CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209299Orig1s000

PRODUCT QUALITY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM

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

DATE: March 19, 2018

FROM: Branch 2/DNDP1/ONDP/OPQ

SUBJECT: Evaluation of the Risk Assessment of Elemental Impurities for NDA 209299

APPLICATION/DRUG: NDA 209299/TAVALISSE™ (fostamatinib) Tablets, 100 and 150 mg

Background:
In response to the Agency's March 1, 2018 telecon, the applicant submitted an amendment on March 7, 2018 providing a risk assessment for elemental impurities in the proposed drug product in accordance with ICH Q3D and USP<232/233>. The applicant provided the risk assessment for one batch of the 150 mg drug product (batch TXVD manufactured with drug substance process validation lot LFIGGB1003). The risk assessment included the evaluation of the following potential vectors for introduction of elemental impurities:

- Residual impurities resulting from elements intentionally added (e.g., catalysts) in the formation of the drug substance, excipients, or other drug product components. The risk assessment of the drug substance should address the potential for inclusion of elemental impurities in the drug product.
- Elemental impurities that are not intentionally added and are potentially present in the drug substance, water, or excipients used in the preparation of the drug product.
- Elemental impurities that are potentially introduced into the drug substance and/or drug product from manufacturing equipment.
- Elemental impurities that have the potential to be leached into the drug substance and drug product from container closure systems.

The applicant committed to analyzing three drug product process validation batches with validated method. The applicant will submit the data to agency by the end of June 2018 as previously

communicated to and agreed upon by the applicant. The applicant further commits to updating the risk assessment as necessary if the process is modified or suppliers of the drug product components are changed.

Applicant's Evaluation of Risk Assessment for Elemental Impurities:
Per ICH Q3D, the following Class 1 and Class 2A elemental impurities should be assessed for oral drug products: (b) (4) The risk assessment was based on a maximum daily dose of 300 mg.

The applicant provided a risk assessment for each of the metals. The applicant provided a risk assessment of the potential sources for the elemental impurities in this submission: intentionally added, container closure system, manufacturing equipment and raw materials (drug substance and excipients). The data provided demonstrates that all the elemental impurities are significantly below the threshold level of 30% of PDE. The summary of the data is included below.

(b) (4)

Comment: Acceptable
The data provided by the applicant is consistent with the applicant's conclusion that the product has a very low risk of contamination from the elemental impurities in the drug product as per ICH Q3D Option 2b.

CONCLUSION: The applicant's evaluation of the initial Risk Assessment of Elemental Impurities for NDA 209299 is acceptable per ICH Q3D as the applicant has a PMC in place to provide their final report.

Sherita McLamore, Ph.D.
Acting Quality Assessment Lead Branch 2,
Division of New Drug Product I (DNDPI)
Office of New Drugs Products (ONDP)

Office of Pharmaceutical Quality/CDER/FDA

Sherita McLamore

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Recommendation: APPROVAL

NDA 209229
Review #1

Drug Name/Dosage Form	TAVALISSE™ (fostamatinib) Tablets
Strength	100 and 150 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Rigel Pharmaceutical, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission (SD 1)	17-Apr-17	All
Amendment (SD 2)	10-May-17	DP, DS, Process
Amendment (SD 12)	7-Aug-17	Process
Amendment (SD 14)	16-Aug-17	DS
Amendment (SD 21)	7-Nov-17	Biopharm
Amendment (SD 22)	21-Nov-17	DS

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Monica Cooper	Benjamin Stevens
Drug Product	William Adams	Anamitro Banerjee
Process	David Anderson	Rahki Shah
Microbiology	n/a	n/a
Facility	Steven Hertz	Ruth Moore
Biopharmaceutics	Kaushalkumar Dave	Okponanabofa Eradiri
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Environmental	William Adams	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	N/A	No Review	Adequate information provided in the NDA
	Type IV			N/A	No Review	Adequate information provided in the NDA
	Type IV			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type IV			N/A	No Review	Adequate information provided in the NDA
	Type IV			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type II			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		(b) (4)
IND	074939	Drug development for the treatment of immune (idiopathic) thrombocytopenia

2. **CONSULTS**
N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Pharmaceutical Quality (OPQ) recommends **APPROVAL** of NDA 209299 for Tavalisse™ (fostamatinib) Tablets, 100 and 150 mg. As part of this action, OPQ grants a (b) (4)-month re-test period for the drug substance when stored at (b) (4) (b) (4) and an 18-month drug product expiration period when stored at stored at controlled room temperature. The Office of Pharmaceutical Quality has the following has the following Post-Marketing Commitments (PMCs) to be conveyed to the applicant:

- PMC-1: Develop a test method for (b) (4) and hardness for the drug product and submit the validation data to the FDA. Include tests for (b) (4) and hardness for drug product release and stability specifications with adequate justification.

  PMC Schedule Milestones: **Study Completion:** **June 30, 2018**

- PMC-2: Test (b) (4) for elemental impurities and submit the data to FDA. (b) (4)

  PMC Schedule Milestones: **Study Completion:** **June 30, 2018**

II. Summary of Quality Assessments

A. Product Overview

NDA 209299 was submitted for Tavalisse™ (fostamatinib) Tablets, 100 and 150 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Fostamatinib is an orally bioavailable, potent and selective spleen tyrosine kinase (SYK) inhibitor indicated for the treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Fostamatinib is a new molecular entity (NME) which was originally investigated under IND (b) (4) IND (b) (4) and IND 074939 (immune (idiopathic) thrombocytopenia and received orphan designation in August of 2015.

Fostamatinib disodium is a prodrug which undergoes rapid conversion to the pharmacologically active metabolite, R406, *in vivo via* hydrolysis. Clinical and non-clinical studies were conducted with the active metabolite R406; however, commercial development of R406 was not achievable due to its pharmaceutical properties (i.e. limited aqueous solubility). Fostamatinib is a small achiral molecule that is manufactured by

(b) (4). The drug substance exists as the disodium hexahydrate and no other crystal forms have been identified. BCS designation has not been established for the drug substance or for the active metabolite; however, the Applicant indicated that the drug substance was treated as a BCS Class IV compound during product development. The drug product is presented as a 100 and 150 mg immediate release, film-coated tablets containing the active together with all compendial, commonly used excipients. The100 and 150 mg tablets are manufactured from a (b) (4) and are differentiated by shape, size and debossing.

The dosing regimen for Tavalisse™ (fostamatinib) Tablets is 100 or 150 mg orally twice daily with or without food (initiate at a dose of 100 mg BID and increase to 150 BID after 4 weeks if platelet count has not increased to ≥50 x10^9/L).

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 209299 and grants a (b) (4)-month re-test period for the drug substance and an 18 month expiration period for the drug product when stored at ICH controlled room temperature in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment
Duration of Treatment	Discontinue after 12 weeks of treatment if the platelet count does not increase to a level sufficient to avoid clinically important bleeding
Maximum Daily Dose	300 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Fostamatinib disodium hexahydrate, drug substance is a white to off-white, non-hygroscopic, highly-crystalline solid that is practically insoluble in water and pH 6.8 phosphate buffer and is soluble in ethanol, methanol, DMSO, water, and neutral to alkaline aqueous buffers. Fostamatinib disodium hexahydrate is a prodrug that converts into the pharmacologically active metabolite, R406, *in vivo*. Clinical and non-clinical studies were conducted with R406; however, commercial development of R406 was not feasible due to its pharmaceutical properties.

