CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210607Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: *Approval*

NDA 210607
Review # 1

Drug Name/Dosage Form	TRADENAME* (tafenoquine) Tablets
Strength	100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	60 Degrees Pharmaceuticals, LLC
US agent, if applicable	Fedora Daye

**The proposed trade name is under evaluation*

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	August 21, 2017	All
Amendment (eCTD 010) (*Resubmission after RTF*)	December 8, 2017	All
Amendment (eCTD 013)	January 25, 2018	Drug Product
Amendment (eCTD 021)	March 7, 2018	Biopharmaceutics
Amendment (eCTD 023)	March 15, 2018	Biopharmaceutics
Amendment (eCTD 025)	March 19, 2018	Biopharmaceutics
Amendment (eCTD 032)	March 27, 2018	Environmental Assessment
Amendment (eCTD 033)	March 30, 2018	Biopharmaceutics
Amendment (eCTD 036)	April 4, 2018	Drug Substance
Amendment (eCTD 039)	April 13, 2018	Drug Product, Biopharmaceutics
Amendment (eCTD 046)	May 4, 2018	Biopharmaceutics

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Katherine Windsor	Charles Jewell
Drug Product	Katherine Windsor	Balajee Shanmugam
Process	Ying Wang	Upinder Atwal
Microbiology*	Ying Wang	Upinder Atwal
Facilities	Khalid Khan	Derek Smith
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Environmental Assessment	Raanan Bloom	Scott Furness
Regulatory Business Process Manager	Anh-Thy Ly	N/A
Application Technical Lead	Dorota Matecka	N/A

** The drug product microbiology assessment is part of the Process Chapter*

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	III		(b) (4)		N/A*	
	III				N/A*	
	IV				N/A*	

**Sufficient information provided in the NDA*

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/ Toxicology	N/A	Adequate	*Refer to DS review*	Owen McMaster
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The majority of the CMC information provided in the NDA for the drug substance and the drug product was found to be adequate. In addition, all manufacturing facilities have been found acceptable by the Office of Process and Facilities (OPF) and the Overall Manufacturing Inspection Recommendation of "Approve" was entered into Panorama on May 8, 2018. Therefore, this NDA can be recommended for approval from the product quality perspective; however, there are several pending quality issues that may potentially be resolved via a post-marketing commitment (PMC), *if needed*. One of them refers to the proposed drug product dissolution method, which has not yet been found acceptable and a response to the recent information request regarding this issue is currently *pending*. Another issue relates to the risk associated with elemental impurities in the proposed drug product, with a response to the recent information request also *pending*. Furthermore, the proposed package insert and the container and carton labels are presently under review by the NDA review team. *The resolution of all the pending quality issues will be documented in a subsequent OPQ Review Addendum (refer to Attachment I).*

II. Summary of Quality Assessments

A. Product Overview

Tafenoquine is a novel antimalarial drug intended to be used for the prevention of malaria in adults, travelling to or living in geographic endemic areas known to be endemic for *Plasmodium falciparum* and *Plasmodium vivax*, for up to 6 months of continuous dosing.

Proposed Indication(s) including Intended Patient Population	Prevention of malaria in adults for up to 6 months of continuous dosing
Duration of Treatment	Up to 6 months (*refer to the package insert for further details*)
Maximum Daily Dose	200 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Tafenoquine is an 8-aminoquinoline, a synthetic analog of primaquine and an antiparasitic agent proposed to be used for the prevention of malaria. Tafenoquine drug substance has been developed (b) (4) drug substance has been consistently isolated throughout development as Form A, the most thermodynamically stable form. Tafenoquine succinate is prepared using (b) (4) The drug substance specification

includes quality attributes such as appearance, identification, assay, succinate content, impurities, water content, residue on ignition, elemental analysis, residual solvents and [redacted]. During the NDA review several revisions were incorporated in the proposed specification at the Agency's request, e.g., a test for succinate content was included and the proposed limit for any individual unspecified impurity has been revised to NMT [redacted]%. [redacted] Available stability data in the NDA support a retest period of [redacted] months for tafenoquine drug substance stored at [redacted] The overall information provided in the NDA for the drug substance, including the proposed specification, was found acceptable.

