult review, we noted that we could not review the thorough QT study (TAF 114582) as the data sets for this study were not submitted to NDA 210607 (DARRTS 01/26/2018). The Division has subsequently asked the QT-IRT, if there were other studies submitted by the sponsor, which could be used for QT assessment. The QT-IRT has determined that the relative bioequivalence study (014), might be adequate to exclude large mean changes (i.e. 20 ms), as it includes repeat dosing of 400 mg (therapeutic dosing is 200 mg) as well as ECG and PK collection at multiple time-points. The sponsor submitted the study report 014 and electronic datasets and the review of this information is the focus of this review.

4.2 QT STUDY

4.2.1 Title

An open-label, randomised study in healthy male and female volunteers to assess the tolerability and relative bioavailability of three consecutive single daily doses of the existing capsule formulation and novel tablet and capsule formulations of SB-252263

4.2.2 Protocol Number

014

4.2.3 Study Dates

Date of first enrollment: 13 August 1999

Date of last subject completed: 23 September 1999

4.2.4 Objectives

The primary objectives of this study were to assess the tolerability and relative bioavailability of two novel formulations of SB-252263 and the existing capsule formulation when administered as single doses on three consecutive days.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, open-label, parallel group bioequivalence study for 3 formulations.

4.2.5.2 Controls

There was no placebo or positive (moxifloxacin) control.

4.2.5.3 Blinding

This is an open-label study.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

SB-252263 was administered as 400 mg [2x200 mg capsules or tablets]:

Formulation A: SB-252263 Phase II capsule (existing formulation)

Formulation B: SB-252263 Phase JII capsule (novel formulation)

Formulation C: SB-252263 Phase III tablet (novel formulation)

4.2.6.2 Sponsor's Justification for Doses

Not stated.

Reviewer's Comment: The doses evaluated in this study are acceptable to allow for exclusion of large mean increases (i.e. 20 ms) in the QTc interval, given that the C_{max} after the last 400 mg dose covers ~2.4-fold of the expected therapeutic $C_{max,ss}$.

4.2.6.3 Instructions with Regard to Meals

On Days 1, 2 and 3, subjects were required to fast from midnight before dosing with SB-252263 in the morning. Subjects were provided with a standardized breakfast with which they took their dose of SB-252263.

Reviewer's Comment: Acceptable, the proposed labeling is (b) (4)

4.2.6.4 ECG and PK Assessments

ECG:

- Day 1: Predose (60, 30 and 10 min pre-dose) and 14 h post-dose
- Days 2, 3 and 8: predose and 14 hours post-dose

PK:

- Day 1: Predose and 2, 4, 8, 10, 12, 14 and 16 h post-dose
- Days 2 and 3: Predose and 4, 8, 12 and 16 h post-dose

Reviewer's Comment: Acceptable. ECGs were collected over multiple days including day 3 (62 h post-dose) and as the T_{max} of tafenoquine is ~60 h and the half-life is ~400 h – the timing of ECG collection is considered adequate to capture timing of peak effect as well as delayed effects.

4.2.6.5 Baseline

The average of QT/QTc values at 3 predose time points on Day 1 was used as baseline.

4.2.7 ECG Collection

A 12-lead ECG after 5 min in the supine position was recorded. Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (a VR, a VL, a VF), and six pre-

cordial leads (V 1-V 6), according to Wilson, were used. CORINA Marquette CardioSys V.3.01 system software was used to assess the parameters HR, RR, PR, QRS, QT and QTc.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 58 healthy subjects (43 males and 15 females) were randomized to the study; all 58 subjects received their doses as scheduled. Overall, 56 subjects completed the study as scheduled and there were 2 withdrawals (SUBJID (b) (6)). Any subject was considered a withdrawal if they didn't reach the last follow-up visit on Week 18. Subjects (b) (6) were counted as withdrawals but both were withdrawn one month after last dose, they were nevertheless evaluable for safety and pharmacokinetics.

The randomization process was stratified by gender and smoking status; there were 16 male smokers and 6 female smokers. The average age (SD) of the 58 subjects was 40.0 (11.4) years, ranging from 20 to 60 years. All 58 subjects were White.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

There was no primary analysis for ECG. The sponsor listed ECG data. All abnormalities were assessed and obvious changes of ECG parameters compared to the pre-medication record were flagged and commented.

The ECG flagging ranges in Table 2 were used by the sponsor.

Table 2: ECG Flagging Ranges of Study SB252263/014

Parameter	Flagging reason
PR interval	> 300msec
	Increase of > 25% when baseline PR > 200msec
	Increase of > 50% when baseline PR <= 200msec
QRS interval	> 200msec
	Increase of > 25% when baseline QRS > 100msec
	Increase of > 50% when baseline QRS <= 100msec
QTc interval	> 500msec
	Increase of > 15% when baseline QTc > 440msec
	Increase of > 30% when baseline QTc <= 440msec

(Source: the sponsor's clinical study report, Table DS15, page 112)

During the study, no ECG value was flagged as being of potential clinical concern. Regardless of the formulation administered, no changes in ECG intervals were observed that were judged clinically important or drug-related by the Principal Investigator. In particular, QTc assessments appeared to be unaffected by the treatment with SB-252263.

Subject (b) (6) showed a fast conduction time with PR <100 msec throughout the study course independent from dosing. Similarly, subject (b) (6) showed an unspecific intra-ventricular conduction delay of QRS >120 msec at all assessments. Both deviations were not considered pathological.

Reviewer's Comments: The sponsor's analysis of ECG is acceptable since the study's primary objectives were to assess the tolerability and relative bioavailability of two novel formulations. Please see the reviewer's analysis for ECG in section 5.2.