Fostamatinib drug substance is small achiral molecule that is manufactured, controlled and packaged (b) (4) using a (b) (4) The drug substance manufacturing process is

(b) (4)

The drug substance is stored in (b) (4)

Pharm/tox reviewer (Brian Cholewa, Ph.D.) was informally consulted regarding the acceptance criteria for specified impurities (specifically impurities (b) (4) ; see drug substance review). It was concluded that several impurities were not qualified to the levels proposed in the original application. This deficiency was conveyed during review cycle and resulted in a revision to the drug substance specification acceptance criteria. It was further noted that the drug substance specification was devoid of tests for elemental impurities as per ICH Q3D. with no justification to demonstrate that these elemental impurities are not present in the drug substance. The reviewer attempted to resolve this deficiency during the review cycle; however, the applicant was unable to provide an acceptable response. Accordingly, the aforementioned Post Marketing Commitment (PMC-2) will be included in the action letter.

With the exception of the specification for elemental impurities, the specifications and acceptance criteria for the drug substance are consistent with ICH Q6A and are adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the drug product. All analytical methods are described in adequate detail and are appropriate for their intended use. All validation parameters, system suitability and system precision, specificity, linearity, range, precision, accuracy, ruggedness, robustness, and stability of solutions are provided in the NDA.

The applicant indicated that 78 batches of the drug substance have been manufactured to date via five different processes: early development, process A, process B, process C and the commercial process. Of the 78 batches produced, 7 of those were manufactured by the commercial process. Representative batch analyses for 28 batches of the drug substance were included in the submission. These batches were used for toxicology, clinical, ICH stability, and validation campaigns and for setting the specification for the drug substance.

The primary registration stability batches were manufactured at *ca* (b) (4) kg per batch using process B. All of the stability results (for primary and validation batches) met the proposed acceptance criteria at long-term, accelerated, stressed, and photostability storage conditions and there were no notable changes after up to 48 months under long term storage condition. The applicant requested (b) (4) -month retest for drug substance. The provided stability data and stress testing supports the proposed retest of (b) (4) months

for the drug substance when stored in the commercial bulk packaging at (b) (4)

The control strategy for fostamatinib disodium utilizes a combination of specification controls (i.e., proposed specifications for starting materials and intermediates), critical process parameters, and in-process controls to ensure all critical quality attributes are consistently achieved. The application is recommended for approval from the drug substance perspective.

Drug Product

The drug product, Tavalisse (fostamatinib) tablet is presented as an immediate release tablet available in 100 mg and 150 mg strengths.

The two strengths are manufactured from a (b) (4) and are differentiated by shape, size and debossing. The 100 mg tablet is presented as a (b) (4) (b) (4) weight, round, biconvex, orange film-coated tablet with a diameter of 9 mm. The commercial 100 mg tablet will be debossed with "R" on one side and "100" on the reverse side. The 150 mg tablet is presented as a (b) (4) (b) (4) weight, oval, biconvex, orange film-coated tablet measuring 7.25 mm x 14.5 mm. The commercial 150 mg tablet will be debossed with "R" on one side and "150" on the reverse side. The tablet core formulation includes USP/NF grade mannitol, sodium bicarbonate, sodium starch glycolate, povidone, and magnesium stearate. The film-coating excipients are USP/NF grade polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide yellow, and iron oxide red. The drug product formulation contains no novel excipient. All excipients are compendial and commonly used in solid oral dosage forms.

The drug product is manufactured, controlled, packaged and release tested by Patheon of Ontario, Canada at a commercial batch size of (b) (4) kg for the 100 mg tablet and (b) (4) kg for 150 mg tablet using a (b) (4) process. The 100 and 150 mg drug products will be packaged in a 60-count, 75cc HDPE bottle with a (b) (4) closure and two 1-gram desiccant canisters. The commercial product will also be packaged in two physician sample presentations (30-count, 45cc and 60-count 75cc, round HDPE bottle with a (b) (4) closure and two 1-gram desiccant canisters). (b) (4) (b) (4)

With the exception of the specifications for (b) (4) and hardness, the drug product specifications are consistent with ICH Q6A and provide adequate controls to ensure the quality of the drug product. The specifications for (b) (4) and hardness are to be addressed in the PMC included above.

In support of the proposed (b) (4) month expiry, the applicant provided 18 months of primary stability data for three batches of the 100 mg (batches TXKM, TXKT and TXKV) and three batches of the 150 mg (batches TXKN, TXKP and TXKS) drug

product. All batches used in the primary stability study were manufactured with the commercial formulation, scale, process and manufacturing site and were packaged in the proposed commercial container closure systems. In addition to the primary stability data, the applicant provided supportive stability data for clinical tablet batches. These batches were manufactured with the commercial core formulation, scale, process and packaging; however, the tablets were not debossed and were manufactured with a different film-coating and at a different manufacturing site. The supportive studies were completed at stored at 30 C, 40 C and 50 C.

The stability studies were executed in accordance with the ICH 1A and Q1B. It was concluded that the stability studies do not establish that tablets are adequately protected from moisture during (b) (4) storage in the primary container closure system. Moreover, the open bottle stability study under accelerated conditions resulted in a considerable drop in tablet hardness after just a month. As the cause of the drop in hardness was unclear, there was a concern that a critical drop in tablet hardness may not be detected and could result in product failure.

Based on the unresolved issues (i.e. PMC-1) pertaining to (b) (4) and hardness testing and the unresolved (b) (4) issues (i.e. lack of a (b) (4) study and established product failure conditions), **the FDA does not accept the proposed (b) (4) month expiry** for the drug product when stored (b) (4) Based on the product developmental studies and the primary and supportive stability data, the drug product will be granted an **18M shelf-life** when stored in the commercial container closure system under USP CRT.

The application is recommended for approval from the drug product perspective.

Process

The drug product is manufactured, packaged and release tested by Patheon of Ontario, Canada at a commercial scale of (b) (4) kg for 100 mg tablets and (b) (4) kg for 150 mg tablets.

(b) (4)

The proposed process parameters and in-process controls were described in sufficient detail and justified. The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters. The application is recommended for approval from a manufacturing process perspective.

The application is recommended for approval from the process perspective.

Biopharmaceutics

Although fostamatinib disodium hexahydrate is a prodrug, it is treated as a BCS Class IV molecule for development purposes. The acceptability of the proposed dissolution

method and acceptance criterion for the routine quality control (QC) testing of the proposed drug product at batch release and on stability was assessed. The dissolution method included a USP Apparatus II (Paddle) at 75 rpm in 900 mL of 0.025M Sodium phosphate buffer, pH 7.4. The proposed dissolution acceptance criterion is Q= (b)(4)% in 30 minute. The proposed in-vitro dissolution test is adequate for quality control. Selection of the dissolution conditions is adequately justified and the proposed dissolution acceptance criterion is adequate for the quality control of the drug product. Accordingly, this application is recommended for approval from a biopharmaceuticals perspective.

Facilities

DRUG SUBSTANCE:

Drug substance, fostamatinib disodium hexahydrate, is manufactured by (b) (4) . This site was responsible for drug substance manufacturing, packaging, release and stability testing. Based on the initial risk assessment, this site was determined to be low facility, process and product risks. There was no pre-approval inspection (PAI) recommended for this site as the facility was last inspected in (b) (4) for profile (b) (4) Accordingly, the facilities reviewer recommends this site for approval under this application for the functions listed in the application.

(b) (4) is included as a Control Testing Laboratories (CTL) for the drug substance. This site will perform NMR testing of the drug substance. The site was found to be within compliance standards and has an acceptable inspectional history and as such no PAI was requested. This site has demonstrated that it has the ability to perform the functions outlined in this NDA. According, the site was approved for the aforementioned function based on its satisfactory inspection history and a current acceptable cGMP compliance status.

