

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207997Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Recommended for APPROVAL from CMC Perspective

**NDA 207997
Review 1 ADDENDUM**

Drug Name/Dosage Form	Rydapt (midostaurin) Soft Capsules
Strength	25 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novartis Pharmaceutical Corporation
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>Amendment (SD#81)</i>	<i>03/02/2017</i>	<i>Drug Product</i>

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gene Holbert	CDER/OPQ/ONDP/DNDAPI
Drug Product	Nina Ni	CDER/OPQ/ONDP/DNDPI/NDPBII
Process	Zhaoyang Meng	CDER/OPQ/OPF/DPAI/PABII
Microbiology	Zhaoyang Meng	CDER/OPQ/OPF/DPAI/PABII
Facility	Steve Hertz	CDER/OPQ/OPF/DIA/IABI
Biopharmaceutics	Ta-Chen Wu	CDER/OPQ/ONDP/DB/BBI
Regulatory Business Process Manager	Rabiya Laiq	CDER/OPQ/OPRO/B1
Application Technical Lead	Anamitro Banerjee	CDER/OPQ/ONDP/DNDPI/NDPBII
Laboratory (OTR)	-	-
ORA Lead	-	-
Environmental Analysis (EA)	N/A	

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for APPROVAL from the CMC point of view.

II. Summary of Quality Assessments

On March 02, 2017, the applicant provided additional data to an IR request (dated December 13, 2016) for extractables and leachables data for the proposed (b) (4) [redacted]. The applicant's original response dated December 20, 2016 was found to be acceptable and the OPQ recommended approval of this NDA from the Quality perspective on February 06, 2017.

The additional data provided by the applicant in the March 02, 2017 amendment was reviewed by the drug product reviewer, Dr. Nina Ni on March 02, 2017 and was found to be acceptable. Her evaluation, conveyed by email is attached below.

The additional data provided in the amendment does not alter the original recommendation of APPROVAL.

Banerjee, Anamitro

From: Ni, Nina
Sent: Thursday, March 02, 2017 1:48 PM
To: Banerjee, Anamitro
Subject: FW: NDA 207997 Rydapt Midostaurin 25 mg

Importance: High
Sensitivity: Confidential

Follow Up Flag: Follow up
Flag Status: Flagged

Anamitro,

In this amendment, the applicant has provided the extractables and leachables data for the drug product packaged using the proposed commercial (b) (4) as per our IR request below:



However, in the Amendment 0059, dated 12/20/2016, the applicant has provided adequate justification to demonstrate there is no safety concern on extractable from (b) (4).

Anyhow, I just quickly reviewed this study and agreed with the conclusion provided by the applicant which is copied below:

(b) (4)

Please let me know how we handle this amendment since CMC review was already in Panorama on 02/06/2017.

Thanks,

Nina

From: Laiq, Rabiya

Sent: Thursday, March 02, 2017 12:18 PM

To: Holbert, Gene W; Ni, Nina; Meng, Zhaoyang; Wu, Ta-Chen; McLamore-Hines, Sherita; Banerjee, Anamitro

Cc: Scott, Kimberly; Hertz, Steven

Subject: FW: NDA 207997 Rydapt Midostaurin 25 mg

Importance: High

Sensitivity: Confidential

Hi Team,

Link below will take you to the submission for the extractable study.

[Application 207997 - Sequence 0084 - 0084 \(81\) 03/02/2017 Multiple Submissions /Multiple Categories/Subcategories](#)

Rabiya

Dear Rabiya –

Here's an email summary of the voice message I left for you, today.

Per our commitment in the response to FDA CMC information request (dated 13 December, 2016) which was submitted by Novartis on 20 December, 2016, Novartis has conducted extractables testing on (b) (4) that is proposed for our commercial blister presentation. In our response, NVS committed to provide this information by the end of February, 2017. This timeline will not be possible and instead, we will submit the information via the FDA Gateway by March 3, 2017.

Please confirm receipt of this email.

