

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210795Orig1s000

PRODUCT QUALITY REVIEW(S)

IQA Addendum for NDA 210795

Product Background: Krintafel (tafenoquine) tablets, 150 mg is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria. The proposed product is to be administered as a single 300 mg dose (2 x 150mg) in conjunction with chloroquine (on the first or second day of chloroquine administration).

Route of Administration: Oral

Applicant Name: GlaxoSmithKline Intellectual Property Development Ltd.

Amendment Submission Date: Amendment 0022 dated 4/25/2018

Summary:

The IQA dated 4/22/2018 indicated that a recommendation from OPQ is pending due to several outstanding issues related to manufacturing process and facilities. Since completing the IQA, the Applicant submitted the above referenced Amendment to address the outstanding IRs summarized below:

- (1) Provide individual (b) (4) and (b) (4) data
- (2) Due to lack of (b) (4), it was recommended that the whole manufacturing time from start of (b) (4) within 30 days.
- (3) Set limit for yield at different manufacturing stages and submit overall manufacturing yield and accountability data for the exhibit batches
- (4) Provide actual (b) (4) data for the exhibit batches and set a reasonable range for the commercial batches.

The assessment of the responses to the above deficiencies is documented in an Addendum (dated 4/30/2018) to the process review. The process reviewer found the responses acceptable and recommended Approval.

Also, the facilities supporting the NDA have been found to be adequate and recommended for Approval (Facilities review dated 4/30/2018).

As documented in the reviews referenced above, all outstanding issues have been successfully resolved.

Review Recommendation: OPQ recommends **Approval** from product quality perspective.

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



Balajee
Shanmugam

Digitally signed by Balajee Shanmugam

Date: 7/09/2018 09:14:09PM

GUID: 50758d5000003c1b1962e036ea11002c

Recommendation: *Pending*

NDA 210795

Review # 1

Drug Name/Dosage Form	Krintafel (tafenoquine) Tablets
Strength	150 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	GlaxoSmithKline Intellectual Property Development Ltd. England
US agent, if applicable	Christian Baumann

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	November 22, 2017	All
Amendment (eCTD 011)	February 22, 2018	Facilities
Amendment (eCTD 012)	March 1, 2018	Biopharmaceutics, Environmental Assessment
Amendment (eCTD 016)	March 19, 2018	Drug Product
Amendment (eCTD 020)	April 17, 2018	Labeling

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Erika Englund	Charles Jewell
Drug Product	Erika Englund	Balajee Shanmugam
Process	Wenzheng (Wendy) Zhang	Ying Zhang
Microbiology*	Wenzheng (Wendy) Zhang	Ying Zhang
Facilities	Wenzheng (Wendy) Zhang	Derek Smith
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Environmental Assessment**	Raanan Bloom	N/A
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

** EA is covered in the Drug Product 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)	Adequate	3/26/2018	Review by Erika Englund
	III				N/A*	
	III				N/A*	
	III				N/A*	
	III				N/A*	
	III				N/A*	

*Sufficient information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	101471	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The final approvability recommendation for this NDA is currently *pending*. The majority of the CMC information provided in the NDA for the drug substance and the drug product was found to be adequate; however, there are several pending issues related to the drug product manufacturing process that will need to be resolved. In addition, cGMP issues were identified at the drug substance facility during the pre-approval inspection (PAI), and this facility remains under evaluation by the Office of Process and Facilities (OPF) at this time. Therefore, the overall recommendation for manufacturing facilities has not been yet entered into Panorama for this NDA. Also, the proposed package insert and the container label are presently under review by the NDA review team.

II. Summary of Quality Assessments

A. Product Overview

Tafenoquine (TQ, SB-252263, and WR 238605) is a novel antimalarial drug co-developed by GlaxoSmithKline (GSK) and the Medicines for Malaria Venture (MMV), with the support of the Walter Reed Army Institute of Research, for the radical cure (prevention of relapse) of *Plasmodium vivax* (*P. vivax*) malaria. The proposed drug product (tafenoquine tablets, 150 mg) is to be administered with food, as a single 300 mg dose (two 150 mg tablets), in conjunction with chloroquine (on the first or second day of chloroquine administration).