DRUG PRODUCT:

Drug product, Tavalisse (fostamatinib) tablet, is manufactured, packaged, release and stability tested by Patheon of Ontario Canada (FEI 3003516812). Although the overall risk assessment of this site was considered "medium" risk by virtue of the drug substance being designated as a new molecule entity (NME) the process risk and facility risk components were considered "low". This facility was inspected in December 2016 for profile TCM and was classified NAI . The inspection covered the Quality, Production, Materials, Facilities and Equipment, and Laboratory Control systems, with limited coverage given to the Packaging and Labeling system. At the conclusion of the inspection, a no FDA-483 was issued and the facilities reviewer and recommended the facility for approval for the functions listed in the application.

Rigel Pharmaceuticals (FEI 3004865166) is included as a Control Testing Laboratories (CTL) for the drug product. This site will perform release and stability monitoring of the drug product. The initial risk assessment determined high facility (due to no previous GMP inspection history), low process, and medium product (due to NME

designation) risks. Thuis the overall initial facility risk assessment was deemed high. This facility was inspected in December 2017 and was classified NAI. According, the site was approved for the aforementioned functions by the primary facilities reviewer.

Environmental Assessment

The applicant requested a categorical exclusion from the requirement for an environmental assessment under 21 CFR 25.15(d) and 21 CFR 25.31(b) based on the calculation of the expected introduction concentration (EIC) value for fostamatinib disodium into the aquatic environment. The EIC was determined to be (b) (4) ppb.

The request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

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

Anamitro

NDA 209299

Tavalisse (fostamatinib) tablets
100 mg and 150 mg

Rigel Pharmaceuticals, Inc.

William M. Adams
Review Branch II
Division of New Drug Products I
Office of New Drug Products

For the Division of Hematology Products
Office of Hematology and Oncology Products

LABELING

R Regional Information
1.14 Labeling

Proposed are 30- and 60-count physician sample and 60-count commercial presentations in HDPE bottles for both the 100mg and 150mg tablet strengths. Carton labels are not included in the NDA; accepted by DMEPA.

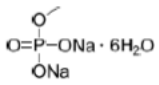
Label and Labeling submissions are as follows:

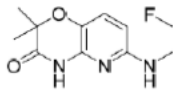
* *Amendment SN001* (dated 04/17/17) includes draft Package Insert and Immediate Container (bottle) labels for all 6 presentations.
* *Amendment SN010* (dated 07/19/17) includes revised Package Insert and 30-count 100mg Bottle label for the physician sample presentation.
* *Amendment SN025* (dated 12/12/17) includes revised Package Insert and 60-count, 100mg/150mg Bottle labels for the commercial presentation (but not the physician sample presentation).

IR comments for the Bottle labels and Package Insert were sent to the applicant by email on 11/29/17, 11/30/17 and 12/04/17.

Nomenclature and Physicochemical attributes from modules 3.2.S.1 and 3.2.P.2 are:

Fostamatinib disodium hexahydrate (left) is a prodrug that converts into the pharmacologically active metabolite R940406 (R406 or RIG-C, right) *in vivo* (module 2.6.4).





USAN	fostamatinib disodium	
IUPAC Name	disodium [6-[[5-fluoro-2-(3,4,5-trimethoxyanilino)pyrimidin-4-yl]amino]-2,2-dimethyl-3-oxo-pyrido[3,2-b][1,4]oxazin-4-yl]methyl phosphate hexahydrate	
Company Codes	R935788, R788, RIG-2-01, RIG-G-201, RIG-G	
Appearance	white to off-white powder	
	Fostamatinib Disodium	***R940406***
Molecular Formula	$C_{23}H_{24}FN_6Na_2O_9P*6H_2O$	$C_{22}H_{23}FN_6O_5$ ($CHNa_2O_4P*6H_2O$)
Molecular Weight	732.52 amu	470.46 amu (262.07 amu freebase)
Solubility at 37±2°C (mg/mL)		
simulated intestinal fluid, pH 6.8	10.9	<0.0001
water	9.4 (pH 9.3)	<0.0001
MeOH	42.5	---

Reviewer's Assessment:

Acceptable

Amendment SN013

Comment 1. Regarding the proposed labels and labeling, neither the proposed stability protocols nor the submitted stability studies are adequate to support approval of this application with the proposed storage and handling statement, '(b) (4)'. We

recommend that you revise this statement to use the USP definition for controlled room temperature and provide additional stability data to support the temperature range in this statement.

Response 1

Rigel disagrees with the Agency's premise that "neither the proposed stability protocols nor the submitted stability studies are adequate to support approval of this application with the proposed storage and handling statement". Refer to the response 9a for stability information.

Based on FDA's request, Rigel commits to revise the storage and handling statement on the proposed labels and labeling to meet the USP definition for controlled room temperature: "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)".

Evaluation

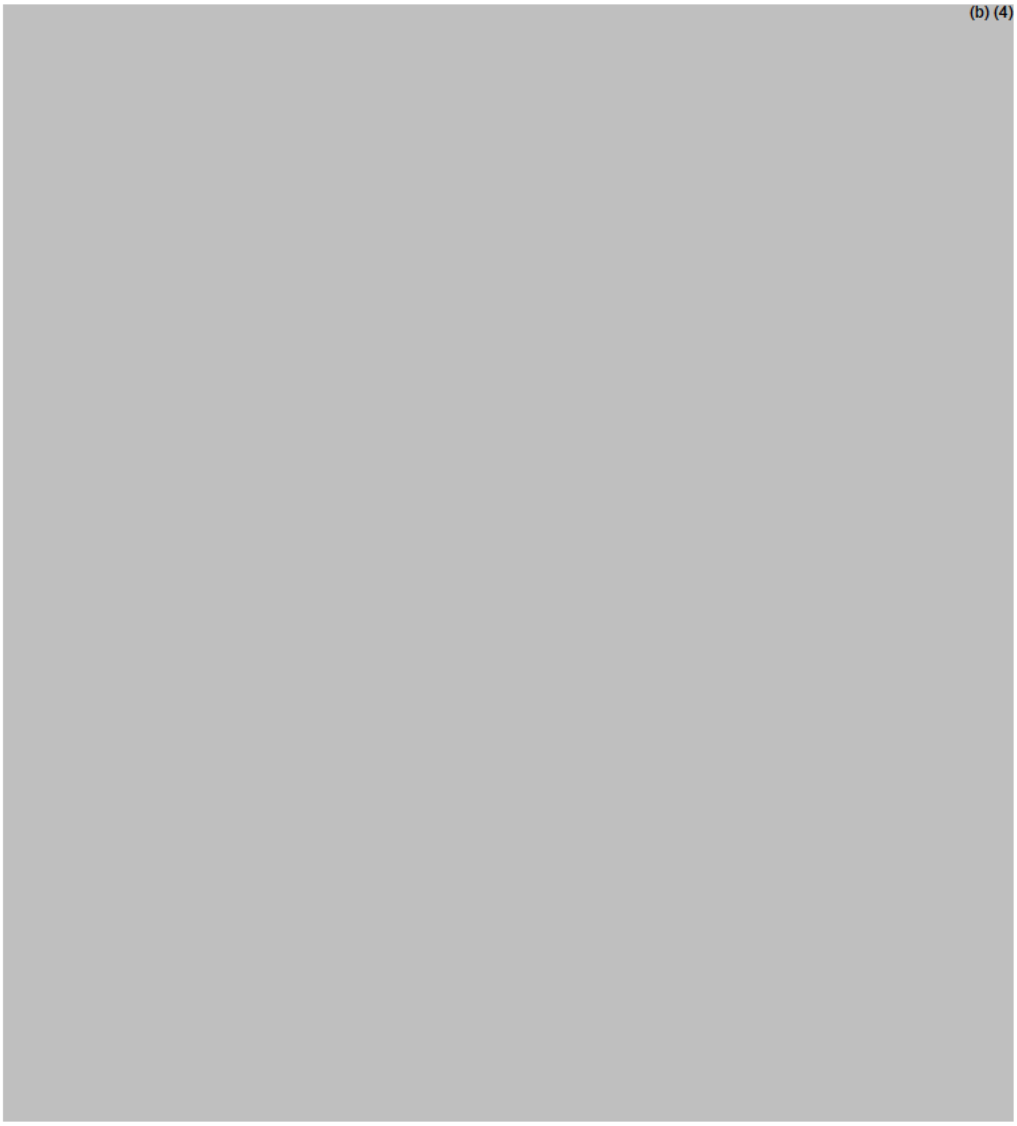
Responses 1 and 9a: Not Acceptable: Package insert in SN010 (07/19/17) does not have the revised storage statement. With the revised label storage statement, the stability protocol should be revised to reflect in-use conditions, ICH LT, and a formal in-use study should be performed to confirm that the commercial and physician sample packages offer adequate protection. The existing studies represent tablets stored in a tight container with a desiccant at elevated temperature which assures that a gradient of residual moisture from the tablets into the desiccant. At 25ºC, this gradient will not be as strong, thus may be reversed over time. Noted that the API is not heat sensitive (forced degradation studies) and the excipients are known to be reasonably stable at (b)(4)ºC, but are labeled as store at room temperature.