Kind regards,
Beth

Elizabeth Purdy, MS, PgCert
Sr. Manager
T: 1-862-778-8490
elizabeth.purdy@novartis.com

RA GDD CMC
Novartis Pharma
One Health Plaza
Bldg 339 - 1256
East Hanover, NJ 07936
USA



Anamitro
Banerjee

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Recommendation: Recommended for APPROVAL from CMC Perspective

**NDA 207997
Review 1**

Drug Name/Dosage Form	Rydapt (midostaurin) Soft Capsules
Strength	25 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novartis Pharmaceutical Corporation
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>NDA submission (SD#2)</i>	<i>05/26/2016</i>	<i>All CMC</i>
<i>Amendment (SD#8)</i>	<i>09/28/2016</i>	<i>Facilities</i>
<i>Amendment (SD#16)</i>	<i>10/20/2016</i>	<i>Facilities</i>
<i>Amendment (SD#34)</i>	<i>11/14/2016</i>	<i>Process, Microbiology</i>
<i>Amendment (SD#48)</i>	<i>12/06/2016</i>	<i>Drug Substance</i>
<i>Amendment (SD#49)</i>	<i>12/09/2016</i>	<i>Drug Substance</i>
<i>Amendment (SD#50)</i>	<i>12/09/2016</i>	<i>Drug Product</i>
<i>Amendment (SD#52)</i>	<i>12/20/2016</i>	<i>Drug Product</i>
<i>Amendment (SD#64)</i>	<i>01/06/2017</i>	<i>Process</i>
<i>Amendment (SD#66)</i>	<i>01/13/2017</i>	<i>All CMC</i>

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gene Holbert	CDER/OPQ/ONDP/DNDAPI
Drug Product	Nina Ni	CDER/OPQ/ONDP/DNDPI/NDPBII
Process	Zhaoyang Meng	CDER/OPQ/OPF/DPAI/PABII
Microbiology	Zhaoyang Meng	CDER/OPQ/OPF/DPAI/PABII
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Application Technical Lead	Anamitro Banerjee	CDER/OPQ/ONDP/DNDPI/NDPBII
Laboratory (OTR)	-	-
ORA Lead	-	-



QUALITY ASSESSMENT



Environmental Analysis (EA)	N/A	

Appears this way on original

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	1/18/2017	Reviewed by Lindsey Saunders
	Type III <i>(if applicable)</i>			N/A	N/A	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	057120	Midostaurin PKC412 capsules

2. CONSULTS

None

Appears this way on original

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for APPROVAL from the CMC point of view.

II. Summary of Quality Assessments

A. Product Overview

NDA 207997 is submitted under section 505(b)(1) in support of the use of midostaurin (RYDAPT®) for the treatment of AML and Advanced SM. Midostaurin is an NME and is not currently marketed in the US or any foreign market. The FDA granted breakthrough therapy designation for this product for both the indications on January 29, 2016. The NDA was submitted under a rolling submission with the initial CMC section submitted on May 26, 2016. The final submission was received on August 29, 2016. Upon request by the applicant, the agency granted priority review for this application on October 28, 2016.

Proposed Indication(s) including Intended Patient Population	<i>Treatment of adult patients with:</i> <i>Newly diagnosed acute myeloid leukemia that is FLT3 mutation-positive as detected by an FDA approved test.</i> <i>Advanced systemic mastocytosis (Advanced SM)</i>
Duration of Treatment	<i>AML: 50 mg twice daily on days 8 to 21 of induction and consolidation chemotherapy, (b) (4)</i> <i>Advanced SM: 100 mg twice daily (b) (4) until unacceptable toxicity occurs.</i>
Maximum Daily Dose	<i>200 mg</i>
Alternative Methods of Administration	<i>NA</i>

B. Quality Assessment Overview

Midostaurin 25 mg capsule is an immediate release dosage form for oral administration.

Midostaurin drug substance is a new molecular entity (NME) produced by (b) (4)

The Midostaurin drug substance specification includes tests and acceptance criteria for appearance; particle size; identification; clarity and color of solution; residual solvents; water; sulfated ash; specific optical rotation; heavy metals; specific impurities, specified, unspecified and total impurities; microbiological quality; and assay.

Analytical methods are adequate for their intended use and have been validated.

Stability data supports a re-test period of (b) (4) months for Midostaurin drug substance when stored in (b) (4)

(b) (4)
Analytical testing of the drug substance is performed at Novartis, Cork, Ireland and (b) (4)

All the facilities are acceptable at this time.

