CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205353Orig1s000

CHEMISTRY REVIEW(S)

NDA 205 353

Panobinostat

NOVARTIS

Danuta Gromek-Woods, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment 1
Branch # 2

CMC REVIEW OF NDA 205 353
For the Division of Hematology Drug Products (DHP)

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CMC Review Data Sheet

1. NDA 205 353

2. REVIEW #: 2

3. REVIEW DATE: 25-Sep-2014

4. REVIEWER: Danuta Gromek-Woods, Ph.D.

5. PREVIOUS DOCUMENTS: Review #1

6. SUBMISSION(S) BEING REVIEWED:

Submission	Document Date	eCTD sequence	Content
Original Submission	23-mar-2014	0000	Original submission
Amendment (BC)	07-May-2014	0005	Response to statistical IR sent on 01-May-2015 (raw drug product stability data & exclusion of (b) (4) factor in statistics model)
Amendment (BC)	15-May-2014	0007	Response to statistical IR sent on 09-May-2015 (additional raw drug product stability data as well as the rational for the statistical evaluation factors.)
Amendment (BC)	29-May-2014	0013	Response to statistical IR sent on 27-May-2015 (raw stability data in Excel or SAS formats for (b) (4))
Amendment (BC)	10-Jun-2014	0017	Response to CMC IR sent on 27-May-2014 (6 drug substance questions and 3 drug product questions)
Amendment (BC)	03-Jul-2014	0023	Response to CMC IR sent on 26-Jun-2014 (b) (4))
Amendment (BC)	07-Aug-2014	0031	Response to CMC IR sent on 31-Jul-2014 (follow-up to previous CMC IR)
Amendment (BC)	18-Aug-2014	0035	Response to CMC IR sent on 17-Aug-2014 (follow-up to previous CMC IR)
Amendment (BC)	18-Sep-2014	0043	Updated drug substance and drug product specifications, as requested in IR sent on 24-Aug-2014 and 26-Aug-2014.

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CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza, East Hanover, 07936-1080, New Jersey, USA
Representative:	Jeannie Shen
Telephone:	(862) 778-3343

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Farydak
b) Non-Proprietary Name: panobinostat
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Type 1, NME
- Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: FARYDAK®, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy.

11. DOSAGE FORM: Hard Gelatin Capsules

12. STRENGTH/POTENCY: 10 mg, 15 mg and 20 mg capsules

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√___Not a SPOTS product

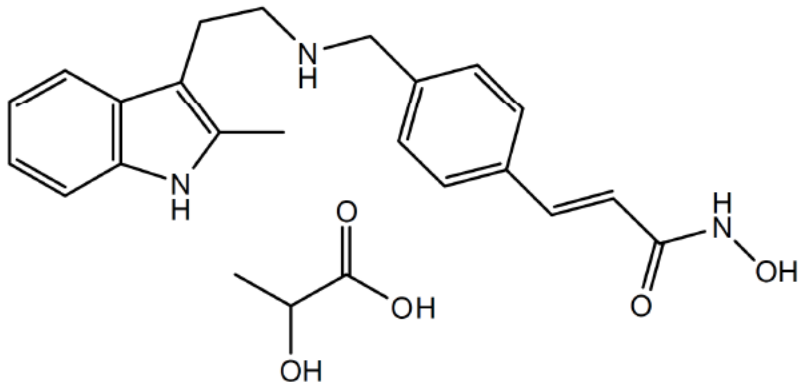
1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (2*E*)-*N*-Hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino} methyl)phenyl]prop-2-enamide 2-hydroxypropanoate (1:1)

Reference ID: 3640753

CMC Review Data Sheet

Structural Formula:



Molecular Formula: $C_{21}H_{23}N_3O_2$. $C_3H_6O_3$
Relative molecular mass: 349.43 (free base) + 90.08 (lactic acid) = 439.51.
Salt/ base ratio: 1.258