The drug product is an immediate release tablet for oral administration containing 125.5 mg of tafenoquine succinate, which is equivalent to 100 mg tafenoquine free base. Tafenoquine tablet is described as a dark pink and capsule shaped tablet, embossed with 'TQ100' on one side and plain on the other side. Each tablet core contains the following compendial excipients: microcrystalline cellulose, mannitol and magnesium stearate. The tablet core is film-coated with dark pink coating [redacted] which also contains all compendial components. Adequate information was provided in the NDA regarding the drug product formulation development, control of excipients, drug product specification, batch data, analytical methods, and container closure information.

The drug product specification includes quality attributes relevant for the proposed dosage form such as appearance, identification, assay, impurities, content uniformity, [redacted] dissolution, [redacted]. During the review, several revisions were incorporated in the proposed drug product specification at the Agency's request, e.g., [redacted] and was found to be acceptable. There are two issues regarding the proposed drug product specification that are currently still under evaluation. One of them refers to the proposed dissolution method (as described below). A response to the information request regarding the dissolution method is currently *pending*. The other issue relates to the elemental impurities assessment in the drug product. Although an elemental impurities risk assessment was conducted for the drug substance, a comprehensive elemental impurities risk assessment for the drug product, that would include analytical results from drug product batches, was not submitted in the NDA. Therefore, a comment requesting these data was conveyed to the Applicant and a response to this comment is currently *pending*.

The drug product, tafenoquine tablets are packaged in aluminum blisters made of a [redacted] polyamide, aluminum and PVC [redacted] formable laminate backed with a peelable layer consisting of a [redacted] polyethylene terephthalate (PET), aluminum foil [redacted] One blister card contains eight tablets, and each box (secondary packaging) contains two blister cards for a total of 16 tablets per box. The proposed container closure system was found safe and suitable to protect the drug product.

The NDA includes 12 months of long-term and 6 months of accelerated stability data for four representative batches of drug product. Because no trending and little variation was observed in the provided data, the proposed 24-month shelf life has been found acceptable for drug product stored at conditions consistent with the room temperature storage (25°C/60% RH) or below 30°C/75% RH.

The drug product manufacturing process is relatively straightforward and involves (b) (4) (b) (4)

The proposed manufacturing process is considered low risk, and was deemed adequately developed, described, and controlled.

The Biopharmaceutics review focused on the assessment of the proposed dissolution method and acceptance criteria, and need for bridging. *In vitro* bridging data are not required because there are no differences in the quality attributes of the tablets used in the pivotal clinical trials and the tablets intended for commercialization. Tafenoquine succinate exhibits pH-dependent solubility, and is considered a low solubility drug substance (per BCS criteria). The data submitted in the NDA for the currently proposed dissolution method demonstrate its limited discriminating ability. During the NDA review, the Applicant was requested to submit additional data related to the discriminating and stability-indicating properties of the proposed dissolution method. The response to the Agency's comments is currently *pending*; therefore, the acceptability of the proposed dissolution method and acceptance criteria for the routine control of the proposed drug product at batch release and stability testing remains under evaluation.

The Applicant has submitted a claim of categorical exclusion under 21CFR 25.31(b) and a statement of "no extraordinary circumstances." Based on the estimated concentration of tafenoquine at the point of entry into the aquatic environment, the criteria for the cited categorical exclusion have been met. Additionally, information was submitted in support of a statement of "no extraordinary circumstances." Therefore, the Applicant's claim of claim of categorical exclusion under 21 CFR 25.31(b) and statement of no extraordinary circumstance have been found acceptable.

The commercial tafenoquine succinate drug substance manufacturer is (b) (4) (b) (4) and the drug product manufacturer is (b) (4) in another location, (b) (4) Several other facilities have been listed in the NDA as the drug substance testing sites. The drug product site and testing facilities have been found acceptable based on the inspectional history and review of the NDA. In addition, the drug substance site (b) (4) (b) (4) was found acceptable following recent pre-approval inspection (PAI) on (b) (4) (b) (4) Based on the overall information available, the OPF has found the proposed manufacturing facilities adequate to support the NDA, and the overall manufacturing inspection recommendation of "Approve" was entered into Panorama on May 8, 2018.