The drug product is a 25 mg oblong shaped soft capsule with “PKC NVR” imprinted in red ink. The capsules are packaged in (b) (4) blisters. (b) (4)

The drug product is manufactured and tested (release) at (b) (4)

The microbial testing is performed by Novartis Pharma AG, Basel, Switzerland. The stability testing is performed by (b) (4)

The primary and secondary packaging of the drug product is done at (b) (4)

respectively. *All the facilities are acceptable at this time.*

No novel excipients or excipients of human or animal origin are used in the formulation. Carmine (b) (4) derived from insects. Apart from the API, which constitutes approximately (b) (4)% of the capsule weight, the drug product contains (b) (4)

(b) (4)

The DMF (b) (4) for (b) (4) was reviewed by Dr. Lindsey Saunders on January 18, 2018 and found to be acceptable. All the excipients were found to be acceptable.

(b) (4)

The drug product specification includes all of the critical drug product quality attributes for oral capsule except for the control of elemental impurities. Based on the risk assessment and batch data provided in the submission, it was determined that controls for elemental impurities are not needed for the drug product. The proposed specifications for the drug product were found to be acceptable. (b) (4)

The applicant will have a (b) (4) testing monograph for this drug product for common global specifications. The applicant will have a country specific addendum which will be used together with the global specifications.

Drug release from the proposed drug product exhibited rapid dissolution in vitro (i.e. >80% of Midostaurin dissolves within 15 minutes and nearly 100% at 30 – 60 minutes) in the proposed QC dissolution medium. The proposed QC dissolution method [USP Apparatus 2 (paddle) at 50 rpm, 900mL of 0.5% Polysorbate 20 (Tween 20)] and acceptance criteria [Q = (b) (4)% at 30 min for Midostaurin] for the routine QC testing of Midostaurin oral soft capsules during batch release and stability testing are both acceptable. The proposed dissolution method was shown to have discriminating power for batches with pellicle formulation upon aging and resulted in a reduction of Midostaurin release rate.

The applicant did not submit a formal request for BCS designation for the drug substance or the drug product. However, Midostaurin behaves like a BCS Class 2 drug based on its characteristics of very poor solubility in aqueous media, high permeability, high lipophilicity, and high oral absorption in humans (>90%).

Relative bioavailability of the to-be marketed and clinical trial formulations were compared and determined to be of no clinically meaningful difference. Hence comparative dissolution testing was not considered necessary.

The drug product stability data submitted in the NDA includes up to 60 months stability data for three registration batches and five supporting batches. The stability data indicate that the drug product is physically and chemically stable with no significant change when stored at 25°C/60% RH. All tested attributes are within the proposed specifications. The stability data submitted in the NDA supports the proposed **expiry dating period of 36 months for the drug product when stored at 25°C (77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).**

The applicant claimed categorical exclusion for environmental assessment under 21 CFR 25.31(b) based on market forecast of direct use of the active moiety through 2021.

Special Product Quality Labeling Recommendations (NDA only)

C. Final Risk Assessment (see Attachment)



Anamitro
Banerjee

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LABELING

{For NDA only}

R Regional Information

1.14 Labeling

1. Package Insert

(a) **“Highlights” Section (21CFR 201.57(a))**
 RYDAPT® (midostaurin) capsules, for oral use
 Initial U.S. Approval: 2017

Capsules: 25 mg (3)

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	RYDAPT® (midostaurin)	Adequate.
Dosage form, route of administration	For oral use	Adequate.
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Capsules: 25 mg	Adequate.

Conclusion: Adequate. See assessment above.

(b) “Full Prescribing Information” Section**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

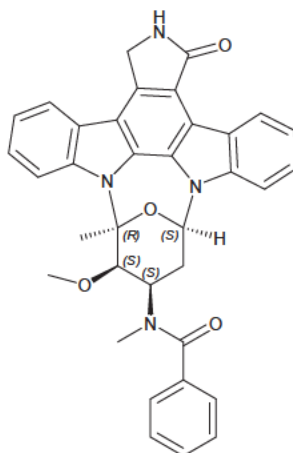
25 mg capsules

Pale orange oblong soft capsule with red ink imprint ‘PKC NVR’.