4.2.8.2.2 Assay Sensitivity

Not Applicable

4.2.8.2.3 Categorical Analysis

Please see section 4.2.8.2.1.

Reviewer's Comments: The reviewer's categorical analysis for ECG is in section 5.2.

4.2.8.3 Safety Analysis

SB-252263 was well tolerated. There were no deaths reported during the study. Two subjects (SUBJID (b) (6)) were withdrawn one or two months after the last dose. One serious adverse event (SAE) occurred on subject (b) (6) which was judged as being unlikely related to the intake of SB-252263. Subject (b) (6) was lost to follow-up. Both subjects were considered as withdrawals since they didn't reach the last follow-up visit on Week 18.

There were no clinically significant abnormalities in ECG recordings of any subject in this study. Assessment of quantitative changes in PQ, QRS and QTc intervals did not reveal any drug-related changes.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 3. C_{max} value in the QT study were approximately 2.41-fold higher following administration of 200 mg qd for 3 days compared with the anticipated $C_{max,ss}$ described in labeling (300 ng/mL).

Table 3: Pharmacokinetic parameters for SB-252263

Parameter	Cmax (ng/mL)	AUC(0-inf) (ug.h/mL)	Tmax* (h)	T1/2 (h)
Formulation A n = 20	758 (188)	315** (68)	60 (52 - 84)	409** (42)
Formulation B n = 19	741 (165)	302** (77)	60 (52 - 72)	412** (65)
Formulation C n = 19	795 (293)	330 (75)	60 (52 - 84)	443 (41)

*Median and range relative to 1st dose; **n = 18.

Formulation Key:

Formulation A – SB-252263 400 mg phase II capsule (reference formulation)

Formulation B – SB-252263 400 mg phase III capsule

Formulation C – SB-252263 400 mg phase III tablet

4.2.8.4.2 Exposure-Response Analysis

The study report for this study did not include exposure-response analysis.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for ECG safety evaluation, which is acceptable since no large changes in heart rate were observed, i.e., mean changes ≤10 bpm (section 5.2.2). Therefore, no assessment of the QT/RR correction methodology is necessary and QTcF is used for all reviewers' assessments.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The By-time Analysis for Tafenoquine (SB-252263)

The statistical reviewer listed descriptive statistics by treatment, day, and time for QTcF and the ΔQTcF effect. The analysis results are listed in the following table.

Table 4: Analysis Results of QTcF and ΔQTcF

			QTcF (ms)		ΔQTcF (ms)			
Treatment	**Day**	**Time (Hour)**	**N**	**Mean (SE)**	**N**	**Mean**	**SE**	**90% CI**
SB-252263 400 mg Phase 2 capsule	1	14	20	403.7 (3.5)	20	3.6	2.5	(-0.8, 8.0)
	2	0	20	408.6 (4.2)	20	8.5	2.4	(4.3, 12.7)
		14	20	401.6 (3.4)	20	1.5	1.9	(-1.8, 4.9)
	3	0	20	405.0 (3.4)	20	4.9	2.5	(0.6, 9.3)
		14	20	404.3 (3.1)	20	4.2	2.2	(0.3, 8.0)
SB-252263 400 mg Phase 3 capsule	1	14	19	403.6 (3.5)	19	2.5	2.4	(-1.6, 6.5)
	2	0	19	400.6 (3.5)	19	-0.6	3.0	(-5.8, 4.6)
		14	19	397.6 (5.5)	19	-3.6	4.5	(-11.4, 4.2)
	3	0	19	403.9 (3.6)	19	2.8	3.4	(-3.1, 8.7)
		14	19	409.1 (4.1)	19	7.9	2.7	(3.3, 12.5)
SB-252263 400 mg Phase 3 tablet	1	14	19	400.7 (3.6)	19	5.5	2.1	(1.9, 9.1)
	2	0	19	401.0 (4.1)	19	5.8	3.5	(-0.3, 11.8)
		14	19	397.9 (4.1)	19	2.7	2.5	(-1.6, 6.9)
	3	0	19	405.1 (2.8)	19	9.9	2.1	(6.2, 13.6)
		14	19	404.4 (2.8)	19	9.1	2.1	(5.4, 12.9)

The largest upper bounds of the 2-sided 90% CI for the mean change from baseline in QTcF were 12.7 ms, 12.5 ms, and 13.6 ms for SB-252263 400 mg Phase 2 capsule, SB-252263 400 mg Phase 3 capsule, and SB-252263 400 mg Phase 3 tablet, respectively.

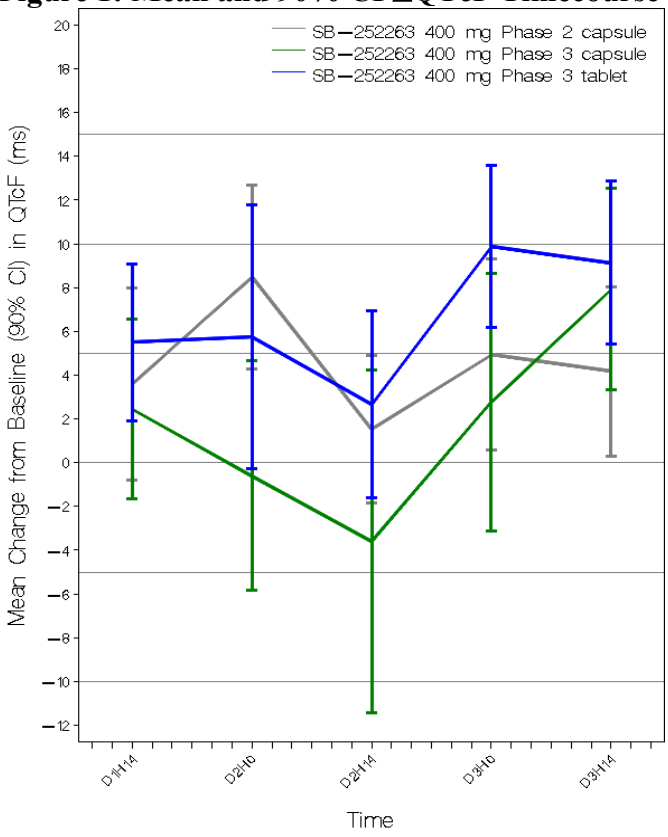
5.2.1.2 Assay Sensitivity Analysis

Not Applicable.