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

Reference ID: 3640753

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69862 and 67091	

Reference ID: 3640753

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Adequate • 25°C/60%RH climate zone I and II) For **PVC/PCTFE** package, the commercial package, the shelf life could be up to **36 month**. (b) (4) [redacted] For **PVC/PCTFE** package, the commercial package, the shelf life could be up to **36 month**. (b) (4) [redacted]	06-Jun-2014	Sutan Wu, Ph.D.
EES	Acceptable, see Attachment 1 for EER	11-Sep-2014	Dholakia, Vipul, Ph.D., Consumer Safety Officer / SPA, Office of Compliance, CDER/FDA
Pharm/Tox	NA		
Biopharm	Recommended for Approval - See review in DARRTS	22-Sep-2014	Elsbeth Chihikhale, Ph.D.
LNC			
Methods Validation	We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified (as per email from Dr. Ali Al Hakim dated 13-Jun-2014).	Methods Validation Consult Request Form was sent on 13-Jun-2014 to FDA Division of Pharmaceutical Analysis, Attn: Michael Trehy, St. Louis, MO 63101, by Janice Brown, please refer to Consult request in DARRTS dated 13-Jun-2014	
DMETS			
EA	The applicant certifies that this submission for qualifies for a categorical exclusion in		Danuta Gromek-Woods, Ph.D.

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CMC Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
	accordance with 21 CFR Part 25.31(b) as the concentration of the active moiety will be significantly < 1 ppb.		
Product Quality Microbiology	Recommended for Approval - See review in DARRTS	29-May-2014	Erica Pfeiler, Ph.D.

Reference ID: 3640753

Chemistry Review for NDA 205 353

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. As indicated in the Risk Assessment table, pg. 11, the primary reviewer recommends an optimization of the drug product method "Assay and degradation products by HPLC" to improve the separation of impurity (b) (4) from Panobinostat, which can be addressed post approval. This issue does not preclude the approvability of NDA 202 353 at this time.

Labels/labeling are under discussion with the Review Team. An "Acceptable" recommendation was issued by the Office of Compliance for Novartis Farmaceutica, Barcelona, Spain on 11-Sep-2014. The Biopharmaceutics' reviewer issued an "Adequate" recommendation on 22-Sep-2014.

Overall, NDA 205 353 is recommended for "Approval" from the CMC perspective.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of CMC Assessments

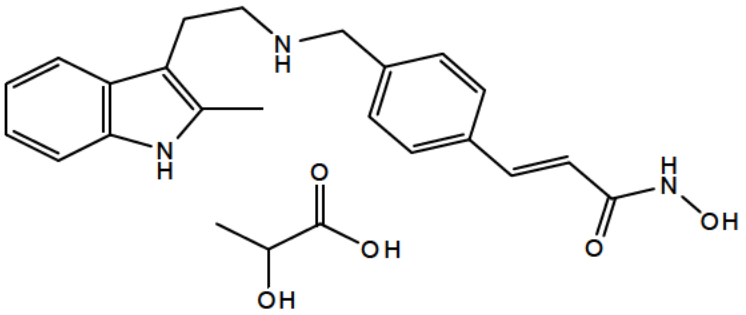
A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

FARYDAK (panobinostat) is a histone deacetylase inhibitor. The Active Pharmaceutical Ingredient of the FARYDAK® hard gelatin capsules is panobinostat lactate anhydrous. This is a New Molecular Entity and the review process for this NDA submission is conducted "under the PDUFA V Program".

The chemical name of panobinostat is 2-Hydroxypropanoic acid, compd. with 2-(E)-N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]methyl]phenyl]-2-propenamide (1:1). The structural formula is provided below:

Reference ID: 3640753



Panobinostat lactate anhydrous is a white to slightly yellowish or brownish powder. The molecular formula is $C_{21}H_{23}N_3O_2 \bullet C_3H_6O_3$ with a molecular weight of 439.51 as a lactate [349.43 (free base) + 90.08 (lactic acid)]. Panobinostat free base is not chiral and shows no specific optical rotation. Panobinostat lactate anhydrous is slightly soluble in water. Solubility of panobinostat lactate anhydrous is pH-dependent, with the highest solubility in buffer pH 3.0 (citrate).

Based on the drug substance stability data and ICH Q1E Guidance *"Evaluation of Stability Data"* , a (b) (4) months re-test period for Panobinostat lactate, anhydrous when packed and stored (b) (4) is granted.

(2) Drug Product

LBH589 (Panobinostat) is a highly potent class I, II, and IV pan-deacetylase inhibitor (DACi) promoting increased acetylation of both histone and non-histone DAC. DAC inhibition affects targets in several different pathways that contribute to the malignant phenotype. LBH589 has the potential for broad anti-cancer activity as a combination partner.