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	25 mg capsules	Adequate.
Strengths: in metric system	25 mg	Adequate.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Pale orange oblong soft capsule with red ink imprint ‘PKC NVR’	Adequate.

Conclusion: Adequate. See assessment above.**#11: Description (21CFR 201.57(c)(12))**

RYDAPT (midostaurin) is a multikinase inhibitor for oral use. The molecular formula for midostaurin is $C_{35}H_{30}N_4O_4$. The molecular weight is 570.65 g/mole. The chemical name of midostaurin is *N*-[(2*S*,3*R*,4*R*,6*R*)-3-Methoxy-2-methyl-16-oxo-29-oxa-1,7,17-triazaoctacyclo[12.12.2.1^{2,6}.0^{7,28}.0^{8,13}.0^{15,19}.0^{20,27}.0^{21,26}]nonacosa-8,10,12,14,19,21,23,25,27-nonaen-4-yl]-*N*-methylbenzamide. The chemical structure of midostaurin is shown below:



RYDAPT is supplied as a soft capsule containing 25 mg of midostaurin. The capsule contains Polyoxyl 40 Hydrogenated Castor Oil, Gelatin, Polyethylene Glycol 400, glycerin 85%, Dehydrated Alcohol, corn oil mono-di-triglycerides, Titanium Dioxide, Vitamin E, ferric oxide yellow, ferric oxide red, carmine, Hypromellose 2910, Propylene Glycol, and Purified Water.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	RYDAPT (midostaurin)	Adequate.
Dosage form and route of administration	a soft capsule	Adequate.
Active moiety expression of strength with equivalence statement for salt (if applicable)	Provided	Adequate.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate.
Statement of being sterile (if applicable)	N/A	Adequate.
Pharmacological/ therapeutic class	Provided	Adequate.
Chemical name, structural formula, molecular weight	Provided	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	N/A	Adequate.

Conclusion: Adequate. See assessment above.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

RYDAPT 25 mg capsules

Pale orange oblong soft capsule with red ink imprint 'PKC NVR'; available in:

56 capsules.....NDC 0078-0698-99

Contents: Each carton contains two inner packs, each with 28 capsules (7 blisters with 4 capsules each)

112 capsules.....NDC 0078-0698-19

Contents: Each carton contains four inner packs, each with 28 capsules (7 blisters with 4 capsules each)

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature. Store in the original package to protect from moisture.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	25 mg	Adequate.
Available units (e.g., bottles of 100 tablets)	Provided	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Pale orange oblong soft capsule with red ink imprint 'PKC NVR' NDC number provided	Adequate.
Special handling (e.g., protect from light, do not freeze)	Store in the original package to protect from moisture	Adequate.
Storage conditions	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature	Adequate.

Manufacturer/distributor name listed at the end of PI, following Section #17

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T201X-XX
Month Year

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Provided	Adequate.

Conclusion: Adequate. See assessment above.

2. Container and Carton Labeling**1) Immediate Container Label**

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Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Provided	Adequate.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Provided	Adequate.
Route of administration (21.CFR 201.100(b)(3))	No need for tablets and capsules	Adequate.
Net contents* (21 CFR 201.51(a))	Not required for capsule packaged in blister	Adequate.
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) (21CFR 201.100(b)(5)**	Not required for oral drugs	Adequate.
Lot number per 21 CFR 201.18	Space allocated	Adequate.
Expiration date per 21 CFR 201.17	Space allocated	Adequate.
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	Adequate.
Storage (not required)	Provided	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or	Provided	Adequate.
Bar Code per 21 CFR	Provided	Adequate.

201.25(c)(2)***		
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Adequate.
Others	N/A	N/A

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate. See assessment above.

2) Carton Labeling

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Provided	Adequate.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Provided	Adequate.
Net contents (21 CFR 201.51(a))	Provided	Adequate.
Lot number per 21 CFR 201.18	Space allocated	Adequate.
Expiration date per 21 CFR 201.17	Space allocated	Adequate.
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][201.10(a), 21CFR201.100(d)(2)]	Not required for oral drugs	Adequate.
Sterility Information (if applicable)	N/A	N/A
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Adequate.
Storage Conditions	Provided	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21	Provided	Adequate.
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate.
Name of manufacturer/distributor	Provided	Adequate.
"See package insert for dosage	Provided	Adequate.

information" (21 CFR 201.55)		
"Keep out of reach of children" (optional for Rx, required for OTC)	N/A	N/A
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Provided	Adequate.