5.2.1.3 Graph of ΔQTcF Over Time

The following figure displays the time profile of ΔQTcF for different treatment groups.

Figure 1: Mean and 90% CI ΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 5 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 5: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<=480 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day 1 Predose/Baseline	58	174	58 (100%)	174 (100%)	0 (0.0%)	0 (0.0%)
SB-252263 400 mg Phase 2 capsule	20	120	20 (100%)	120 (100%)	0 (0.0%)	0 (0.0%)

	Total N		QTcF<=450 ms		450<QTcF<=480 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
SB-252263 400 mg Phase 3 capsule	19	114	18 (94.7%)	113 (99.1%)	1 (5.3%)	1 (0.9%)
SB-252263 400 mg Phase 3 tablet	19	114	18 (94.7%)	113 (99.1%)	1 (5.3%)	1 (0.9%)

* Day 8 follow-up visit were included for all categorical analysis tables.

Table 6 lists the categorical analysis results for ΔQTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 6: Categorical Analysis of ΔQTcF

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
SB-252263 400 mg Phase 2 capsule	20	120	19 (95.0%)	118 (98.3%)	1 (5.0%)	2 (1.7%)
SB-252263 400 mg Phase 3 capsule	19	114	16 (84.2%)	111 (97.4%)	3 (15.8%)	3 (2.6%)
SB-252263 400 mg Phase 3 tablet	19	114	15 (78.9%)	110 (96.5%)	4 (21.1%)	4 (3.5%)

5.2.2 HR Analysis

The same descriptive analysis was performed based on HR and ΔHR. The point estimates and the 90% confidence intervals for ΔHR are presented in Table 7. The largest upper limits of 90% CI for ΔHR were 7.7 bpm, 8.2 bpm, and 5.8 bpm for SB-252263 400 mg Phase 2 capsule, SB-252263 400 mg Phase 3 capsule, and SB-252263 400 mg Phase 3 tablet, respectively.

The outlier analysis results for HR are presented in Table 8.

Table 7: Analysis Results of HR and ΔHR

			HR (bpm)		ΔHR (bpm)			
Treatment	Day	Time (Hour)	N	Mean (SE)	N	Mean	SE	90% CI
SB-252263 400 mg Phase 2 capsule	1	14	20	61.6 (1.9)	20	5.0	1.4	(2.5, 7.5)
	2	0	20	57.4 (1.5)	20	0.8	1.0	(-1.0, 2.6)
		14	20	60.8 (1.7)	20	4.2	1.7	(1.3, 7.1)
	3	0	20	57.7 (2.4)	20	1.1	2.1	(-2.5, 4.7)
		14	20	62.2 (1.7)	20	5.6	1.2	(3.5, 7.7)
SB-252263 400 mg Phase 3 capsule	1	14	19	62.9 (1.9)	19	4.3	1.7	(1.4, 7.2)
	2	0	19	55.9 (1.9)	19	-2.6	1.0	(-4.4, -0.9)
		14	19	60.8 (1.8)	19	2.2	1.5	(-0.3, 4.8)
	3	0	19	57.7 (2.1)	19	-0.9	1.6	(-3.6, 1.9)

			HR (bpm)		ΔHR (bpm)			
Treatment	**Day**	**Time (Hour)**	**N**	**Mean (SE)**	**N**	**Mean**	**SE**	**90% CI**
		14	19	64.2 (1.7)	19	5.6	1.5	(3.0, 8.2)
SB-252263 400 mg Phase 3 tablet	1	14	19	59.4 (1.4)	19	1.9	1.2	(-0.1, 3.9)
	2	0	19	57.9 (1.8)	19	0.4	0.6	(-0.7, 1.5)
		14	19	58.5 (1.4)	19	1.0	1.0	(-0.7, 2.7)
	3	0	19	58.1 (1.9)	19	0.6	0.8	(-0.9, 2.0)
		14	19	61.2 (1.7)	19	3.7	1.2	(1.5, 5.8)

Table 8: Categorical Analysis for HR

	Total N	**HR<=100 bpm**	**HR>100 bpm**	**HR>45 bpm**	**HR<=45 bpm**
Treatment Group	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**
Day 1 Predose/Baseline	58	58 (100%)	0 (0.0%)	51 (87.9%)	7 (12.1%)
SB-252263 400 mg Phase 2 capsule	20	20 (100%)	0 (0.0%)	18 (90.0%)	2 (10.0%)
SB-252263 400 mg Phase 3 capsule	19	19 (100%)	0 (0.0%)	17 (89.5%)	2 (10.5%)
SB-252263 400 mg Phase 3 tablet	19	19 (100%)	0 (0.0%)	17 (89.5%)	2 (10.5%)

5.2.3 PR Analysis

The same descriptive analysis was performed based on PR and ΔPR. The point estimates and the 90% confidence intervals for ΔPR are presented in Table 9. The largest upper limits of 90% CI for ΔPR were 3.2 ms, 5.6 ms, and 7.2 ms for SB-252263 400 mg Phase 2 capsule, SB-252263 400 mg Phase 3 capsule, and SB-252263 400 mg Phase 3 tablet, respectively.