C. Special Product Quality Labeling Recommendations (N/A)

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Process

CHAPTER IV: Biopharmaceutics

CHAPTER V: Environmental Assessment

CHAPTER VI: Facilities

ATTACHMENT I: List of Pending IRs

25 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

Lifecycle Management Considerations

List of Deficiencies:

Review Recommendation:

Based on the material provided by the Applicant, approval of this NDA is recommended from the drug substance perspective.

Primary Drug Substance Reviewer Name and Date:

Katherine Windsor, Ph.D.
Chemist
FDA/CDER/OPQ/ONDP/New Drug API Branch 1
23-APR-2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Charles F. Jewell, Ph.D.
Acting Branch Chief
FDA/CDER/OPQ/ONDP/New Drug API Branch 1
23-APR-2018

Katherine Windsor

Digitally signed by Katherine Windsor
Date: 4/23/2018 02:25:42PM
GUID: 53b5ace500005715409fd1cfb61e5fed

Charles Jewell

Digitally signed by Charles Jewell
Date: 4/23/2018 04:37:15PM
GUID: 504e331900000700b896c504b8c57bb3

17 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Reviewer's Assessment: Adequate. The applicant commits to testing the first three marketed batches on long-term stability through at least 24 months according to an acceptable stability protocol. This commitment is sufficient to ensure the quality of the drug product over the proposed 24-month shelf life.

R Regional Information

Environmental

The applicant requested a categorical exclusion from the requirement to prepare an Environmental Assessment, given that the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion.

Reviewer's Assessment: Adequate. Under 21 CFR 25.31, categorical exclusion from an Environmental Assessment applies for action on an NDA if the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb. This application does not require the preparation of an Environmental Assessment, as confirmed by EA Reviewer Dr. R. Bloom (e-mail 17-APR-2018). See the Environmental Review for additional details.

Methods Verification Package

Reviewer's Assessment: NA

Comparability Protocols

Reviewer's Assessment: NA

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: NA

Lifecycle Management Considerations

List of Deficiencies

Review Recommendation:

Based on the material provided by the Applicant, approval of this NDA is recommended from the drug product perspective.

Primary Drug Product Reviewer Name and Date:

Katherine Windsor, Ph.D.
Chemist
FDA/CDER/OPQ/ONDP/New Drug API Branch 1
24-APR-2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Balajee Shanmugam, Ph.D.
Branch Chief
FDA/CDER/OPQ/ONDP/DNDP1/New Drug Products Branch 3
24-APR-2018

Katherine Windsor

Digitally signed by Katherine Windsor
Date: 4/24/2018 08:34:11PM
GUID: 53b5ace500005715409fd1cfb61e5fed

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 4/24/2018 08:36:02PM
GUID: 50758d5000003c1b1962e036ea11002c

7 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

List of Deficiencies: None

Primary Process Reviewer Name and Date:

Ying Wang, PhD, 4/17/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Upinder Atwal, Ph.D./04/23/2018

Ying Wang

Digitally signed by Ying Wang
Date: 4/23/2018 04:40:36PM
GUID: 507d9e62000062a9767f4c6811b0b650

Upinder Atwal

Digitally signed by Upinder Atwal
Date: 4/24/2018 08:37:33AM
GUID: 508da70600028a62bcd780a1a126a76c

BIOPHARMACEUTICS

Product Background:

NDA: 210607; 505(b)(1), NME, Priority and Fast Track Designation Statuses Granted; Breakthrough Therapy Designation (b) (4) Pending

Drug Product Name/Strength: Tafenoquine Succinate Tablet, 100 mg (as free base; equivalent to 125 mg succinate salt)

Route of Administration: Oral

Proposed Indication: For prevention of malaria in adults

Proposed prophylactic regimen: 200 mg per day for 3 days as a loading dose followed by 200 mg once weekly while exposed to *Plasmodia* in an endemic region and finally at 1 week after leaving the endemic region.

Applicant Name: 60 Degrees Pharmaceuticals, LLC

Review Summary:

From the Biopharmaceutics perspective, NDA 210607 submitted for Tafenoquine Tablets (100 mg) is **PENDING** at this time due to a **PENDING response** to FDA Information Request Comments related to the QC dissolution method and acceptance criteria.