Conclusion: Adequate. See assessment above.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Adequate. See assessment above.
Nina Ni, Ph. D., Drug Product Reviewer
01/31/2017

Secondary Review Comments and Concurrence: I concur.
Anamitro Banerjee, Ph. D., Acting Branch Chief
February 01, 2017



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Anamitro
Banerjee

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BIOPHARMACEUTICS

Product Background:

NDA: 207997-ORIG-1 [505(b)(1)]

Drug Product Name / Strength: RYDAPT™ (Midostaurin, PKC412) Capsules / 25 mg

Route of Administration: Oral

Applicant Name: Novartis Pharmaceuticals Corporation

Review Summary:

The Biopharmaceutics review for this submission is focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criteria for Midostaurin 25 mg soft capsule.

The proposed QC dissolution method [USP Apparatus 2 (paddle) at 50 rpm, 900mL of 0.5% Polysorbate 20 (Tween 20)] and acceptance criteria [$Q = \frac{(b)}{(4)}\%$ at 30 min for Midostaurin] for the routine QC testing of Midostaurin oral soft capsules during batch release and stability testing are both ACCEPTABLE.

Drug release from the proposed drug product exhibited rapid dissolution in vitro (i.e., >80% of Midostaurin dissolves within 15 min and nearly 100% at 30~60 min) in the proposed QC dissolution medium. The discriminating power of the proposed dissolution method may be limited because of the rapid drug release after shell disintegration. However, the proposed dissolution method was shown to have discriminating power for batches with pellicle formulation upon aging and resulted in a reduction of midostaurin release rate.

The Applicant did not submit a formal request for BCS designation for the drug substance or drug product. However, Midostaurin behaves like a BCS Class-2 drug based on its characteristics of very poor solubility in aqueous media (pH-independent; <0.001 mg/mL in water and pH1.0~6.8 aqueous media), high permeability, relatively high lipophilicity, and high oral absorption in humans (>90%).

Relative bioavailability of the to-be marketed and clinical trial formulations were compared and determined to be of no clinically meaningful difference. Given that, comparative dissolution testing is not considered to be necessary at this point in view of the in vivo results and rapid in vitro drug release.

From the Biopharmaceutics perspective, NDA 207997 for Midostaurin Capsules, 25 mg, is recommended for APPROVAL.

The approved dissolution method and the agreed upon acceptance criterion are summarized as follows:

Apparatus	USP Apparatus II (paddles)
Dissolution Media	Deionized water with 0.5% Polysorbate 20
Dissolution Volume	900 mL
Rotation Speed	50 rpm
Temperature	37°C ± 0.5 °C
Acceptance Criterion	Q = ^(b) ₍₄₎ % in 30 minutes

List Submissions being reviewed (table):

\\Cdsesub1\evsprod\NDA207997

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment:

The Applicant did not submit a formal request for BCS Class 1 or Class 3 designation for the drug substance or drug product. Based on characteristics of very poor solubility in aqueous media (pH-independent; <0.001 mg/mL in water and pH1.0~6.8 aqueous media), high permeability, relatively high lipophilicity, and high oral absorption in humans (>90%), Midostaurin may be considered a BCS Class-2 drug. The rationale is summarized in the sections below.

Solubility:

Midostaurin has relatively high lipophilicity (Log P=5.5) and very poor solubility in water and aqueous media across the pH range of 1.0~6.8 (<0.001 mg/mL). In the proposed soft capsules, midostaurin is ^(b)₍₄₎ upon oral administration (^(b)₍₄₎). Disintegration time of the soft capsules was set to be no longer than ^(b)₍₄₎ min.

Permeability:

In Caco-2 cells, Midostaurin was shown to be highly permeable, neutral, highly lipophilic, non-ionizable, and not subject to P-glycoprotein efflux. As reported, permeability could not be established in this in vitro assay due to high non-specific binding.