IMMEDIATE CONTAINER LABELS

Amendment SN001

100mg Presentation Labels

150mg Presentation Labels



Reviewer's Assessment: Not Acceptable

Each item of CFR required information is addressed in each draft label. Presentations are differentiated by color for strength and presence of the physician sample designation under the strength; all other information is identical in location and type size. Safety warnings, contents, dosing, lot#/exp.date, NDC, drug name/strength, tablet count, manufactured by/for, bar code and revision date information is correct and acceptable. Color coding is addressed by DMEPA.

The proposed label storage statement is not supported by the information in module 3.2.P.8. Revise the statement to 'store at controlled room temperature (20°C to 25°C), excursions to 30°C permitted.' Light protection is not mandated. 'Do not remove desiccants' statement is provided to address the need for moisture protection.

Amendment SN010

150mg Physician Sample Presentation Label

Reviewer's Assessment: Not Acceptable

This draft label has the same information and format as in the amendment SN001 labels; the storage statement has not been revised.

Amendment SN025

100mg Commercial Presentation Label

150mg Commercial Presentation Label

Reviewer's Assessment: Not Acceptable

Draft labels for the commercial 100mg and 150mg strength presentations are provided, but the physician sample presentations are not. Presume that the physician sample labels include the same information and format, thus the comments on the commercial presentation will apply equally to the physician sample presentations.

The format has been revised, but CFR required information is addressed, except as noted below.

** The location of the lot#/expiry date is not indicated; present on the SN001 and SN010 labels. This will be addressed in a memo by DMEPA.

** The temperature range for the storage condition has been revised to use the DMEPA recommended range, however the ºF/ºC sequence should be revised from '68ºF to 77ºF (20ºC to 25ºC)" to "20ºC to 25ºC (68ºF to 77ºF)". Noted that the "excursion to 30ºC (86ºF)" statement is not included. The sequence and range should be the same in the Bottle labels, the Package Insert and the Patient Information leaflet; see comments below.

CARTON LABELS: None provided

PACKAGE INSERT

Amendment SN025

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TAVALISSE™ safely and effectively. See full prescribing information for TAVALISSE.

TAVALISSE™ (fostamatinib) 100 mg and 150 mg tablets, for oral use.

Initial U.S. Approval: XXXX

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 100 mg, 150 mg (3)

FULL PRESCRIBING INFORMATION

3 DOSAGE FORMS AND STRENGTHS

TAVALISSE is available as:

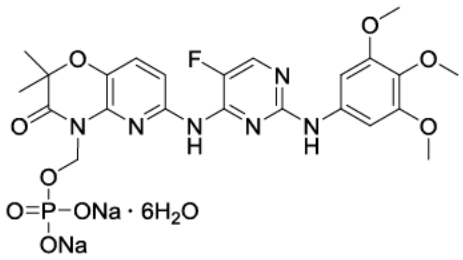
- 100 mg tablet: orange, film-coated, round, biconvex tablets debossed with "100" on one side and "R" on the reverse side.
- 150 mg tablet: orange, film-coated, oval, biconvex tablets debossed with "150" on one side and "R" on the reverse side.

11. DESCRIPTION

TAVALISSE is a tyrosine inhibitor. TAVALISSE is formulated with the disodium salt of fostamatinib, a phosphate prodrug that converts to the pharmacologically active metabolite, R406, in vivo.

The chemical name for fostamatinib disodium is disodium (6-[[5-fluoro-2-(3,4,5-trimethoxyanilino) pyrimidin-4-yl]amino]-2,2-dimethyl-3-oxo-pyrido[3,2-b][1,4]oxazin-4-yl)methyl phosphate hexahydrate.

Fostamatinib disodium has the molecular formula $C_{23}H_{24}FN_6Na_2O_9P \cdot 6H_2O$, and the molecular weight is 732.52. The structural formula is:



Fostamatinib disodium is a white to off-white powder that is practically insoluble in pH 1.2 aqueous buffer, slightly soluble in water, and soluble in methanol.

(b) (4)

The inactive ingredients of the tablet core are mannitol, sodium bicarbonate, sodium starch glycolate, povidone, and magnesium stearate and the inactive ingredients of the coating are polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide yellow, and iron oxide red.

16. HOW SUPPLIED/STORAGE AND HANDLING

TAVALISSE 100 mg tablets are round, biconvex, orange, film-coated tablets debossed with "100" on one side and "R" on the reverse side and available in bottles of 60: NDC 71332-001-01

TAVALISSE 150 mg tablets are oval, biconvex, orange, film-coated tablets debossed with "150" on one side and "R" on the reverse side and available in bottles of 60: NDC 71332-002-01.

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30oC (59°F to 86°F) [see USP Controlled Room Temperature]. Do not remove desiccants.

Reviewer's Assessment:

Header, Section 3 and Section 11 are Acceptable for CMC information.

** Section 16: Revise the storage statement to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to ~~between 15°C and~~ 30°C (59°F to 86°F) [see ~~USP~~ Controlled Room Temperature]. Do not remove desiccants." There are no stability studies to support a storage at low temperature. This storage statement should be used for each of the Bottle Presentation labels and the Patient Information Leaflet. The rest of the information in this section is Acceptable.

PATIENT INFORMATION

TAVALISSE™ (TAV-a-leese)
(fostamatinib)
Tablets, for oral use

How should I store TAVALISSE tablets?

* Store TAVALISSE at room temperature, between 20oC to 25oC (68oF and 77oF).

(b) (4).

* Do not remove the 2 desiccant (b) (4) that help to keep your medicine dry.

Keep TAVALISSE and all medicines out of the reach of children.

What are the ingredients in TAVALISSE?
Active ingredient: fostamatinib disodium
Inactive ingredients: The tablet core contains mannitol, sodium bicarbonate, sodium starch glycolate, povidone, and magnesium stearate. The coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide yellow, and iron oxide red.