Proposed Indication(s) including Intended Patient Population	Radical cure (prevention of relapse) of <i>Plasmodium vivax</i> (<i>P. vivax</i>) malaria in patients 16 years old and older.
Duration of Treatment	One-time, a single dose of 300 mg tafenoquine (two 150 mg tablets).
Maximum Daily Dose	300 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Tafenoquine (TQ, SB-252263, and WR 238605) is a novel 8-aminoquinoline antimalarial drug, a synthetic analog of primaquine, intended for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria. The drug substance has been developed as (b) (4) succinate salt, which is manufactured as a single, more (b) (4) form (i.e., (b) (4)). The synthesis of tafenoquine succinate, involves a (u) (4) process, which has been used to prepare the drug substance used in Phase 3 clinical trials, all drug substance and drug product primary

stability batches, and is the intended commercial method of manufacture. Tafenoquine drug substance is described as a pale green or pale orange to orange solid, very slightly soluble in water and soluble in methanol. The drug substance specification includes quality attributes such as description, identification by IR, assay, impurities, (b) (4) residue on ignition, (b) (4) residual solvents and particle size distribution. The routine testing of solid state form has not been proposed, since only one form was consistently obtained during the drug substance manufacture. In addition, the drug product release and stability data did not reveal any polymorphic changes. Available stability data in the NDA support the proposed retest period of (b) (4) months for tafenoquine drug substance stored up to (b) (4). 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 188.2 mg of tafenoquine succinate, which is equivalent to 150 mg tafenoquine free base. Tafenoquine tablet is described as pink film coated, capsule shaped tablet, 17.1 mm by 9.0 mm, plain on one side and debossed with 'GS J11' on the other side. Each tablet core contains the following excipients: microcrystalline cellulose, mannitol and magnesium stearate. The tablet core is film-coated with an (b) (4). The proposed commercial container closure for the drug product includes (b) (4) high density polyethylene (HDPE) bottles with (b) (4) child-resistant closures, and a (b) (4). A (b) (4) desiccant canister will be included in each bottle. Tafenoquine tablets will be available in two packaging configurations, the patient pack containing two tablets and the pharmacy dispensing pack consists of 30 tablets, each supplied in an HDPE bottle.

The drug product specification includes quality attributes relevant for the proposed dosage forms such as description, identification, assay, uniformity of dosage units, assay, impurities, dissolution, and microbial controls. During the review, several comments regarding the proposed drug product specification were conveyed by the review team and accepted by the Applicant. These include a revision of the proposed acceptance criterion for dissolution (as discussed below) and inclusion of testing for impurities (b) (4). The proposed microbial control for the drug product was assessed as part of the process review and was found to be acceptable; therefore, the overall drug product specification, including the analytical procedures and validation data, were found to be adequate. In addition, the elemental impurity assessment (b) (4) was included in the NDA and found acceptable.

Stability of the proposed drug product, tafenoquine tablets, 150 mg, packaged in the proposed container closure system has been demonstrated through adequate 18-month long-term (25°C/60% RH) and 6-month accelerated (40°C/75% RH) stability data for three representative drug product batches. No significant changes in the assay or impurities values were observed, and only some increase in (b) (4) content was noted. In addition, testing for polymorphic form, which was included in the primary stability batches testing following previous FDA recommendation, did not reveal any changes over time, i.e., only (b) (4) was reported in the stability samples. Therefore, the

proposed expiry dating of 24 months for the drug product, tafenoquine tablets, 150 mg, packaged in HDPE bottles, and to be stored at controlled room temperature, has been found acceptable. The adequate in-use stability data were also submitted in the NDA for the pharmacy dispensing pack containing 15 doses (30 tablets). These data support the proposed labeling for the pharmacy dispensing pack, which includes a statement that the product should be used within 3 months once the bottle is opened.