Pharmacokinetics in humans: T_{max} was approximately 1~3 hours. The absorption of the drug formulated in a soft capsule depends on the rupture of the capsule shell and subsequent release of the fill content into the gastrointestinal fluids. Oral absorption of Midostaurin in humans was high (>90%) in a human mass-balance study when administered as (b) (4).

Dissolution:

In vitro drug release from the proposed drug product was rapid (i.e., >80% of Midostaurin dissolves within 15 min and nearly 100% at 30~60 min) in the proposed QC dissolution medium ((b) (4) with 0.5% Tween 20). Since Midostaurin is formulated as a (b) (4) and is administered in (b) (4) soft capsules, the dissolution and rupture of the capsule shell and subsequent release of the fill content to the gastrointestinal track presents the rate-limiting step for drug release. Fast release of filled solution in the dissolution media with initial mixing results in greater variability. The characteristics of rapid dissolution after shell disintegration seems to correspond with relatively rapid oral absorption of Midostaurin in humans, giving T_{max} of approximately 1~3 hours after oral administration.

Dissolution Method and Acceptance Criteria**Reviewer's Assessment:****{Assess method development, method robustness, and criteria; modeling approach}**

Midostaurin formulated as (b) (4). The dissolution profile of Midostaurin shows that the (b) (4) the fill solution is dispersed in aqueous fluids. Therefore, the fill solution is released in the dissolution media once the capsule shell disintegrates and a fast and complete release of the drug substance seem to be achieved.

The Applicant's proposed the dissolution acceptance criterion is $Q = \frac{(b)}{(4)}\%$ in 30 min. The disintegration time of the capsule shell and the time required for a homogenous dispersion in the dissolution vessel contributed to the higher variability at earlier timepoints (e.g., 15 min) of dissolution testing. Of note, dissolution profiles of final market image (FMI) formulations were provided to support the approval.

Dissolution Method Development:

(b) (4)

Discriminating Power of Dissolution Method:

On the basis of rapid drug release following the capsule shell disintegration and the relatively rapid oral absorption in humans, as reflected by attainment of peak drug concentration (i.e., T_{max} ~1-3 hours), this reviewer believes that the discriminatory power of the proposed dissolution method may be limited but unlikely rise to the level of concern.

During drug development, the Applicant investigated the drug substance dissolution during (b) (4) for batches manufactured at pilot scale. Drug dissolution times increased with increasing API particle sizes [i.e., Fine (X50 = (b) (4) μm ; X90 = (b) (4) μm), Standard (X50 = (b) (4) μm ; X90 = (b) (4) μm), and Coarse (X50 = (b) (4) μm ; X90 = (b) (4) μm)].

Capsule variants with decreased extent and increased variability of drug release was observed for 2 batches of Midostaurin 25 mg soft capsules stored at 30°C/75% RH for 60 months. The root cause was attributed to cross-linking of gelatin that causes the shell to become swollen, rubbery and insoluble in water, which leads to formation of a very thin film during the dissolution testing and prevents the fill from being released. Dissolution (%) after 30min decreased to 78% and 75%, on average, for the 2 batches at 60 months. The Applicant employed a two tier procedure by adding pepsin (2.0 g) as digestive enzyme in the dissolution medium, as recommended from USP<711> Dissolution, eliminated the influence of pellicle formation and resulted in near complete dissolution (95% and 92%, on average) for the 2 batches at 60 months. Therefore, the adapted dissolution method (Tier 1) for Midostaurin 25 mg soft capsule and the Tier 2 approach provided discriminatory ability to detect the failure to the specifications. The Tier 2 dissolution testing is only applicable during stability testing.

Dissolution Acceptance Criterion:

For routine QC testing of the proposed midostaurin soft gelatin capsules at batch release and during stability, the Applicant proposed an acceptance criterion of $Q^{(b)(4)}\%$ in 30 minutes. (Release and stability: USP acceptance table levels 1 and 2 only). The proposed QC dissolution method is summarized in the table below.