Manufactured for:
Rigel Pharmaceuticals, Inc.
1180 Veterans Blvd.
South San Francisco, CA 94080 USA

Manufactured by:
Patheon Whitby
111 Consumers Drive
Whitby, Ontario L1N 525 Canada

Reviewer's Assessment:

Header: Acceptable
How should I store Tavalisse tablet?: The revised statement is Acceptable.
What are the ingredients in Tavalisse?: Information is correct.
Manufactured for and Manufactured b: Information is correct.

List of Deficiencies:
Bottle Labels

The location of the lot#/expiry date is not indicated; present on the SN001 and SN010 labels. This will be addressed in a memo by DMEPA.

The storage statement should be revised from "68ºF to 77ºF (20ºC to 25ºC)" to "20ºC to 25ºC (68ºF to 77ºF)" to reflect the nomenclature sequence used in the Package Insert.

Package Insert

In section 16, revise the storage statement to "Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted to ~~between 15ºC and~~ 30ºC (59ºF to 86ºF) [see ~~USP~~ Controlled Room Temperature]. Do not remove desiccants." There are no stability studies to support a storage at low temperature.

Primary Labeling Reviewer Name and Date:
William Adams, January 25, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Anamitro Banerjee January 24, 2018

Secondary Comment: The excursion temperature of "15°C ~~and~~ to 30°C (59°F to 86°F)" should stay as per USP statement. I do not see any added risk to the product during an excursion to 5°C lower than the storage temperature.

William Adams

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Anamitro Banerjee

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BIOPHARMACEUTICS	
Application No./Submission Date	NDA 209299-ORIG-1 Dated 04/17/2017
Clinical Division	DHP
Applicant Name	Rigel Pharmaceuticals, Inc.
Product Name	Fostamatinib Disodium
Dosage Form/Strength	Tablets, 100 mg and 150 mg
Route of Administration	Oral
Primary Reviewer	Kaushalkumar Dave, Ph.D.
Secondary Reviewer	Okpo Eradiri, Ph.D.
RECOMMENDATION	**ADEQUATE**

EXECUTIVE SUMMARY

Submission: The Applicant is seeking approval for NDA 209299 for Fostamatinib Tablets, 100 mg and 150 mg, via 505(b)(1) route for the treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

Review: The Biopharmaceutics review for this submission is focused on the evaluation of the data supporting approval of the proposed dissolution method and acceptance criterion for Fostamatinib Tablets.

Assessment: The proposed in vitro dissolution test is adequate for quality control. The selection of the dissolution conditions (e.g., medium, rotation speed, etc.) is adequately justified. The proposed dissolution acceptance criterion is adequate for the quality control of Fostamatinib Tablets, 100 mg and 150 mg.

The analytical method used in the quantifying fostamatinib in the dissolution samples and its validation will be evaluated by the CMC-drug product Reviewer.

From a Biopharmaceutics perspective, NDA 209299 for Fostamatinib Tablets, 100 mg and 150 mg, is recommended for **APPROVAL**.

The approved dissolution method and the associated acceptance criterion agreed to with the Applicant are summarized in the table below:

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	75 rpm
Volume	900 ml
Medium	0.025M Sodium Phosphate Buffer, pH 7.4

Temperature	37.0 ± 0.5°C
Acceptance Criteria	Q = (b)(4)% at 30 Minutes

BIOPHARMACEUTICS ASSSESSMENT

1. LIST OF SUBMISSIONS REVIEWED

eCTD sequence #	Received date	Document
0001	04/17/2017	Original NDA Submission
0021	11/07/2017	Quality/Response to Information Request

2. DRUG PRODUCT

The proposed drug product, Fostamatinib Tablets, 100 mg and 150 mg, is a round (100 mg strength) or oval shaped (150 mg strength) immediate release (IR) orange film coated (OFC) tablet (b) (4) Fostamatinib disodium hexahydrate (abbreviated as fostamatinib disodium) is the drug substance used in preparation of Fostamatinib Tablets, 100 mg and 150 mg. Fostamatinib disodium is a phosphate prodrug which is hydrolyzed in vivo by alkaline phosphatases to its active metabolite named by the Applicant as R940406. The two strengths of the proposed product are prepared from the (b) (4), and differ only in the size, shape, weight, and debossing of the tablets (100 mg tablets debossed with 'R' on one side and '100' on the other side; 150 mg tablets debossed with 'R' and one side and '150' on the other side). Composition of the proposed product is provided in Table 1.

Table 1: Qualitative and quantitative composition of the proposed drug product, Fostamatinib Tablets, 100 mg and 150 mg

Component	Tablet Quantity (mg) (per 100 mg tablet)	Tablet Quantity (mg) (per 150 mg tablet)	Function	Quality Standard
Core Tablet				
Fostamatinib disodium	126.2[a]	189.3[b]	Drug substance	Rigel Specification
Mannitol	(b) (4)			USP
Sodium bicarbonate				USP
Sodium starch glycolate				USP/NF
Povidone				USP
Magnesium stearate				USP/NF
(b) (4)				USP
(b) (4)				
Tablet Coating[d]				
(b) (4)				
Total weight (mg)	343	515		

a 126.2 mg of fostamatinib disodium hexahydrate is equivalent to 100 mg of fostamatinib (b) (4)

b 189.3 mg of fostamatinib disodium hexahydrate is equivalent to 150 mg of fostamatinib (b) (4)

(b) (4).

(b) (4)

Development history of the proposed drug product

At the beginning of the clinical evaluation, the Applicant studied R940406 as the active drug substance. As R940406 had limited aqueous solubility, the Applicant synthesized its prodrug. The Applicant stated that in comparison to R940406, the phosphate prodrug, fostamatinib disodium, offered increased solubility and higher absorption of R940406 from an immediate release formulation. Initial (Phase I) clinical studies were performed with a (b) (4) oral solution of the active metabolite (R940406), and an oral suspension of the prodrug (fostamatinib disodium) in orange juice. All subsequent studies were performed with tablet formulations of fostamatinib disodium, the prodrug of R940406. First, the Applicant developed 25 mg white (b) (4) tablets manufactured by (b) (4) which were administered at 75 mg, 100 mg, 125 mg, 150 mg and 175 twice daily for a phase 2 study, and at 100 mg, 200 mg and 300 mg single dose for a dose proportionality study. Since the dosing required multiple (b) (4) tablets at each administration, the Applicant developed 50 mg and 100 mg blue film coated (BFC) tablets which were used for the subsequent phase 2 studies. Composition of BFC tablets is provided in Table 2. While 50 mg and 100 mg BFC tablets had same (b) (4), the 100 mg BFC tablets exhibited (b) (4) phenomenon, and hence dissolution issues in (b) (4) Due to this issue, in all phase 3 clinical studies, 50 mg BFC tablets were used. The Applicant argued that (b) (4) . The Applicant reformulated the product and developed orange film coated tablets with (b) (4) coating (OFC-I tablets) (b) (4) Phase 3 studies for ITP were performed with 100 mg and 150 mg OFC-I tablets administered twice daily. The proposed to-be-marketed formulation (OFC) is different than the pivotal clinical study formulation in terms of the (b) (4). The tablet core for OFC-I and OFC tablets is the same (Table 1); however, the tablets used in the pivotal clinical studies (OFC-I tablets) had an (b) (4) based coating (b) (4) while the proposed commercial formulation (OFC tablets) has a (b) (4) based coating (b) (4) Compositions of (b) (4) based coting) and (b) (4) based coating) are provided in Table 3 and Table 4 respectively. The Applicant stated that there were not differences or changes in terms of formulation or manufacturing method, except the change of non-functional, cosmetic color coating, between the OFC-I tablets and OFC tablets. An in vivo BE study was performed to compare the pre-change "OFC-I tablet(s)" and post-change "OFC tablet(s)". The BE studies/results will be reviewed by Office of Clinical Pharmacology.