LBH589 was initially developed at Novartis Pharmaceuticals Corporation (NPC) and (b) (4) The process was subsequently transferred to Novartis Barbera, Spain for scale-up and commercialization. LBH589 has been developed as immediate release hard gelatin capsules for oral administration.

FARYDAK hard gelatin capsules contain 10 mg, 15 mg or 20 mg panobinostat free base. The inactive ingredients are magnesium stearate, mannitol, microcrystalline cellulose and pregelatinized starch. The capsules contain gelatin, FD&C Blue 1 (10 mg capsules), yellow iron oxide (10 mg and 15 mg capsules), red iron oxide (15 mg and 20 mg capsules) and titanium dioxide.

Based on drug product stability data and statistical analysis, the expiration dating period for the Panobinostat capsules is 36 months. Product should be stored at 20° to 25°C (68° to 77°F), excursions permitted between 15° and 30°C (59° and 86°F).

B. Basis for Approvability or Not-Approval Recommendation

Executive Summary Section

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. As indicated in the Risk Assessment table, pg. 11, the primary reviewer recommends an optimization of the drug product method "Assay and degradation products by HPLC" to improve the separation of impurity (b) (4) from Panobinostat, which can be addressed post approval. This issue does not preclude the approvability of NDA 202 353 at this time.

Labels/labeling are under discussion with the Review Team. An "Acceptable" recommendation was issued by the Office of Compliance for Novartis Farmaceutica, Barcelona, Spain on 11-Sep-2014. The Biopharmaceutics' reviewer issued an "Adequate" recommendation on 22-Sep-2014.

Overall, NDA 205 353 is recommended for "Approval" from the CMC perspective.

RISK ASSESSMENT

From Initial Quality			Review Assessment		
CQAs	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations / Comments**
Assay, stability		L	**Suitability of analytical methodology :** The reviewer found (and the applicant confirmed in response to the agency's IR) that Assay and degradation products by HPLC method for the drug product is not specific enough to accurately quantitate impurities (b) (4) and (b) (4) (b) (4) • Impurity (b) (4) is a (b) (4) This impurity is well controlled in the drug substance at the level of NMT (b) (4) % (the drug substance HPLC method resolves well all impurities and the active), see Review#1, pg.51-52 for details. • Impurity (b) (4) is a (b) (4) is controlled as 'Any unspecified impurity' in the drug substance, at a level of NMT (b) (4) %. • Since the capsules are packaged in blisters and the blisters are packaged in a secondary carton container, the risk (b) (4) is minimal. As per label, the product has to be stored in an original container and protected from light. Conclusion: Although impurities (b) (4) and (b) (4) (b) (4) taking in account the above considerations, this issue does not preclude the approvability of NDA 202 353 at this time.	L	**Drug product: Monitor level of individual and total impurities on stability, especially for the impurity (b) (4) controlled as 'Any unspecified impurity' (limit of NMT (b) (4) %) . Optimization of the drug product method "Assay and degradation products by HPLC" to improve the separation of impurity (b) (4) from the active is recommended by the primary reviewer.**

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Executive Summary Section

From Initial Quality			Review Assessment		
CQAs	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations / Comments**
Physical stability (solid state)	• Formulation • Crystallinity of drug substance (polymorphism) • Process parameters	L	Anhydrous form of Panobinostat lactate (b) (4) is used: • See Review#1,pg. 47-51 and 115-120 for polymorph characterization in drug substance and drug product. • XRPD test is included in drug substance specification • (b) (4) (b) (4) (b) (4)	L	**If any changes in drug substance synthesis or drug product manufacturing process occur in the future, polymorphic stability should be re-visited.**
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment	M	• Robust manufacturing process. • Adequate analytical methodology to test content uniformity.	L	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site Finished product (b) (4)	L	See the Quality microbiology review in DARRTS.	Acceptable	Refer to the Microbiology Review.
Dissolution	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipment • Site	M	See Biopharmaceutics reviews in DARRTS dated 22-Sep-2014	Acceptable	Refer to the Biopharmaceutics Review.