(b) (4)

The biopharmaceutics review focused on the assessment of the proposed dissolution method and acceptance criteria, and need for bridging. Based on information provided, the proposed dissolution method was found acceptable and the acceptance criterion of $Q = \frac{(b)(4)}{(4)}\%$ at $(b)(4)$ minutes (as recommended by the FDA) was accepted by the Applicant. In addition, the bridging between the debossed film-coated tablets produced by the proposed commercial manufacturing site (GSK, Zebulon, NC) and the unmarked film-coated tablets produced by the Phase 3 clinical supply manufacturing site ($(b)(4)$), was also found acceptable, as demonstrated by comparative *in vitro* dissolution data.

The commercial tafenoquine succinate drug substance manufacturer is $(b)(4)$, and the drug product manufacturer is GlaxoSmithKline LLC, Zebulon, NC. Several other facilities (also used during the drug development) have been listed in the NDA as the drug substance and the drug product testing sites. While the drug product GSK site and testing facilities have been found acceptable, the PAI inspection of the drug substance site ($(b)(4)$) resulted in cGMP deficiencies, which are currently under evaluation by OPF. Therefore, the overall recommendation for facilities is currently *pending* for this NDA in Panorama.

The Applicant's claim of categorical exclusion from the Environmental Assessment per 21 CFR 25.31(b) has been found acceptable. Since the proposed active ingredient is a salt, the labeling assessment focused on issues related to the salt policy and appropriate equivalency statement. In addition, several comments regarding the CMC sections of the package insert and the proposed container label were conveyed to the Applicant. The labeling is currently under review by the NDA review team.

C. Special Product Quality Labeling Recommendations (see labeling review)

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Process

CHAPTER IV: Biopharmaceutics

CHAPTER V: Labeling

ATTACHMENT I: List of Pending Issues

89 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background:

NDA: 210795; 505(b)(1); PRIORITY

Drug Product Name / Strength: KRINTAFEL® (tafenoquine succinate) Oral Tablets, contains (188.2 mg tafenoquine succinate) the equivalent of 150 mg free base

Route of Administration: Oral

Proposed Indication: For the radical cure (prevention of relapse) of *P. vivax* malaria in patients 16 years and older

Proposed Dosage: a one-time dose of 300 mg (two 150 mg tablets), with food; given on the first or second day of chloroquine administration

Applicant Name: GlaxoSmithKline Intellectual Property Development Ltd

Review Recommendation: Adequate

Review Summary:

This Biopharmaceutics Review focused on the evaluation of the proposed QC dissolution method and acceptance criterion, and the *in vitro* dissolution bridging data.

The proposed QC dissolution method and the revised dissolution acceptance criterion as tabulated below are approved for the routine QC testing of the Tafenoquine 150 mg Tablets (submitted under NDA 210795).

USP Apparatus	Speed	Medium	Volume	Acceptance criteria
2 (paddle)	75 rpm	0.01M sodium phosphate buffer, pH 6.8 ± 0.05, with 0.20% w/v of Polysorbate 20, 37 ± 0.5°C	900 mL	Q = ^(b) ₍₄₎ % at ^(b) ₍₄₎ min

The proposed commercial drug product has the same formulation and manufacturing process, API supplier and the same/similar batch size (^(b)₍₄₎ kg) as those used for the primary stability (registration) lots and the Phase 3 clinical trial lots. The proposal to add debossing to the tablet, and an alternate drug product manufacturing site for commercialization were supported with evidence of comparable *in vitro* dissolution profiles between the pre-change and the post-change drug products.

Additionally, if needed for bridging purposes, data are available to compare the PK of the different tafenoquine capsule and tablet formulations used during clinical development. The evaluation of PK bridging is not within the scope of this review.

List of Submissions reviewed:

SDN-1, 11/22/2017 (Original NDA)
SDN-5, 01/24/2018 (Response to Biopharmaceutics Early Information Request)
SDN-13, 03/01/2018 (Response to Quality Information Request)

Highlight Key Outstanding Issues from Last Cycle:

Not Applicable

Concise Description Outstanding Issues Remaining:

None

BCS Designation

There is no formal BCS designation request for tafenoquine succinate. However, because of the low aqueous solubility and indeterminate Caco-2 permeability measurements for the API, the Applicant considers tafenoquine succinate as either a BCS-2 (low solubility/high permeability) or BCS-4 (low solubility/low permeability) drug substance.