Tafenoquine succinate exhibits pH-dependent solubility, and is considered a low solubility drug substance (per BCS criteria). The currently proposed QC dissolution method demonstrated limited discriminating ability. On 04/19/2018, the Applicant was requested to submit pending data related to the discriminating power for the proposed QC method for changes in API particle size distribution, as well as data related to the method's stability indicating potential and other information. Thus, the acceptability of the proposed dissolution method and acceptance criteria as tabulated below for the routine QC of the proposed drug product at batch release and stability testing will be determined upon submission and review of the requested information, i.e., by 5/7/2018.

(b) (4)

In vitro bridging data are not required because there are no noted differences in the quality attributes of the tablets used in the pivotal clinical trials and the tablets intended for commercialization. The Clinical Pharmacology Reviewer confirms adequate *in vivo* PK bridging between the proposed to-be-marketed tablets used in pivotal clinical trials and the capsules used in earlier key clinical efficacy trials.

List Submissions being reviewed:
SDN-1, 8/27/2017, Original NDA
SDN-9, 12/8/2017, Resubmission
SDN-10, 12/18/2017, Partial Response to Non Refuse To File Biopharmaceutics Comments (Part 1: Drug Product Batch Overview - Clinical Trials)
SDN-21, 3/7/2018, Partial Response to Non Refuse-To-File Biopharmaceutics Comments and email (Part 2: Dissolution Reports)
SDN-23, 3/15/2018, Response to Biopharmaceutics Information Request 3/6/2018
SDN-25, 3/19/2018, Response to Biopharmaceutics Information Request 3/9/2018
SDN-35, 3/30/2018, Response to Biopharmaceutics Information Request 3/21/2018
SDN-40, 04/13/2018, Response to Biopharmaceutics Information Request 4/5/2018

Concise Description Outstanding Issues Remaining:
Pending Response to Information Request dated 4/19/2018

BCS Designation

The Applicant did not request a BCS designation for the proposed drug substance/product.

Reviewer's Assessment:

Solubility: *Low*
Per BCS criteria, tafenoquine succinate is a low solubility drug substance. The solubility of tafenoquine succinate is ≤ 0.1 mg/mL in pH 7 aqueous medium and ≥ 0.5 mg/mL in pH 1, 2, and 4 at 37°C. Refer to Section 3.2.S.1.3, and for the pH-solubility profile of tafenoquine succinate in aqueous buffers at 25 and 37°C. See also Table 11 of the Section 1.11.1 for the solubility of [redacted] (b) (4)

Note that for malaria prophylaxis, the proposed dosage is [redacted] (b) (4)

Permeability: *Indeterminate*
This NDA did not include specific permeability data, but has right of reference to the data generated for tafenoquine tablets by Glaxo Smith Kline (GSK) under IND [redacted] (b) (4), as follows. [redacted] (b) (4)

4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

However, the final determination cannot be made until after evaluation of the Applicant's pending response to the information request dated 4/19/2018.

Note that the proposed expiration dating period is 24 months for the drug product when stored at conditions consistent with the 25°C or 30°C long term studies. This Reviewer requested (IR dated 4/19/2018) the dissolution profile data of the pivotal clinical trial lot and primary registration stability batches, generated using the currently proposed QC dissolution method, as well as when using an alternative paddle speed.

Bridging of Formulations

Reviewer's Assessment: *ADEQUATE*

The proposed to-be-marketed drug product has the same dosage form (tablet), formulation, strength (100 mg free base), appearance, drug product manufacturing process, site (b) (4) and scale (b) (4) and API manufacturer (b) (4) as the batch (TFATA6001) tested in PK Study TQ-2016-01 as well as the batches undergoing registration (stability) testing. Note that TFATA6001 is also a prequalification (stability) batch. [A third clinical trial (Study 60PH04) is underway using Batch TFATA6002.]

Note also that capsule formulations were used in 5 other studies that were designated as key/pivotal efficacy clinical trials (Studies 030, 033, 043, 045, and 058); the capsules used contained (b) (4) drug except in the case of some dose-ranging studies that included (b) (4) for lower dose groups. The Applicant notes that (b) (4)

To support PK bridging of the tablet and capsule dosage forms used during clinical development, the PK data following oral administration of two units of the proposed to-be-marketed product (100 mg tablet) from Fed Bioequivalence Study TQ-2016-01 were compared to the PK data of the the 200 mg capsule administered (under fed conditions) in Study 022. As confirmed by the Clinical Pharmacology Reviewer (Dr. Amit Somani), the tafenoquine C_{max} and AUC_{∞} of the to-be-marketed tablets and the capsules used in Study 22 are comparable when adjusted to 70 kg bodyweight; for details related to the statistical comparisons of the relative PK data, refer to Dr. Somani's review.