Reference ID: 3640753

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Danuta Gromek-Woods, Ph.D., Chemistry Reviewer

B. Endorsement Block:

(See appended electronic signature page)

Ali Al Hakim, Ph.D., Branch Chief, Branch 2, ONDQA

C. CC Block: entered electronically in DFS

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

Reference ID: 3640753

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

/s/

DANUTA E GROMEK-WOODS
10/07/2014

ALI H AL HAKIM
10/07/2014

NDA 205 353

Panobinostat

NOVARTIS

Danuta Gromek-Woods, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment 1
Branch # 2

CMC REVIEW OF NDA 205 353
For the Division of Hematology Drug Products (DHP)

Reference ID: 3617102

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CMC Review Data Sheet

1. NDA 205 353

2. REVIEW #: 1

3. REVIEW DATE: 10-Jun-2014

4. REVIEWER: Danuta Gromek-Woods, Ph.D.

5. PREVIOUS DOCUMENTS: NA

6. SUBMISSION(S) BEING REVIEWED:

Submission	Document Date	eCTD sequence	Content
Original Submission	23-mar-2014	0000	Original submission
Amendment (BC)	07-May-2014	0005	Response to statistical IR sent on 01-May-2015 (raw drug product stability data & exclusion of '(b) (4)' factor in statistics model)
Amendment (BC)	15-May-2014	0007	Response to statistical IR sent on 09-May-2015 (additional raw drug product stability data as well as the rational for the statistical evaluation factors.)
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Amendment (BC)	07-Aug-2014	0031	Response to CMC IR sent on 31-Jul-2014 (follow-up to previous CMC IR)
Amendment (BC)	18-Aug-2014	0035	Response to CMC IR sent on 17-Aug-2014 (follow-up to previous CMC IR)

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation

Reference ID: 3617102

CMC Review Data Sheet

Address:	One Health Plaza, East Hanover, 07936-1080, New Jersey, USA
Representative:	Jeannie Shen
Telephone:	(862) 778-3343

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Farydak
b) Non-Proprietary Name: panobinostat
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Type 1, NME
- Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: FARYDAK®, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy.

11. DOSAGE FORM: Hard Gelatin Capsules

12. STRENGTH/POTENCY: 10 mg, 15 mg and 20 mg capsules

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

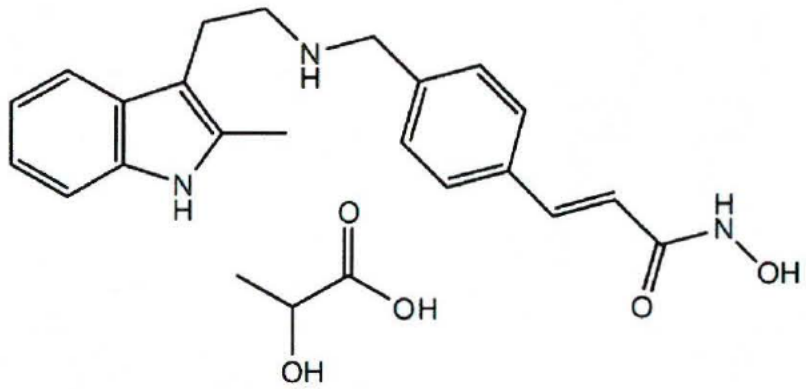
__√__Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (2*E*)-*N*-Hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]prop-2-enamide 2-hydroxypropanoate (1:1)

Structural Formula:

Reference ID: 3617102



Molecular Formula: $C_{21}H_{23}N_3O_2 . C_3H_6O_3$
Relative molecular mass: 349.43 (free base) + 90.08 (lactic acid) = 439.51.
Salt/ base ratio: 1.258

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

Reference ID: 3617102

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69862 and 67091	
NDA		

Reference ID: 3617102

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Adequate • 25°C/60%RH climate zone I and II) For **PVC/PCTFE** package, the commercial package, the shelf life could be up to **36 month.** (b) (4) [redacted] For **PVC/PCTFE** package, the commercial package, the shelf life could be up to **36 month.** (b) (4) [redacted]	06-Jun-2014	Sutan Wu, Ph.D.
EES	Pending		Dholakia, Vipul, Ph.D., Consumer Safety Officer / SPA, Office of Compliance, CDER/FDA
Pharm/Tox	NA		
Biopharm	Pending		Elsbeth Chihikhale, Ph.D.
LNC			
Methods Validation	We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified (as per email from Dr. Ali Al Hakim dated 13-Jun-2014).	Methods Validation Consult Request Form was sent on 13-Jun-2014 to FDA Division of Pharmaceutical Analysis, Attn: Michael Trehy, St. Louis, MO 63101, by Janice Brown, please refer to Consult request in DARRTS dated 13-Jun-2014	
DMETS			
EA	The applicant certifies that this submission for qualifies for a categorical exclusion in		Danuta Gromek-Woods, Ph.D.