Table 2: Composition of Fostamatinib 50 mg and 100 mg Blue Film Coated (BFC) Tablets

Component	mg per 50 mg tablet	% w/w for 50 mg tablet	mg per 100 mg tablet	% w/w for 100 mg tablet	Standard
Core Tablet					
Fostamatinib disodium[a]	(b) (4)	(b) (4)	126.2	(b) (4)	Rigel
				(b) (4)	NF
					NF
Povidone				(b) (4)	USP
Sodium starch glycolate					USP/NF
Magnesium stearate					USP/NF
(b) (4)					USP
Total					
Tablet Coating					
				(b) (4)	Manufacturer specification
					USP
Total	(b) (4)		520.0		

[a] (b) (4) 126.2 mg of fostamatinib disodium hexahydrate is equivalent to 100 mg of fostamatinib (b) (4)

(b) (4)

(b) (4)

Table 3: (b) (4) Based Film Coat Composition

Components	Quantity, % w/w		Function	Standards
	For 100 mg tablet	For 150 mg tablet		
(b) (4)			(b) (4)	USP
Titanium dioxide				USP
Polyethylene glycol (b) (4)				NF
Iron oxide yellow				NF
Iron oxide red				NF
(b) (4)				USP
				(b) (4)

Table 4: (b) (4) Based Film Coat Composition

Components	Quantity, % w/w		Function	Standards
	For 100 mg tablet	For 150 mg tablet		
Polyvinyl alcohol			(b) (4)	USP
Titanium dioxide				USP
Polyethylene glycol 3350				NF
Talc				USP
Iron oxide yellow				NF
Iron oxide red				NF
(b) (4)				USP
				(b) (4)

3. BCS DESIGNATION

The drug substance in the proposed product is a phosphate prodrug of its active metabolite, R940406. The Applicant states that "fostamatinib undergoes rapid conversion to R940406 in the gastrointestinal tract via hydrolysis, which is catalyzed by alkaline phosphatases, followed by the absorption of R940406".

The Applicant did not request BCS designation for the drug substance or the proposed drug product; however, the Applicant stated that the drug substance was treated as a BCS Class IV compound during product development for risk management.

Solubility

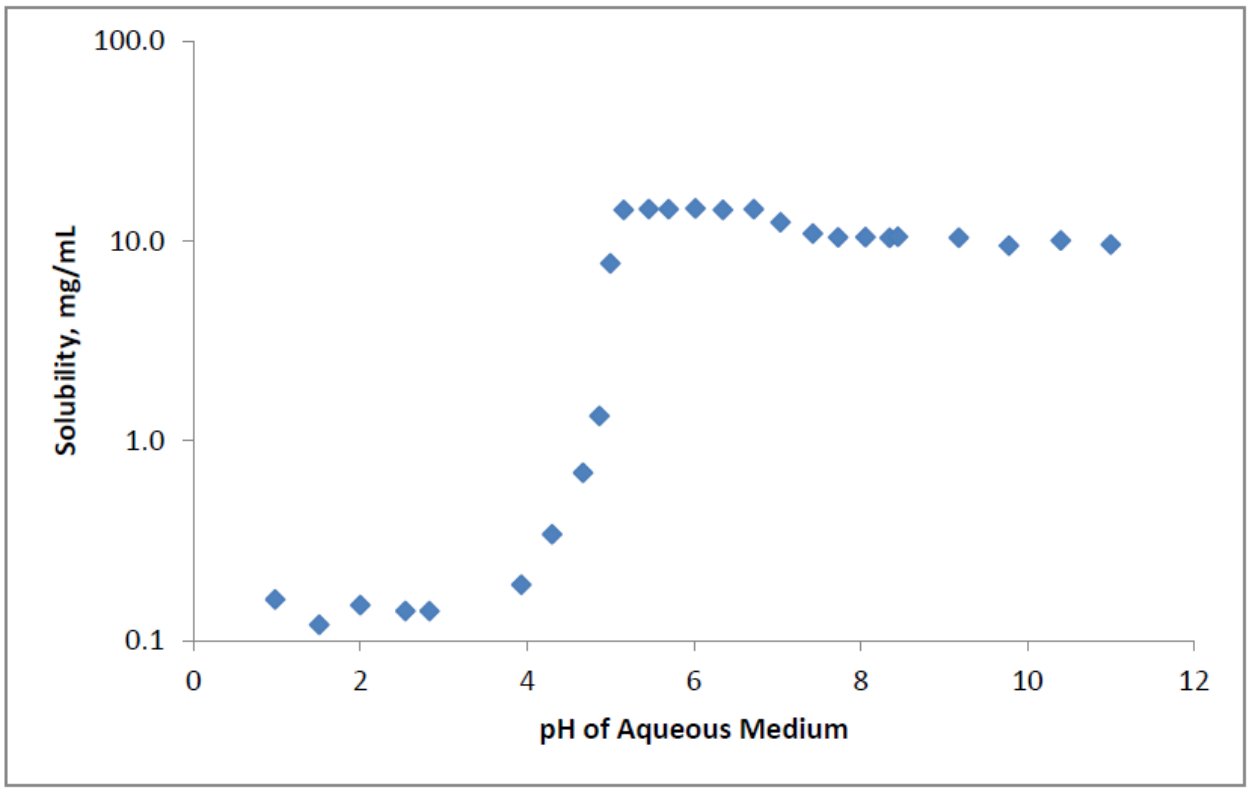
The Applicant performed solubility studies for fostamatinib disodium as well as for R940406 in various aqueous media including water and 0.025 M sodium phosphate buffer (pH 7.4) at 20±5°C, and simulated gastric fluid (pH 1.2), acetate buffer (pH 4.5), simulated intestinal fluid (pH 6.8) and water at 37±2°C (Table 5). The provided solubility study data indicate that although the prodrug shows higher solubility of the drug substance in comparison to the active metabolite in the studied media by several-fold, the prodrug (as well as the active metabolite) exhibits poor solubility as per the BCS.

Table 5: Solubility and other physicochemical properties of fostamatinib disodium and R940406

Property	Value for Fostamatinib Disodium	Value for R940406
Molecular formula	$C_{23}H_{24}FN_6Na_2O_9P.6H_2O$	$C_{22}H_{23}FN_6O_5$
Molecular weight	732.52	470.46
pKa	1.7 (calculated), 4.2, 6.5	3.8, 11.6
LogD in octanol/water	-0.6 at pH 1	4.0 at pH 6.5
Solubility in organic solvents/water at 20±5°C , mg/mL		
Ethanol	1.5	0.9
Dimethyl sulfoxide	84.6	39
Water	10.0 (pH 8.6)	0.015 (pH 1.5)
0.025 M sodium phosphate buffer (pH 7.4)	4.5	<0.0001
Solubility in USP buffer at 37±2°C, mg/mL		
Simulated gastric fluid, pH 1.2	0.095	0.031
pH 4.5 acetate buffer	0.30	<0.0001
Simulated intestinal fluid, pH 6.8	10.9	<0.0001
Water	9.4 (pH 9.3)	<0.0001

Fostamatinib disodium has three pKa's, 1.7, 4.2 and 6.5. The compound shows several-fold higher solubility in aqueous medium above pH 4.5 where it exists in anionic form (Figure 1).