The outlier analysis results for PR are presented in Table 10.

Table 9: Analysis Results of PR and ΔPR

			PR (ms)		ΔPR (ms)			
Treatment	**Day**	**Time (Hour)**	**N**	**Mean (SE)**	**N**	**Mean**	**SE**	**90% CI**
SB-252263 400 mg Phase 2 capsule	1	14	20	147.7 (5.3)	20	-2.8	1.5	(-5.4, -0.3)
	2	0	20	149.1 (5.8)	20	-1.4	1.5	(-4.0, 1.1)
		14	20	149.5 (5.0)	20	-1.0	1.6	(-3.8, 1.7)
	3	0	20	150.8 (5.3)	20	0.3	1.7	(-2.7, 3.2)
		14	20	147.8 (5.4)	20	-2.7	2.2	(-6.5, 1.1)
SB-252263 400 mg Phase 3 capsule	1	14	19	157.1 (4.3)	19	-0.8	2.3	(-4.8, 3.1)
	2	0	19	158.8 (4.3)	19	0.9	1.5	(-1.6, 3.5)

			PR (ms)		ΔPR (ms)			
Treatment	**Day**	**Time (Hour)**	**N**	**Mean (SE)**	**N**	**Mean**	**SE**	**90% CI**
		14	19	158.3 (4.9)	19	0.4	1.8	(-2.8, 3.6)
	3	0	19	160.2 (4.9)	19	2.3	1.9	(-0.9, 5.6)
		14	19	159.6 (4.8)	19	1.7	2.1	(-2.0, 5.4)
SB-252263 400 mg Phase 3 tablet	1	14	19	163.3 (4.8)	19	-0.5	2.4	(-4.7, 3.6)
	2	0	19	165.5 (5.9)	19	1.7	2.3	(-2.4, 5.7)
		14	19	166.4 (5.7)	19	2.6	2.7	(-2.0, 7.2)
	3	0	19	165.7 (5.5)	19	1.9	2.0	(-1.6, 5.4)
		14	19	164.3 (5.4)	19	0.5	2.6	(-3.9, 5.0)

Table 10: Categorical Analysis for PR

	Total N		PR<=200 ms		200<PR<=220 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day 1 Predose/Baseline	58	174	56 (96.6%)	170 (97.7%)	2 (3.4%)	4 (2.3%)
SB-252263 400 mg Phase 2 capsule	20	120	20 (100%)	120 (100%)	0 (0.0%)	0 (0.0%)
SB-252263 400 mg Phase 3 capsule	19	114	18 (94.7%)	113 (99.1%)	1 (5.3%)	1 (0.9%)
SB-252263 400 mg Phase 3 tablet	19	114	15 (78.9%)	106 (93.0%)	4 (21.1%)	8 (7.0%)

5.2.4 QRS Analysis

The same descriptive analysis was performed based on QRS and ΔQRS. The point estimates and the 90% confidence intervals for ΔQRS are presented in Table 11. The largest upper limits of 90% CI for ΔQRS were 3.4 ms, 0.9 ms, and 1.2 ms for SB-252263 400 mg Phase 2 capsule, SB-252263 400 mg Phase 3 capsule, and SB-252263 400 mg Phase 3 tablet, respectively.

The outlier analysis results for QRS are presented in Table 12.

Table 11: Analysis Results for QRS and ΔQRS

			QRS (ms)		ΔQRS (ms)			
Treatment	**Day**	**Time (Hour)**	**N**	**Mean (SE)**	**N**	**Mean**	**SE**	**90% CI**
SB-252263 400 mg Phase 2 capsule	1	14	20	98.5 (2.1)	20	0.3	1.0	(-1.4, 2.1)
	2	0	20	99.3 (2.1)	20	1.1	1.3	(-1.1, 3.4)
		14	20	97.6 (2.0)	20	-0.6	0.7	(-1.7, 0.6)
	3	0	20	96.8 (2.0)	20	-1.4	0.7	(-2.5, -0.2)
		14	20	98.7 (2.1)	20	0.5	0.8	(-0.8, 1.9)

			QRS (ms)		ΔQRS (ms)			
Treatment	**Day**	**Time (Hour)**	**N**	**Mean (SE)**	**N**	**Mean**	**SE**	**90% CI**
SB-252263 400 mg Phase 3 capsule	1	14	19	101.1 (2.2)	19	-0.9	0.5	(-1.7, 0.0)
	2	0	19	101.6 (1.9)	19	-0.3	0.7	(-1.6, 0.9)
		14	19	101.4 (2.0)	19	-0.5	0.8	(-2.0, 0.9)
	3	0	19	101.0 (2.2)	19	-1.0	0.6	(-2.1, 0.2)
		14	19	101.5 (2.2)	19	-0.5	0.8	(-1.9, 0.9)
SB-252263 400 mg Phase 3 tablet	1	14	19	94.8 (2.7)	19	-0.5	0.8	(-1.9, 1.0)
	2	0	19	94.7 (2.8)	19	-0.6	0.7	(-1.8, 0.7)
		14	19	95.3 (2.5)	19	-0.0	0.6	(-1.1, 1.0)
	3	0	19	95.6 (2.8)	19	0.3	0.6	(-0.7, 1.2)
		14	19	95.4 (2.8)	19	0.1	0.7	(-1.1, 1.2)