Biowaiver Request

Reviewer's Assessment: *NOT APPLICABLE*

A biowaiver request is not needed because the PK and clinical efficacy/safety of the proposed drug product (100 mg tablet) were investigated.

Post-Approval Commitments

Reviewer's Assessment:

None at this time. However, note that there are pending information request comments.

List of Deficiencies:

The below information requests were sent to the Applicant on 4/19/2018; responses were requested by 5/7/2018.

(b) (4)

Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, PhD (4/23/2018)

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Elsbeth Chikhale, PhD (4/24/2018)

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 5/07/2018 09:31:18AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

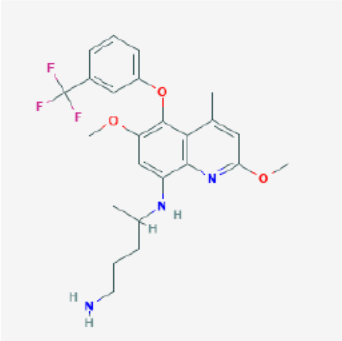
Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 5/07/2018 09:33:43AM
GUID: 50743ccc000031928b54eba1769a5df9

ENVIRONMENTAL

R Regional Information

Application: NDA 210607
API: Tafenoquine
Indication: Tafenoquine tablets are indicated for the prevention of malaria in adults.



The applicant has submitted a claim of categorical exclusion under 21CFR 25.31(b) and a statement of "no extraordinary circumstances." The applicant provided additional information in response to an IR (SN 0032) to support the claim.

Based on the estimated concentration of tafenoquine at the point of entry into the aquatic environment (EIC) of < 1ug/L (ppb), the application meets the criteria for the cited categorical exclusion. This review then evaluates the "extraordinary circumstances" statement to determine if available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment (21 CFR 25.21a).

Environmental

FDA utilized the fish plasma model (FPM; Nallani et al., 2016 and Huggett et al., 2003) to help screen for CBD aquatic environmental risk. The following inputs were used:
Production volume = (b) (4) kg/year (Environmental analysis document (SN0032; 2018 March27; Response to Information Request – Quality Information amendment)
Expected Introduction Concentration (EIC) = (b) (4) ppb = (b) (4) µg/L
Cmax = approx. (b) (4) ng/mL; Cmin = (b) (4) ng/mL
Log D (pH=7) = (b) (4)

ER = (b) (4) (considering Cmax)
ER = (considering Cmin)

- According to the FPM, tafenoquine is not estimated to reach concentrations in fish plasma that are associated with pharmacological effects in humans. The effect ratio is (b) (4) indicating that this substance would not be prioritized for the conduct of fish chronic studies for this application.

Aquatic toxicity predictions for tafenoquine are reported in the Danish QSAR toolbox database:

Fathead minnow: 96h LC50 estimated to be (b) (4) µg/L
Daphnia magna: 48h EC50 estimated to be (b) (4) µg/L
Pseudokirchneriella s. 72h EC50 estimated to be (b) (4) µg/L

- Predicted acute toxicity concentrations are at least (b) (4)-fold higher than the EIC.

Potential for interaction with estrogen and androgen receptors were determined:

Predictions for Estrogen receptor activity reported in Mansouri et al., 2016 (CERAPP project paper):

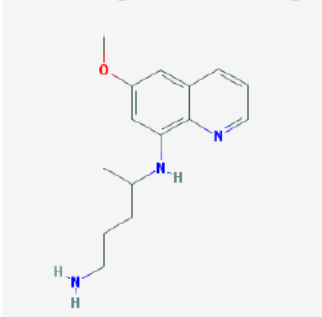
- INACTIVE in binding, agonist and antagonist ER models

Predictions for Androgen receptor activity (COMPARA models):

- VERY WEAK activity in binding and antagonist AR models

Animal data summarized in the labeling information indicates (b) (4)
(b) (4)

An analogue of tafenoquine is primaquine



An ECOTOX search provided algicide activity (Lowest complete inhibition concentration)
Oscillatoria perornata: (b) (4) µM = (b) (4) mg/L = (b) (4) µg/L
Selenastrum capricornutum: (b) (4) µM = (b) (4) mg/L = (b) (4) µg/L

- These toxicity concentrations are at least (b) (4)-fold higher than the EIC.