Reviewer's Assessment:

Solubility: *Low.* Per BCS criteria, tafenoquine succinate is a low solubility drug substance. The equilibrium solubility of tafenoquine succinate is pH dependent, and is at least 0.01 mg/mL in water and in biorelevant media. The reported solubilities of tafenoquine succinate at ambient temperature are >85 mg/mL in simulated gastric fluid (SGF; pH 1.2), 0.54 mg/mL in water, 0.01 mg/mL in Fasted State Simulated Intestinal Fluid (FaSSIF; pH 6.5), and 1.05 mg/mL in Fed State Simulated Intestinal Fluid (FeSSIF; pH 6.5). API solubility in pH 2, 4, 6, 7, 8 Britton-Robinson Buffer media ranged from 0.02 – 18.28 mg/mL.

Note that for the radical cure of *P. vivax* malaria in adults and adolescents, the proposed dosage is two tablets (totaling 300 mg tafenoquine base) as a single dose with food, co-administered on Day 1 or 2 of chloroquine dosing.

Permeability: *Indeterminate.* The Applicant indicated that it was not possible to reliably determine the permeability values for tafenoquine due to issues pertaining to the health of the Caco-2 cell line model, and non-specific binding of the drug to the apparatus. However, using the MDCKII-MDR1 cell line, the passive membrane permeability obtained for the drug in FaSSIF buffer was 69 ± 20 nm/s, suggesting moderate permeability.

Dissolution: *Not Rapid nor Very Rapid.* When using 900 mL of medium with surfactant and the operating parameters of the proposed QC dissolution method, the proposed drug product exhibits $> \frac{(b)}{(4)}\%$ dissolution within $\frac{(b)}{(4)}$ minutes.

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

Primary Biopharmaceutics Reviewer: Gerlie Gieser, Ph.D. (3/12/2018)

Secondary Reviewer (and Secondary Summary, as needed): Elsbeth Chikhale, Ph.D. (3/13/2018)



Gerlie
Gieser

Digitally signed by Gerlie Gieser
Date: 3/13/2018 10:34:21AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb



Elsbeth
Chikhale

Digitally signed by Elsbeth Chikhale
Date: 3/13/2018 10:43:01AM
GUID: 50743ccc000031928b54eba1769a5df9

LABELING

IQA Review Guide Reference

I. Package Insert

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Krintafel (tafenoquine) tablets
Dosage form, route of administration	Tablets, for oral use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 150 mg of tafenoquine

2. Section 2 Dosage and Administration

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Swallow tablets whole. Do not break or crush

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(4))
Available dosage forms	tablets
Strengths: in metric system	150 mg
Active moiety expression of strength with equivalence statement (if applicable)	150 mg of tafenoquine. Refer to discussion of equivalency statement below.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Pink, film-coated, capsule shaped tablets debossed with 'GS J11' on one side.

4. Section 11 Description

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Krintafel and tafenoquine
Dosage form and route of administration	Tablet and oral administration
Active moiety expression of strength with equivalence statement (if applicable)	150 mg of tafenoquine, equivalent to 188.2 mg of tafenoquine succinate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	N/A
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	antimalarial
Chemical name, structural formula, molecular weight	(±) 8-[(4-amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline succinate C ₂₄ H ₂₈ F ₃ N ₃ O ₃ • C ₄ H ₆ O ₄ MW = 581.6 (succinate salt) MW free base = 463.5
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Tafenoquine succinate is a pale green or orange solid

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	150 mg
Available units (e.g., bottles of 100 tablets)	30 tablets (pharmacy pack) 2 tablets (patient pack)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	pink, film coated, capsule-shaped, and debossed with 'GS J11' on one side. No scoring. Pharmacy pack NDC = 0173-0889-13 Patient pack NDC = 0173-0889-39
Special handling (e.g., protect from light)	Store in the original package to protect from moisture. Keep the bottle tightly closed and do not remove the desiccant.
Storage conditions	Store at 20°C to 25°C (68°F to 77°F). Temperature excursions are permitted to 15°C to 30°C (59°F to 86°F)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	GSK is listed at the end of the label.