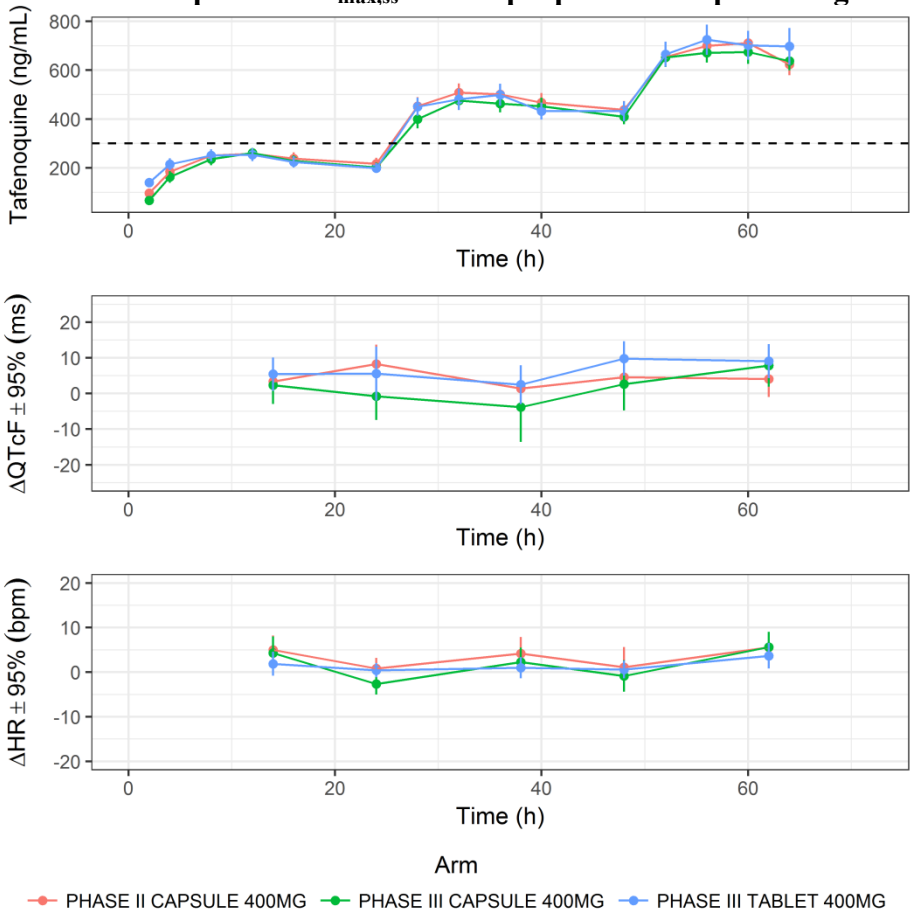
Table 12: Categorical Analysis for QRS

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day 1 Predose/Baseline	58	174	49 (84.5%)	155 (89.1%)	9 (15.5%)	19 (10.9%)
SB-252263 400 mg Phase 2 capsule	20	120	16 (80.0%)	112 (93.3%)	4 (20.0%)	8 (6.7%)
SB-252263 400 mg Phase 3 capsule	19	114	16 (84.2%)	96 (84.2%)	3 (15.8%)	18 (15.8%)
SB-252263 400 mg Phase 3 tablet	19	114	17 (89.5%)	102 (89.5%)	2 (10.5%)	12 (10.5%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

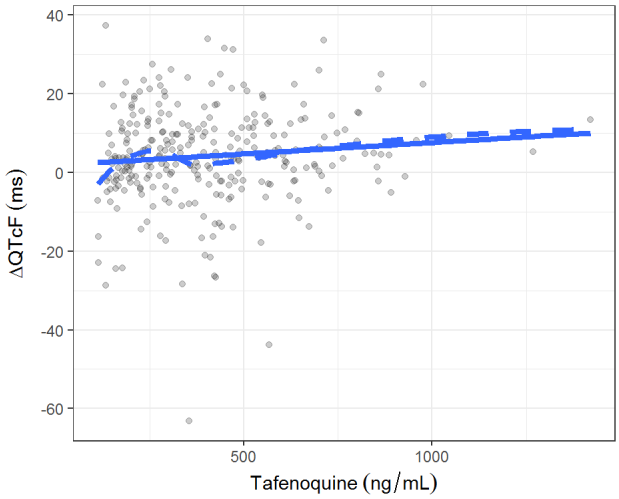
Prior to conducting concentration-QTc analysis, the time-course of tafenoquine plasma concentration and changes in ΔQTcF and ΔHR were explored (Figure 2). This analysis does not suggest the presence of delayed effects in the QTcF or significant changes in the heart rate. As can be seen in the figure not all the ECGs were collected together with a time-matched PK sample. The ECGs at 38 and 62 h did not have a corresponding PK sample, however, both ECGs are in between two PK samples (38 h: 36 and 40 h; 62 h: 60 and 64 h). For the subsequent exploration of the relationship between tafenoquine plasma concentration and changes in the QTcF interval, the PK values for 38 and 62 h post-dose were estimated via interpolation.