Table 2: The proposed QC dissolution method

Apparatus	USP Apparatus II (paddles)
Dissolution Media	Deionized water with 0.5% Polysorbate 20
Dissolution Volume	900 mL
Rotation Speed	50 rpm
Temperature	37°C ± 0.5 °C

This Reviewer considers the Applicant’s proposed dissolution acceptance criteria ($Q^{(b)(4)}$ % in 30 minutes) acceptable for the following reasons:

- The dissolution profiles of the proposed 25mg capsules were all rapidly dissolving, with at least 80% dissolution being achieved in 15 minutes (the first sampling timepoint) and approximately 90% in 30 min in the chosen dissolution medium at 50 rpm agitation speed.
- With the addition of $^{(b)(4)}$, nearly complete dissolution (96~100%, on average) was achieved by 30 min or up to the last sampling time, which is considered acceptable for final drug product QC specification for immediate-release oral dosage forms.
- The applicant’s justification seems reasonable with regards to higher variability at 15min timepoint due to disintegration of the capsule and time required for the capsule fill to homogeneously disperse in the dissolution vessels.
- The dissolution method is deemed acceptable.
- The proposed dissolution method was shown to have discriminating power for detecting cross-linking of gelatin which results in pellicle formulation upon aging.

Analytical Method Validation:

Quantification of Midostaurin in the dissolution samples (Tier 1) was accomplished and validated using HPLC with UV detection at 405~330 nm and validated for linearity (68%~135% concentration range; 14-116% of 25mg label claim), precision/intermediate precision, repeatability, linearity, accuracy (67%, 96% and 134% of declared amount), solution stability (sample and standard solution), robustness (with respect to HPLC), as shown in Table 4. Additional validation was performed for Tier 1 dissolution samples after 30 min tested for parameters, including linearity (14~116% of 25mg label claim) and accuracy (15%, 60% and 120% of declared amount), and confirms validity of the analytical method. The analytical method validation is considered adequate; the results met the acceptance criteria and are acceptable.

Table 3: Validation results for Midostaurin (PKC412) by HPLC

Validation parameter	Indicator	Acceptance criteria	Results ¹	Complies yes / no
Identity (active ingredient PKC412)				
Selectivity/Specificity	• Resolution between peak from 512-03 (1) and 512-03 (2)	• ≥ 2.0	3.8	yes
	• All peaks	• No interference, peaks are separated	No interference, peaks are separated	yes
	• Peak purity (using DAD)	• No indication of another peak under the peak for PKC412	No indication of another peak under the peak for PKC412	yes
Identity (absence of PKC412 in placebo capsules)				
Selectivity/Specificity	• see identity for active ingredient: table 2-1 above	• see identity for active ingredient: table 2-1 above	see identity for active ingredient: table 2-1 above	yes
Limit of quantitation	• LOQ: $10 \sigma/S$ from linearity ²	• LOQ $\leq$ reporting level of 0.1%	0.1%	yes

Selectivity/Specificity	See identity for active ingredient: Table 2-1	See identity for active ingredient: Table 2-1	See identity for active ingredient: Table 2-1	yes
Precision (determined by Kojima design)	Repeatability	$s_{rel} \leq 2.0\%$	0.9% (16 mg) 0.8% (25 mg)	yes
	Intermediate precision	$s_{rel} \leq 2.0\%$	0.8% (16 mg) 0.7% (25 mg)	yes
Linearity	Correlation coefficient	$r \geq 0.998$	1.000	yes
	y-intercept (relative to the response of a 100% solution) ²	$\leq 2.0\%$	1.7%	yes
	Residual standard deviation (relative to the response of a 100% solution) ²	$\leq 2.0\%$	0.2%	yes
Accuracy	Recovery (mean)	98.0-102.0%	100.6%	yes
	Relative standard deviation	$s_{rel} \leq 2.0\%$	1.2%	
Range	Based on linearity and accuracy	ICH: 70-130%	68-134%	yes
Completeness of extraction	Second extraction	$\leq 0.4\%$	0.01%	yes
Stability of test solution	Relative change of the content of PKC412 at 20-25°C ³	$\leq 2.0\%$	0.6% (16 mg) ⁵	yes
		$\leq 2.0\%$	1.1% (25 mg) ⁵	
	Relative change of the content of PKC412 at 2-8°C ⁴	$\leq 2.0\%$	1.5% (16 mg) ⁵ 0.8% (25 mg) ⁵	yes
Stability of reference solution 1 (100%)	Relative change of the content of PKC412 at 20-25°C ³	$\leq 2.0\%$	1.1% ⁵	yes
	Relative change of the content of PKC412 at 2-8°C ⁴	$\leq 2.0\%$	1.1% ⁵	yes