References:

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7):1789-1799.

Nallani G., Venables B., Constantine L., Huggett D. 2016. Comparison of measured and predicted bioconcentration estimates of pharmaceuticals in fish plasma and prediction of chronic risk. Bulletin of Environmental Contamination and Toxicology, 96(5):580-584.

Mansouri, K., Abdelaziz, A., Rybacka, A., Roncaglioni, A., Tropsha, A., Varnek, A., et al. CERAPP: Collaborative Estrogen Receptor Activity Prediction Project. Environ Health Perspect. 2016;124(7):1023-33. doi: 10.1289/ehp.1510267.

Reviewer's Assessment: ***Adequate***

The applicant has submitted a claim of categorical exclusion under 21CFR 25.31(b) and a statement of "no extraordinary circumstances." Based on the estimated concentration of tafenoquine at the point of entry into the aquatic environment, the application meets the criteria for the cited categorical exclusion. Available information supports a statement of "no extraordinary circumstances." Significant impact to the environment due to approval of this application is not anticipated.

The applicant's claim of claim of categorical exclusion under 21 CFR 25.31(b) and statement of no extraordinary circumstance is acceptable

Primary Environmental Reviewer: Raanan A. Bloom, Ph.D.

Secondary Reviewer: Scott Furness, Ph.D.

Raanan Bloom

Digitally signed by Raanan Bloom
Date: 4/20/2018 03:57:04PM
GUID: 508da72a0002a6d1071f3297897e4f1f

Michael Furness

Digitally signed by Michael Furness
Date: 4/23/2018 08:44:25AM
GUID: 502e8c7600003dd8331cf6eebf43697a

9 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

IQA Addendum for NDA 210607

Product Background: Arakoda (tafenoquine) tablets, 100 mg is a novel antimalarial drug intended to be used for the prevention of malaria.

Route of Administration: Oral

Applicant Name: 60 Degrees Pharmaceuticals, LLC

Amendment Submission Date: Amendment 0058 dated 6/8/2018

Summary:

The NDA was recommended for Approval from a product quality perspective (IQA dated 5/08/2018). The IQA also noted that an assessment of the outstanding IRs from drug product and biopharmaceutics will be documented in an OPQ review addendum. Since completing the IQA, the Applicant submitted the above referenced Amendment to address the IR which sought elemental impurities data for representative batches of drug product tested using a USP <233> method to demonstrate that the proposed controls for elemental impurities in the individual drug product components are sufficient to mitigate potential risk from elemental impurities in the drug product.

Applicants response:
The elemental impurities data for all drug product registration batches (including TFATA6001) using USP <233> (ICP-MS) methodology are provided. The data demonstrate that the individual and total elemental impurity levels from all sources (i.e., drug substance, excipients, processing equipment, etc.) in the drug product are all significantly less than 30% of the permitted daily exposure. Additionally, these results represent beyond worst case values since the maximum daily drug product dose is about 10 times less than the 10-gm daily intake assumed for the USP <232> limits. Accordingly, the conclusion is that no additional elemental impurity specifications are required.

Reviewer Assessment:
The Applicant provided elemental impurities data for the four drug product batches tested using (b) (4) registration/stability batches TFATA6002, TFATA003, and TFATA6004 and prequalification/clinical/stability batch TFATA6001. Levels of all elements (Class 1, 2A, 2B, and 3) were <30% of the respective PDEs. Therefore, no additional elemental impurities controls are required.
The drug product reviewer found the response acceptable and recommended Approval.

Regarding biopharmaceutics IR, the new QC dissolution method submitted in response to the IR was found not optimal due to incomplete dissolution by the biopharmaceutics reviewer. Post-Marketing Commitment (PMC) was determined to be an appropriate path to addressing this issue since it does not escalate to be an approvability issue but

rather when addressed will further ensue product quality. Furthermore, the proposed indication for which the drug product is being sought for approval supports the PMC path. An outline of the agreed upon PMC is summarized below. The signed PMC document has been filed in DARRTS.