Figure 2: Time-course of tafenoquine PK (top), ΔQTcF (middle) and ΔHR (bottom). Dashed line represents $C_{max,ss}$ for the proposed therapeutic regimen



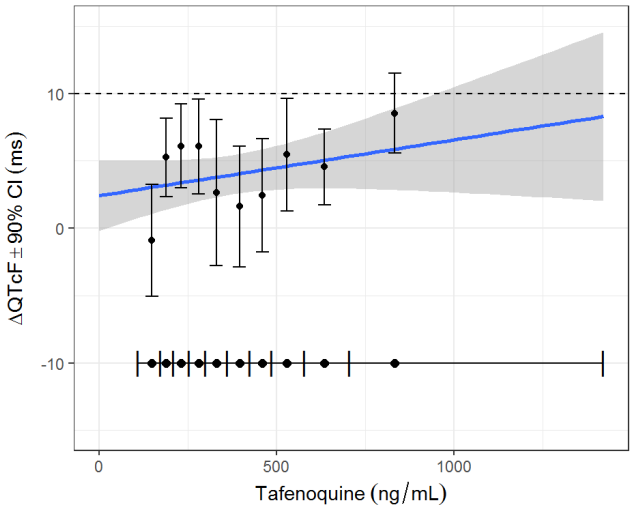
After confirming the absence of delayed effects and significant changes in the heart rate, the appropriateness of a linear model was explored. The results of this analysis are shown in Figure 3, which suggests that a linear model would be appropriate for evaluating the relationship.

Figure 3: Assessment of the linearity of the tafenoquine-ΔQTc relationship



Lastly, the relationship between tafenoquine concentration and changes in the ΔQTc interval was evaluated (Figure 4). This analysis showed a positive, but not significant, slope between tafenoquine concentration and changes in the ΔQTcF interval.

Figure 4: Goodness-of-fit plot for the linear concentration-QTc model



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

ECG waveforms were not collected digitally and paper ECGs were not available.

5.4.3 PR and QRS Interval

No clinically significant changes in PR and QRS intervals were observed.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	Loading dose of 200 mg QD for 3 days, followed by 200 mg q7d while in the malarious area and a single 200 mg dose in the week following the exit from the malarious area. Mean Cmax of 200 mg at steady state with the maximum proposed clinical dosing regimen is 300 ng/mL	
Exposures Achieved at Maximum Tested Dose	Single Dose	600 mg: 273 ng/mL Cmax and 98686 ng*h/mL AUC
	Multiple Dose	400 mg qd for 3 days 795 ng/mL and 300 ug*h/L AUC
Range of linear PK	Single dose of 16 to 600 mg	
Accumulation at steady state	~2.7-fold accumulation with 400 mg qd for 3 days	
Metabolites	No tafenoquine metabolites have been identified in plasma	
Absorption	Absolute/Relative Bioavailability	Unknown
	Tmax	7 h
Distribution	Vd/F or Vd	2470 L (24%)
	% bound	>99.5% bound
Elimination	Route	Human radiolabeled mass balance studies have not been conducted.
	Terminal t½	17 days
	CL/F or CL	4.17 L/h (24%)
Intrinsic Factors	Age	Age was identified as a significant covariate on clearance in population PK analysis, however, effect of sex and race was not explored in the full model due to correlation with weight.
	Sex	
	Race	
	Hepatic & Renal Impairment	Not studied
Extrinsic Factors	Drug interactions	Chloroquine: Cmax: 1.38 (Day 2) and 1.13 (Day 3) AUC: 1.24 (Day 2) and 1.12 (Day 3)
	Food Effects	Single dose food effect study: AUC (fed/fasted): 1.41 Cmax (fed/fasted): 1.31 Based on population PK analysis the sponsor predicts the impact of food to be lesser at steady state.
Expected High Clinical Exposure Scenario	Worst case exposure scenario has not been identified.	

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/s/

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LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 23, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210607
Product Name and Strength:	Tafenoquine Tablets, 100 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	60° Pharmaceuticals, LLC
Submission Date:	December 18, 2017
OSE RCM #:	2017-1724
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW

As part of the approval process for Tafenoquine Tablets, 100 mg, the Division of Anti-Infective Products (DAIP) requested that we review the proposed container label (blister card), carton labeling, and prescribing information to identify areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY AND MATERIALS REVIEWED

2.1 REGULATORY HISTORY

The Applicant originally submitted their NDA on August 21, 2017. The preliminary review of this August 21, 2017 application submission was found not to be sufficiently complete for a substantive review. Therefore, a refuse to file (RTF) notification was sent to the Applicant on October 20, 2017. After this, a Type A meeting was held on November 21, 2017 with a follow-up teleconference on December 1, 2017 to discuss a plan to resubmit this NDA. Subsequently, on December 8, 2017 the Applicant resubmitted their Application. The December 18, 2017 Amendment includes the proposed container label (blister card), carton labeling, and prescribing information which are the subject of this review.

2.2 MATERIALS REVIEW

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C – N//A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

We note that the previously submitted packaging configuration, under IND 129656, (b) (4) However, the packaging configuration submitted under NDA 210607 is for 16 tablets per carton. To understand the Applicant's reasoning for (b) (4) we sent the Applicant an Information Request (IR) on March 19, 2018. In addition, within this IR we requested that the Applicant clarify if the proposed blister cards are perforated and provide an explanation of why this product is to only be dispensed in the original container.

In response to our March 19, 2018 IR, the Applicant states, that the proposed carton containing 2 blisters of 8 tablets each is intended to cover the majority of travel durations. In addition, the Applicant clarified that the blister cards are not perforated and provides an explanation of why the product is to be dispensed only in the original container. Reasons for using a blister card included: protection of the tablets from the environment, similar packaging utilized for other anti-malarial products, and to comply with product serialization requirements.[a]

We find the Applicant's rationale, clarification, and explanation acceptable from a medication error perspective.

Tables 2 and 3 below include the identified medication error issues with the submitted container label (blister card), carton labeling, and prescribing information, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anti-Infective Products

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
General Issues			
1.	(b) (4)		
Highlights of Prescribing Information, *Indications and Usage*			
1.	As currently presented the product is "indicated for the prevention of malaria in adults for up to 6 months…"	It is unclear what age is considered to be an adult for this product (e.g., 18 years of age and older). This lack of clarifying information with regards to what age is considered an adult could result in	We recommend that additional clarifying information be added regarding what specific age is considered to be an adult for this product.