Bridging of Formulations

Reviewer's Assessment:

The compositions of FMI for commercial and clinical service form (CSF) formulations used in clinical trials do not appear to be proportionally similar (see Appendix). In-vitro bridging via comparative dissolution testing was not conducted, which is considered acceptable in this case because of the available in-vivo bridging.

Bridge between the to-be marketed and clinical trial formulations:

In vivo:

The Applicant conducted a relative bioavailability study to compare CSF (Phase 1/2), FMI (Phase 3; the to-be marketed), and oral solution formulations under fasted state. Review by the Office of Clinical Pharmacology (in DARRTS) concluded that “no clinically meaningful difference in exposure following administration of the clinical formulation used during early clinical development and the final market image formulation used in late clinical development”.

In vitro:

Only dissolution results of FMI formulations are provided for supporting the approval. In vitro formulation bridging via comparative dissolution testing is not considered to be necessary at this point in view of the available in vivo bridging.

Biowaiver Request

Reviewer's Assessment:



QUALITY ASSESSMENT



N/A

List of Deficiencies: None

Overall Review Recommendation:

From the Biopharmaceutics perspective, NDA 207997 for Midostaurin Capsules, 25 mg, is recommended for APPROVAL.

Primary Biopharmaceutics Reviewer Name and Date: *Ta-Chen Wu, Ph.D.; 2/2/2017*

Secondary Reviewer Name and Date: *Okpo Eradiri, Ph.D.; 2/2/2017*

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Appendix. Compositions of formulations

Midostaurin 25 mg soft gelatin capsule has yellow to greenish-yellow to very dark yellow to very dark greenish-yellow solution in pale orange, oblong capsule with red imprint ‘PKC NVR’. The compositions of FMI for commercial and CSF formulations used in clinical trials do not appear to be proportionally similar.

Table: Composition of Midostaurin 25 mg soft capsules

Component	Amount per capsule [mg]		Function
	Clinical service form (CSF)	Final market image (FMI)	
	3754959.003	3754959.011	
	3754959.004	3754959.013	
	3754959.005		
Midostaurin	25.00	25.00	Active ingredient
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Polyoxyl 40 hydrogenated castor oil	(b) (4)	(b) (4)	(b) (4)
Gelatin	(b) (4)	(b) (4)	(b) (4)
(b) (4) Polyethylene glycol 400	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Dehydrated alcohol	(b) (4)	(b) (4)	(b) (4)
Corn oil mono-di-triglycerides	(b) (4)	(b) (4)	(b) (4)
Titanium dioxide	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Vitamin E	(b) (4)	(b) (4)	(b) (4)
(b) (4) yellow/Ferric oxide	(b) (4)	(b) (4)	(b) (4)
(b) (4) red/Ferric oxide	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Carmines	(b) (4)	(b) (4)	(b) (4)
Hypromellose 2910	(b) (4)	(b) (4)	(b) (4)
Propylene glycol	(b) (4)	(b) (4)	(b) (4)
Water, purified/Purified water	(b) (4)	(b) (4)	(b) (4)
Theoretical weight of the capsule	810.56 ^a	1281.82 ^a	

Of note, drug products were produced at 2 manufacturing sites:

- The clinical service form (CSF) and the final market image (FMI) soft capsules containing 25mg of Midostaurin: (b) (4)
- Hard gelatin capsule (HGC) containing 12.5 mg, 25mg or 75mg of Midostaurin, used in early Phase 1 studies: (b) (4)



Ta-Chen
Wu

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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment – NDA 207997

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	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	
Content Uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Dissolution – BCS Class I & III	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Leakage (Soft Gel Capsules)	• Formulation • Excipient change • Process parameters • Scale/equipments • Site	L	(b) (4)	Acceptable	
(b) (4)	• Formulation • Excipient change • Process parameters • Scale/equipments • Site	L		Acceptable	



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