Figure 1: pH-solubility profile of fostamatinib disodium



Permeability

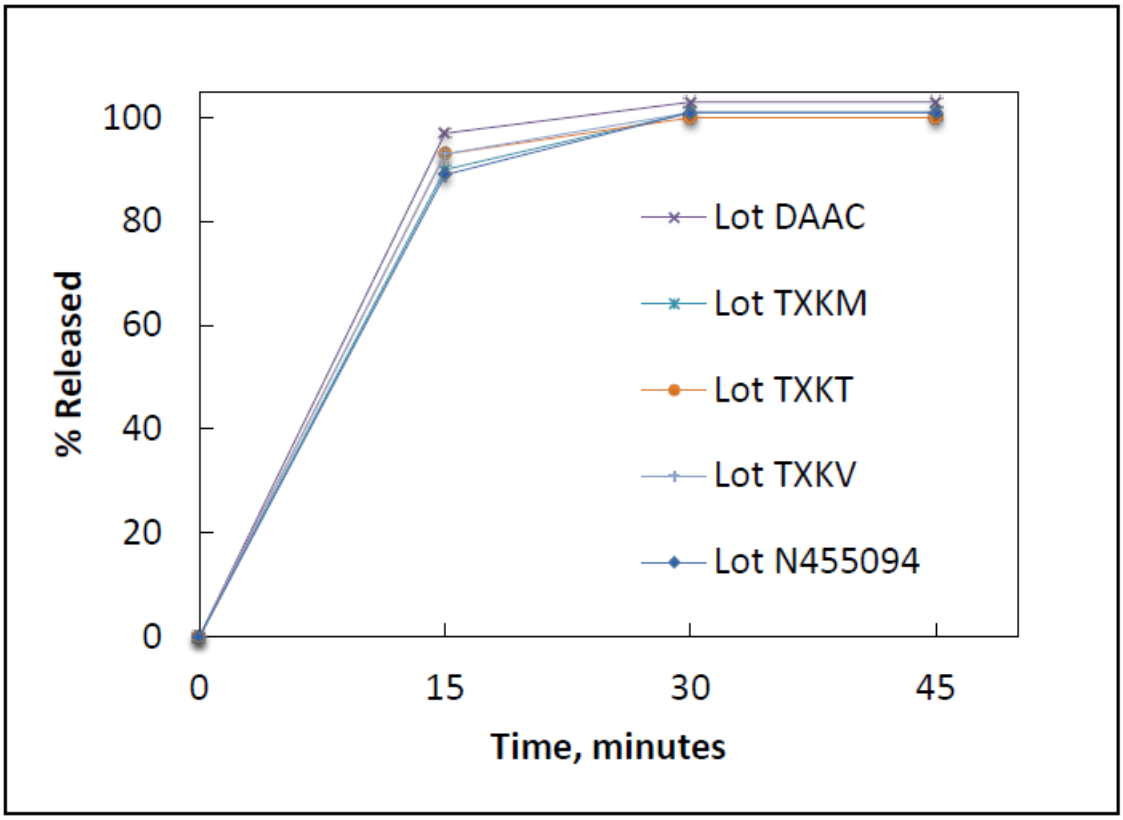
Fostamatinib is a prodrug which undergoes rapid hydrolysis to R940406 in the gastrointestinal tract. The Applicant states that the permeability of R940406 is medium to high in Caco-2 cell layers compared to reference compounds with known permeability properties; however, no permeability data were provided.

BCS designation of the proposed drug was not evaluated under this review.

4. DISSOLUTION INFORMATION

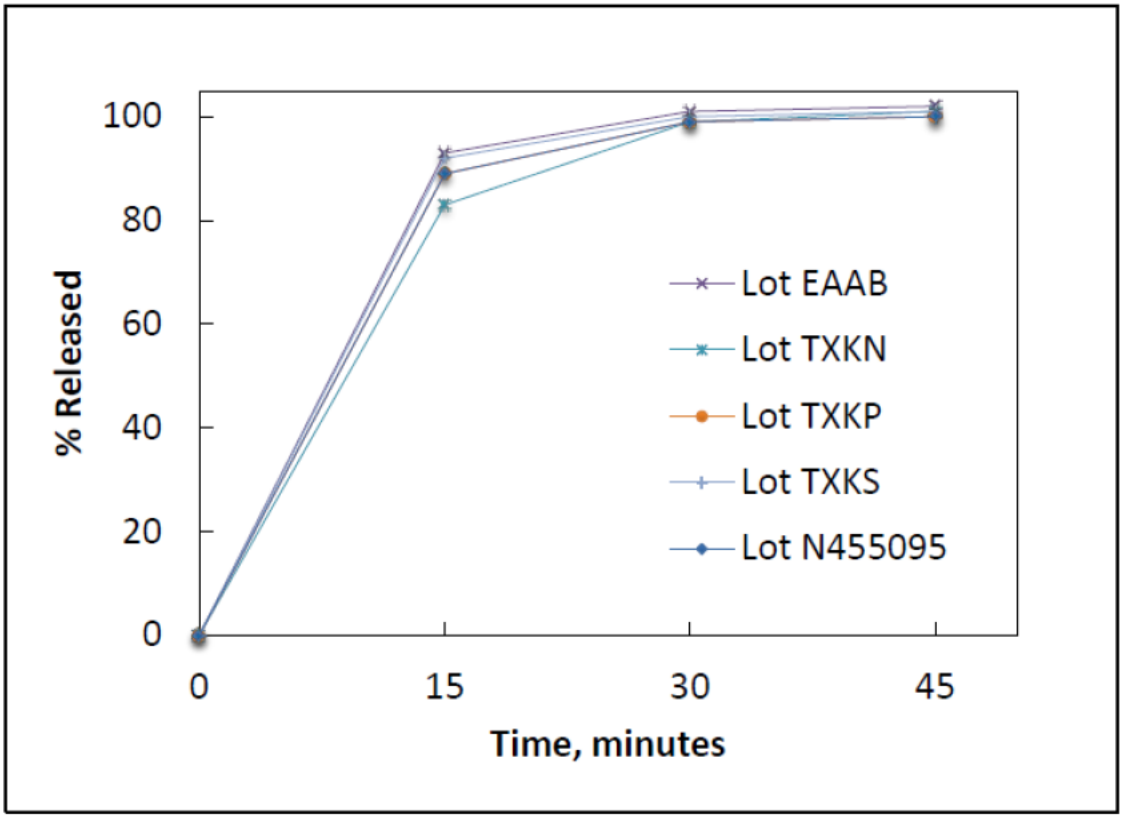
As shown in Figures 2 and 3, The Applicant provided dissolution profiles of three commercial batches for each of the two strengths of the proposed product with the proposed dissolution method. Also, the Applicant provided dissolution profiles for OFC-I tablets (with (b) (4) coating unlike the proposed commercial product which has (b) (4) coating) manufactured at AstraZeneca and (b) (4) The provided dissolution data show that the proposed product shows rapid dissolution in the studied conditions and that no difference in dissolution between the studied batched was observed.

Figure 2: Dissolution Profile of Fostamatinib 100 mg Tablets in 0.025 M Sodium Phosphate Buffer, pH 7.4



Lot DAAC (OFC-I tablets) is from AstraZeneca, lot N455094 (OFC-I tablets) from (b) (4) and lots TXKM, TXKT TXKV (commercial formulation) from Patheon.

Figure 3: Dissolution Profile of Fostamatinib 150 mg Tablets in 0.025 M Sodium Phosphate Buffer, pH 7.4



Lot EAAB (OFC-I tablets) is from AstraZeneca, lot N455095 (OFC-I tablets) from (b) (4) and lots TXKN, TXKP, TXKS (commercial formulation) from Patheon.