[a] Full communication available at the following link \\cdsesub1\evsprod\nda210607\0030\m1\us\cover.pdf

		medication errors involving the product being prescribed and/or administered to a patient of an inappropriate age.	
Highlights of Prescribing Information, *Dosage and Administration*			
1.	As currently presented the "Timing" of the "Terminal" Dosing and Administration within the table is not clear. For example, if one were to leave for a malarious area on the 4th of the month, they should dose 200 mg (2 of the 100 mg tablets) once daily on the 1st, 2nd, and 3rd of the month of travel. This same patient should then dose 200 mg (2 of the 100 mg tablets) on the 10th, 17th, 24th of the month while in the malarious area. If the patient were to return home on the 31st of the month, when should the terminal dose be taken? Does it matter when "in the week following exit from the malarious area" the "Terminal" dose is taken?	If the dosing and administration is unclear the product may not be prescribed or administered correctly which may result in lack of protection against malaria.	We recommend providing clarity to the "Timing" of the "Terminal" Dosing and Administration within the Table, as well as defining/clarifying "In the week following exit from the malarious area."
Full Prescribing Information (FPI), Section 1, *Indications and Usage*			
1.	See above under the header, Highlights of	See above under the header, Highlights of	See above under the header, Highlights of Prescribing

<table>
<tr><td></td><td>Prescribing Information, Indications and Usage.</td><td>Prescribing Information, Indications and Usage.</td><td>Information, Indications and Usage.</td></tr>
<tr><td colspan="4">FPI, Section 2, Dosage and Administration</td></tr>
<tr><td>1.</td><td>See above under the header, Highlights of Prescribing Information, Dosage and Administration.</td><td>See above under the header, Highlights of Prescribing Information, Dosage and Administration.</td><td>See above under the header, Highlights of Prescribing Information, Dosage and Administration.</td></tr>
<tr><td>2.</td><td>As currently presented in the text following (b) (4) only provides information for what to do if one of the “weekly” doses is missed.</td><td>There is no information regarding how to handle if a “loading” or “terminal” dose is missed.</td><td>We recommend also including information in this section regarding how to handle if a “loading” or “terminal” dose is missed.</td></tr>
<tr><td>3.</td><td colspan="3">As currently presented the text regarding missed doses may be difficult to understand. Since the missed dose information is complex, we recommend that a table might be a better manner to communicate this information (see example below):

<table>
<tr><th>Number of Doses Missed</th><th>How to replace missed dose:</th></tr>
<tr><td>1 weekly dose</td><td>1 dose of 200 mg (2 of the 100 mg tablets) on any day up to the time of the next scheduled weekly dose.</td></tr>
<tr><td>2 weekly doses</td><td>1 dose of 200 mg (2 of the 100 mg tablets) on any day before the next scheduled weekly dose.</td></tr>
<tr><td>3 or more weekly doses</td><td>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 before the next weekly dose.</td></tr>
</table></td></tr>
<tr><td colspan="4">FPI, Section 3, Dosage Forms and Strengths</td></tr>
<tr><td>1.</td><td>As currently presented the appropriate information to facilitate identification of the dosage form is not included.</td><td>A description of identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(4)(ii).</td><td>We recommend that the description of identifying characteristics be added to facilitate identification of the dosage form, such as; imprinting, scoring, shape, color, and coating.</td></tr>
</table>

FPI, Section 16, *How Supplied/Storage and Handling*			
1.	As currently presented the storage statement includes "…excursions permitted to 15-30°C (59-86°F)."	The degree symbol (°) and units of temperature measurement (Centigrade and Fahrenheit) following the first numbers in the temperature ranges (e.g., the degree and Centigrade symbols (°C) following the 15 and the degree and Fahrenheit symbols (°F) following the 59) are missing.	Add the degree and Centigrade symbols (°C) following the 15 and degree and Fahrenheit symbols (°F) following the 59 within the storage information to provide clarity. To provide further clarity, consider replacing the hyphens with their intended meaning "to." For example, "…excursions permitted to 15°C to 30°C (59°F to 86°F)."
2.	As currently presented the storage statement included in Section 16 of the FPI, "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15-30°C (59-86°F)." (b) (4) (b) (4)	(b) (4)	(b) (4)
3.	The statements "Protect from moisture. Dispense only in the original carton." are included in the Section 16 of the FPI. However, this dispensing information is not included on the carton labeling.	Specific information for appropriate dispensing of the drug product to maintain its identity, strength, quality, and purity should be included on the carton labeling.	We defer to OPQ to determine the appropriateness of these statements "Protect from moisture. Dispense only in the original carton." If OPQ deems this, or similar statements to those currently in Section 16 as appropriate, we recommend that OPQ additionally request inclusion

			of these statements on the carton labeling.
4.	As currently displayed the National Drug Code (NDC) number is denoted by a placeholder (NDC ABCDEFGH).	N/A	Since the NDC number on the carton labeling is also denoted by a placeholder (NDC: ABCDEFGH), we are requesting that the Applicant submit the NDC number for this product for our review.
5.	We note that the appropriate information to facilitate identification of the dosage form is not included.	A description of identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(17)(iii).	We recommend that the description of identifying characteristics to facilitate identification of the dosage form, such as; imprinting, scoring, shape, color, and coating be added.