Reviewer’s Assessment of Package Insert: {Adequate}

The drug substance in NDA 21795 is tafenoquine succinate. According to the FDA Guidance *Naming of Drug Products Containing Salt Drug Substances* and MAPP 5021.1 (*Naming of Drug Products Containing Salt Drug Substances*, effective 12/7/2017), the strength of the product should be expressed in terms of the free base of the salt. The strength of the product is 150 mg of tafenoquine, which is equivalent to 188.2 mg of tafenoquine succinate.

The 2017 labeling review tool describes the strength should be described according to the USP salt policy in Highlights Dosage Forms and Strengths, section 3, section 11, and section 16. The 2017 labeling review tool only describes the use of the equivalency statement in section 11.

B. The DOSAGE FORMS AND STRENGTHS section¹⁷ clearly states the product contents in a manner that allows the reader to understand whether the strength is based on the active moiety or active ingredient (salt).

Example #1 (when the USP Salt Policy applies):

Tablets: 10 mg of drug-x

Example #2 (when an exception to the USP Salt Policy has been granted):

Tablets: 10.5 mg of drug-x hydrochloride

MAPP 5021.1 provides additional details about the wording that should be used to describe the strength. This MAPP describes that in the dosage forms and strengths section, the strength should be written in a manner that clearly states whether the strength is based on a salt or the free base. The example from MAPP 5021.1 is copied above. The PI for tafenoquine originally described the strength as only 150 mg. *A CMC comment was added to the OND edited PI that the strength should be updated to “150 mg of tafenoquine” per MAPP 5021.1.*

MAPP 5021.1 includes a description of the equivalency statement for section 11 in the PI. The example from the MAPP is copied below. Section 11 of the PI states: *Each KRINTAFEL tablet contains 150 mg of tafenoquine (equivalent to 188.2 mg tafenoquine succinate).* This is acceptable.

C. The DESCRIPTION section¹⁸ for drug products containing an active ingredient that is a salt clearly identifies the active ingredient (salt), the active moiety, and the strengths of each, which can be accomplished with the use of an equivalency statement. For example:

DRUG-X contains 100 mg of drug-x equivalent to 123.7 mg of drug-x hydrochloride

Section 16 of the PI included an equivalency statement, but according to the labeling review tool, this equivalency statement isn't required in section 16. *A CMC recommendation to delete this line was included in the OND edited PI.*

There are instructions in the PI and container labels that the product should not be crushed. These instructions were added by OND to the Dosage and Administration section. The product is immediate release and the film coating is not described as functional. However, there was no data in the NDA about the stability of the crushed tablets. Since there was no data about the quality or stability of the crushed tablets, it is acceptable from a CMC perspective to include the statement that the tablets should not be crushed.

Krintafel (tafenoquine) tablets are for oral use. The dosage forms and strengths section of the PI describes that the tablets are described as pink, film-coated, capsule shaped tablets debossed with 'GS J11' on one side. This description is also consistent with the description found in the NDA.

The description section of the PI includes the equivalency statements, and a description of the MW and formula for both the succinate salt and free base. Tafenoquine is racemic and the chemical name starts with (+/-) to convey that this drug substance is racemic. The original list of excipients included (b) (4). Per 21 CFR 201.10(c)(3), proprietary names should not be used in the description section. The following comment was added to the OND edited PI: *Replace “(b) (4)” with the names of the inactive ingredients in (b) (4).*

This is an oral product, and the inactive ingredients are not included on the container label, therefore the statement regarding (b) (4) did not need to be sent for any other sections in the labeling.

Statements are included in section 16 of the PI and on the container labels for the pharmacy dispensing pack (30 tablets) that the product should be used within 3 months. There is adequate data in the NDA to support that the product is stable for 3 months after the bottle is opened

➤ *Any deficiencies should be listed at the end in the “List of Deficiencies”*

Refer to the discussion above about the comments that were added to the OND edited PI.

II. Labels:

1. Container Labels



Patient pack (2 tablets)

(b) (4)

Pharmacy Pack (30 tablets)

2. Container Label

No Carton Labels are included in this NDA.