Dissolution Method and Acceptance Criterion

The proposed dissolution method and acceptance criteria are summarized in Table 6.

Table 6. Dissolution method and acceptance criteria proposed by the Applicant

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	75 rpm
Volume	900 ml
Medium	0.025M Sodium Phosphate Buffer, pH 7.4
Temperature	37.0 ± 0.5°C
Acceptance Criteria	Q = (b) (4)% at 30 Minutes

4.1 Selection of the proposed dissolution method

(b) (4)

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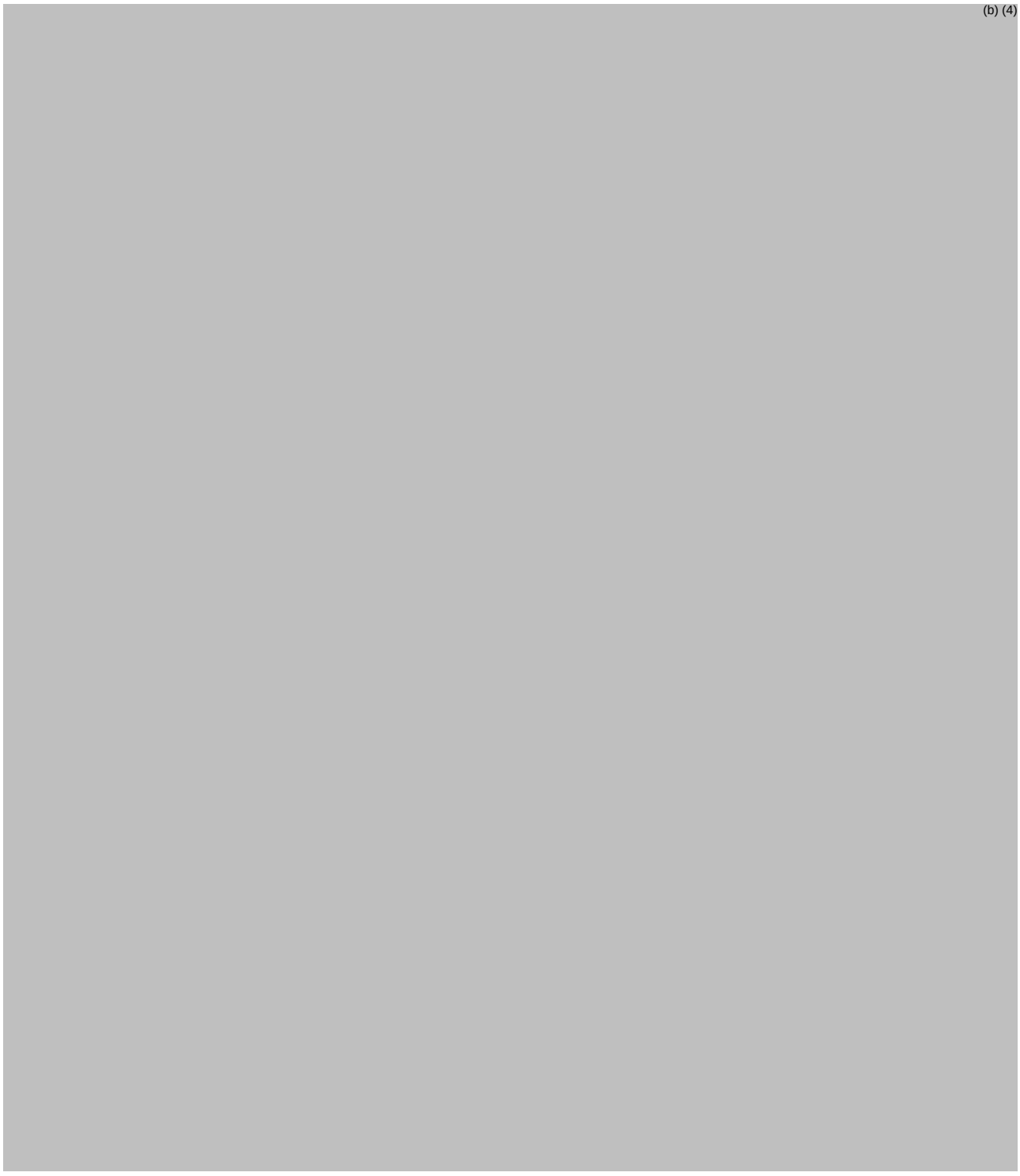

On the basis of above studies, the Applicant proposed USP Apparatus 2 with 900 mL of pH 7.4 0.025M sodium phosphate buffer and 75 rpm as the dissolution method for the proposed product.

The selection of the dissolution method is appropriately justified and supported by the data provided by the Applicant. Therefore, the proposed dissolution method is **acceptable**.

4.2. Dissolution Acceptance Criterion

Dissolution studies for the Clinical (Pivotal) and the Registration/Exhibit Batches

The Applicant's proposed dissolution acceptance criterion is 'Not less than (b)(4)% (Q) at 30 minutes'. In the original submission, the applicant did not provide dissolution data, using the proposed dissolution method, for the pivotal clinical study batch and for the exhibit/registration batches. Via an Information Request (IR) sent on 11/02/2017, the Applicant was requested to provide this information. In a response on 11/06/2017, the Applicant provided the requested dissolution data for the pivotal-clinical and the exhibit study batches for Fostamatinib Tablets, 100 mg and 150 mg strengths. Below tables summarize the provided dissolution data.

Table 7: Summary of Pivotal Clinical and Exhibit Batches Dissolution Profile Data (% Release) for Fostamatinib Tablets in pH7.4 Phosphate Buffer

Batch Use	Drug Product	Batch#
Pivotal Clinical (C788-047, C788-048)	Fostamatinib 100 mg OFC-I Tablets	DAAC
	Fostamatinib 150 mg OFC-I Tablets	EAAB
Clinical (C788-049)	Fostamatinib 100 mg OFC-I Tablets	N455094
	Fostamatinib 150 mg OFC-I Tablets	N455095
Exhibit (Registration)	Fostamatinib 100 mg OFC Tablets	TXKM
		TXKT
		TXKV
	Fostamatinib 150 mg OFC Tablets	TXKN
		TXKP
		TXKS

OFC = orange film-coated

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The provided dissolution data indicate that the proposed dissolution acceptance criterion of 'Not less than (b) (4)% (Q) at 30 minutes' is appropriately selected and adequate for quality control of the proposed product. Therefore, the proposed dissolution acceptance criterion is acceptable.

5. REVIEWER'S OVERALL CONCLUSIONS

- The Applicant's in vitro dissolution test method development and validation are acceptable.
- The proposed acceptance criterion of 'Not less than (b) (4)% (Q) at 30 minutes' is adequate for the quality control of Fostamatinib Tablets, 100 mg and 150 mg.

6. RECOMMENDATION

From a Biopharmaceutics perspective, NDA 209299 for Fostamatinib Tablets, 100 mg and 150 mg, is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date:

Kaushalkumar Dave, Ph.D., 11/15/2017
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Reviewer Name and Date:

Okpo Eradiri, Ph.D., 11/20/2017
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Kaushalkumar Dave

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 209299 Tavalisse (fostamatinib) Tablets 100 and 150 mg

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability At release and stability)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Physical Stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Content Uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Justification is provided, refer to OPF review.
Dissolution – BCS Class II & IV	• Formulation • Raw Materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval, refer to BioPharm review.

Sherita McLamore

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Sherita McLamore

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