Table 3: Identified Issues and Recommendations for 60° Pharmaceuticals, LLC (entire table to be conveyed to Applicant)

Container Label (blister card) and Carton Labeling			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	(b) (4)		
2.	As currently presented the established name "tafenoquine" is not enclosed in parentheses.	This layout is not consistent with the presentation of the proprietary name, established name, strength,	The established and proprietary names should be displayed in a manner consistent with the FDA regulations, taking into

		and dosage form for drug products.[b] "…the established name shall be placed in direct conjunction with the proprietary name or designation, and the relationship between the proprietary name or designation and the established name shall be made clear by use of a phrase such as "brand of" preceding the established name, by brackets surrounding the established name, or by other suitable means."[c]	account all pertinent factors including typography, layout, contrast, and other printing features (for drugs see 21 CFR 201.10(g)(2)). Revise the presentation as follows: TRADENAME (tafenoquine) tablets 100 mg
Container Label (blister card)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	As currently presented the graphic design for "Sixty Degrees Pharma" is the most prominent information on the blister. Specifically, the font size (height) of the letters included in the graphic design for "Sixty Degrees Pharma" are taller and more prominent than the	The proprietary and established names should be the most prominent information on the container label (blister). Additionally, the product strength is considered to be "critical information."[d] To avoid strength confusion, the product strength statement should be prominently displayed on	We recommend you decrease the prominence, font size (height) of the letters within your graphic design for "Sixty Degrees Pharma," as well as decreasing the size and prominence of the numeral "60" within your graphic design.

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 336-342). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[c] 21 CFR 201.10(g)(1).

[d] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 134-151). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

	established name “tafenoquine.” Additionally, the text font in your graphic design is bolder and more prominent your strength statement (100 mg). Of further concern is that the numeral “60” within your graphic design is more prominent that the strength statement.	the principal display panel (PDP). As currently presented, the numeral “60” within your graphic design is more prominent than the strength statement which could lead to confusion or wrong strength medication errors.	
2.	(b) (4)		
3.	As currently presented the location for the lot number is not provided.	The lot number statement is required on the immediate container per 21 CFR 201.10(i)(1).	Include the intended location for the lot number on the container label (blister card) and submit for our review.
4.	As currently presented there is no barcode included on your proposed container label (blister card).	The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the product barcode to each individual blister as required per 21CFR 201.25(c)(2) and submit for our review.
5.	As currently presented there is no National Drug Code (NDC) included on your proposed container label (blister card).	The NDC number is often used as an additional verification prior to drug dispensing in the pharmacy and is an important safety feature.	Add the intended National NDC number to each individual blister and submit for our review.
Carton Labeling			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**

1.	As currently displayed the National Drug Code (NDC) is denoted by a placeholder (NDC: XXXXX).	N/A	Add the intended NDC number to the carton labeling and submit for our review.

4 CONCLUSION

DMEPA's evaluation of the proposed container label (blister card), carton labeling, and prescribing information identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to 60° Pharmaceuticals, LLC so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for tafenoquine that 60° Pharmaceuticals, LLC submitted on December 18, 2017.

<table>
<tr><th colspan="2">Table 4. Relevant Product Information for Tafenoquine (NDA 210607)</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>tafenoquine</td></tr>
<tr><td>Indication</td><td>For the prevention of malaria in adults for up to 6 months of continuous dosing.</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>tablet</td></tr>
<tr><td>Strength</td><td>100 mg</td></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><th>Regimen Name</th><th>Timing</th><th>Dose</th></tr>
<tr><td>Loading regimen</td><td>For each of the 3 days before travel to a malarious area</td><td>200 mg (2 of the 100 mg tablets) once daily for 3 days</td></tr>
<tr><td>Maintenance regimen</td><td>While in the malarious area</td><td>200 mg (2 of the 100 mg tablets) once weekly – start 7 days after the last loading regimen dose</td></tr>
<tr><td>Terminal prophylaxis regimen</td><td>In the week following exit from the malarious area</td><td>200 mg (2 of the 100 mg tablets) one time</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>Each carton contains 16 tablets (2 blister cards each containing 8 tablets).</td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture. Dispense only in the original carton.</td></tr>
<tr><td>Container Closure</td><td>The proposed commercial container closure system consists of aluminum blisters, made of a [(b) (4)] polyamide [(b) (4)] aluminum and PVC [(b) (4)] formable laminate backed with a peelable layer consisting of a [(b) (4)] polyethylene terephthalate (PET), aluminum foil and paper, with eight (8) blisters per card. The secondary packaging consists of boxes each containing two (2) blister cards for a total of 16 packaged tablets per box. The boxes are intended to facilitate transport and storage and do not contribute to the drug product integrity.</td></tr>
</table>

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DEBORAH E MYERS
03/23/2018

OTTO L TOWNSEND
03/23/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/19/2018

TO: Division of Anti-Infective Products
Office of Antimicrobial Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 210607

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

SHILA S NKAH
03/19/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 26, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Gregory DiBernado, RPM
DAIP

Subject: QT-IRT Consult to NDA 210607

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 11/10/2017 requesting review of a thorough QT study report (TAF 114582) submitted to NDA 210607. To review a thorough QT study report, we require submission of the datasets for the study, which was not submitted by the Applicant. An information request was therefore sent to the Applicant, to request submission of the datasets (DARRTs 12/22/2017). The Applicant responded (NDA 210607, sequence 0011), that they are unable to submit the datasets as they only have the study report. We note that the datasets have been submitted to NDA 210795, however, unless the Applicant for this NDA has right to reference these datasets, we cannot use them. Of note, we have received a request to review the thorough QT study for the other NDA and the completion date for our review is 3/28/2018. Because of the missing datasets, we are unable to review the thorough QT study report for this NDA.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

LARS JOHANNESEN
01/26/2018

CHRISTINE E GARNETT
01/26/2018