PMC Description: Conduct further studies to identify an optimal QC dissolution method and acceptance criteria for the finished drug product.
Timeline for Submission of Final PMC (as a Prior-Approval Supplement): 18 months after NDA approval.

The biopharmaceutics reviewer recommends Approval.

Review Recommendation: At this time all outstanding product quality issues have been successfully resolved. Therefore, OPQ recommends **Approval** of the NDA from product quality perspective.

Balajee Shanmugam, Ph.D.
ATL/Branch Chief, ONDP, OPQ.

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 7/12/2018 03:51:33PM
GUID: 50758d5000003c1b1962e036ea11002c

BIOPHARMACEUTICS
(REVIEW ADDENDUM)

Product Background:

NDA: 210607; 505(b)(1), NME, Priority and Fast Track Designation Statuses Granted; (b) (4)

Drug Product Name/Strength: Tafenoquine Succinate Tablet, 100 mg (as free base; equivalent to 125 mg succinate salt)

Route of Administration: Oral

Proposed Indication: For prevention of malaria in adults

Proposed prophylactic regimen: 200 mg (2 tablets) per day for 3 days as a loading dose followed by 200 mg (2 tablets) once weekly while exposed to *Plasmodia* in an endemic region and finally at 1 week after leaving the endemic region; with food for better gastrointestinal tolerability

Applicant Name: 60 Degrees Pharmaceuticals, LLC

Note that the original Biopharmaceutics Review was uploaded and signed in Panorama on 5/7/2018, and was incorporated in the Integrated Quality Assessment Review dated 5/8/2018.

Recommendations:

From the Biopharmaceutics perspective, NDA 210607 submitted for Tafenoquine Tablets (100 mg) is recommended for **APPROVAL**.

Post-Marketing Commitment (PMC) Study:

The Applicant agreed to conduct further studies to identify an optimal QC dissolution method and acceptance criteria for the finished drug product, and to submit the interim and the final dissolution method development and validation reports within 12 months and 18 months, respectively, of NDA approval.

Review Summary:

Tafenoquine succinate exhibits pH-dependent solubility, and is considered a low solubility drug substance (per BCS criteria). The final proposed QC dissolution method demonstrated stability indicating potential and limited discriminating power for changes in critical quality attributes. On an interim basis, the currently proposed QC dissolution method and the revised dissolution acceptance criteria (as tabulated below) was deemedacceptable for the routine QC of the proposed drug product at batch release and during stability testing.

USP Apparatus	Speed	Medium	Volume	Acceptance criteria
2 (paddle)	50 rpm	pH 3.2 acetate buffer (USP) 37 ± 0.5°C	500 mL	NLT (b) (4)% at 10 min NLT (b) (4)% (Q) at 90 min

In the 06/12/2018 Response to Biopharmaceutics Information Request dated 06/7/2018, the Applicant agreed to adopt the FDA recommended dissolution acceptance criteria, and updated the finished product QC specifications and other pertinent NDA documents accordingly.

In vitro bridging data are not required because there are no noted differences in the quality attributes of the tablets used in the pivotal clinical trials and the tablets intended for commercialization. Of note, the Clinical Pharmacology Reviewer confirms adequate *in vivo* PK bridging between the proposed to-be-marketed tablets used in pivotal clinical trials and the capsules used in earlier key clinical efficacy trials.

Post-Approval Commitments

Reviewer's Assessment: *ADEQUATE*

On 06/12/2018, the Applicant agreed to the following Post-Marketing Commitment.

PMC Description: Conduct further studies to identify an optimal QC dissolution method and acceptance criteria for the finished drug product

PMC Schedule Milestones:
Interim Report Submission: 12 months from NDA approval date
Final Report Submission: 18 months from NDA approval date

PMC Study Objectives:

(b) (4)

List of Deficiencies:
None

Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, PhD (7/9/2018)

Secondary Reviewer Name and Date: Elsbeth Chikhale, PhD (7/10/2018)

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 7/10/2018 08:22:13AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 7/10/2018 08:27:48AM
GUID: 50743ccc000031928b54eba1769a5df9