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Krintafel (tafenoquine) tablets	N/A
Dosage strength	150 mg	N/A
Net contents	2 or 30 tablets	N/A
“Rx only” displayed prominently on the main panel	Yes	N/A
NDC number (21 CFR 207.35(b)(3)(i))	NDC 0173-0889-39 (2 tablets) and NDA 0173-0889-13 (30 tablets)	N/A
Lot number and expiration date (21 CFR 201.17)	Yes	N/A
Storage conditions	Store at 20°C to 25°C (68°F to 77°F). Temperature excursions are permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].	N/A
Bar code (21CFR 201.25)	Yes	N/A
Name of manufacturer/distributor	GlaxoSmithKline	N/A
And others, if space is available		N/A

Reviewer’s Assessment of Labels: {Adequate}

Refer to the discussion above concerning the USP salt policy and expression of strength. The expression of strength for this product is acceptable. The NDC numbers listed on the container labeling is consistent with the NDC numbers in section 16 of the PI. The storage conditions are supported by the stability data in the NDA.

The drug product is manufactured by GlaxoSmithKline in Zebulon North Carolina. The corporate address is listed on the container label above the statement (b) (4) the drug product is only manufactured in North Carolina. (b) (4) GSK address in NC.

The following comment was sent regarding the container labeling:

The container labels currently state (b) (4) The drug substance is manufactured (b) (4) the drug product is manufactured in North Carolina. We

recommend that the drug product manufacturing site be listed on the label instead.

There is a line at the bottom of the container label that states “ (b) (4)”. The following comment will be sent for the removal of this line.

Remove “ (b) (4)” from the container labels.

➤ ***Any deficiencies should be listed at the end in the “List of Deficiencies”***

Refer to discussion above.

List of Deficiencies:

Refer to discussion above.

Overall Assessment and Recommendation:

Recommended edits in the labeling were sent to OND. The labeling will be adequate once these edits are made.

Primary Labeling Reviewer Name and Date:

Erika E. Englund, Ph.D.

04/02/2018

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



Erika
Englund

Digitally signed by Erika Englund
Date: 4/09/2018 05:39:53PM
GUID: 51389ea30003450414230afb8c3e8114



Balajee
Shanmugam

Digitally signed by Balajee Shanmugam
Date: 4/10/2018 03:25:16PM
GUID: 50758d5000003c1b1962e036ea11002c

ATTACHMENT I: List of Pending Issues

1. cGMP deficiencies were identified at the drug substance manufacturing facility during its recent PAI inspection - evaluation of this site and the overall recommendation for the manufacturing facilities listed in the NDA are currently pending.
2. Review of the proposed labeling is currently pending.
3. Outstanding issues regarding the manufacturing process (*comments conveyed to the Applicant via IR dated April 19, 2018*):
 - a. Please provide individual (b) (4) and (b) (4) data for your exhibit batches. Please provide (b) (4) sampling scheme.
 - b. Since you did not provide (b) (4), we recommend you to define the (b) (4) of packaging within 30 days. You could change this time after completion of the (b) (4) study in batch validation.
 - c. You have set limit for accountability but not for yield at different manufacturing stages. Please set limit for yield based on your exhibit batch data. Please also set limit for overall manufacturing yield and accountability of the whole manufacturing process (from start of (b) (4)). Please provide overall manufacturing yield and accountability data for your exhibit batches.
 - d. In your exhibit batch records at coating stage, (b) (4) shows (b) (4) °C through the whole coating process, which is not reasonable. Please explain and provide actual (b) (4) data for your exhibit batches. Please set a reasonable range for (b) (4) in commercial batch records.

OVERALL ASSESSMENT

Due to the pending issues related to the manufacturing process and facilities, the final OPQ approvability recommendation for NDA 210795 is currently *pending*.

On behalf of the OPQ Team

Dorota Matecka, ATL

Dorota M.
Matecka -S

Digitally signed by Dorota M. Matecka, S
DN: c=US, ou=U.S. Government, ou=HHS,
ou=FDA, ou=People,
o=9 2342 19200000 100 1 1-1300123291
cn=Dorota M. Matecka, S
Date: 2018.04.22 12:21:17 -0400