Reference ID: 3617102

CMC Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
	accordance with 21 CFR Part 25.31(b) as the concentration of the active moiety will be significantly < 1 ppb.		
Product Quality Microbiology	Recommended for Approval - See review in DARRTS	29-May-2014	Erica Pfeiler, Ph.D.

Reference ID: 3617102

Chemistry Review for NDA 205 353

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels/labeling are under discussion with the Review Team. From a CMC perspective, this NDA is recommended for "Approval" pending an "Acceptable" recommendation from the Office of Compliance and an "Adequate" recommendation from the Biopharmaceutics' reviewer.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

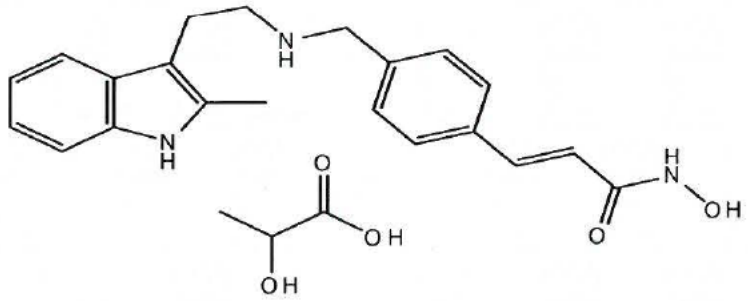
II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

FARYDAK (panobinostat) is a histone deacetylase inhibitor. The Active Pharmaceutical Ingredient of the FARYDAK® hard gelatin capsules is panobinostat lactate anhydrous. This is a New Molecular Entity and the review process for this NDA submission is conducted "under the PDUFA V Program".

The chemical name of panobinostat is 2-Hydroxypropanoic acid, compd. with 2-(E)-N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]methyl]phenyl]-2-propenamide (1:1). The structural formula is provided below:



Reference ID: 3617102

Panobinostat lactate anhydrous is a white to slightly yellowish or brownish powder. The molecular formula is $C_{21}H_{23}N_3O_2 \cdot C_3H_6O_3$ with a molecular weight of 439.51 as a lactate [349.43 (free base) + 90.08 (lactic acid)]. Panobinostat free base is not chiral and shows no specific optical rotation. Panobinostat lactate anhydrous is slightly soluble in water. Solubility of panobinostat lactate anhydrous is pH-dependent, with the highest solubility in buffer pH 3.0 (citrate).

Based on the drug substance stability data and ICH Q1E Guidance *"Evaluation of Stability Data"*, a (b)(4) months re-test period for Panobinostat lactate, anhydrous when packed and stored (b)(4) is granted.

(2) Drug Product

LBH589 (Panobinostat) is a highly potent class I, II, and IV pan-deacetylase inhibitor (DACi) promoting increased acetylation of both histone and non-histone DAC. DAC inhibition affects targets in several different pathways that contribute to the malignant phenotype. LBH589 has the potential for broad anti-cancer activity as a combination partner.

LBH589 was initially developed at Novartis Pharmaceuticals Corporation (NPC) and (b)(4) . The process was subsequently transferred to Novartis Barbera, Spain for scale-up and commercialization. LBH589 has been developed as immediate release hard gelatin capsules for oral administration.

FARYDAK hard gelatin capsules contain 10 mg, 15 mg or 20 mg panobinostat free base. The inactive ingredients are magnesium stearate, mannitol, microcrystalline cellulose and pregelatinized starch. The capsules contain gelatin, FD&C Blue 1 (10 mg capsules), yellow iron oxide (10 mg and 15 mg capsules), red iron oxide (15 mg and 20 mg capsules) and titanium dioxide.

Based on drug product stability data and statistical analysis, the expiration dating period for the Panobinostat capsules is 36 months. Product should be stored at 20° to 25°C (68° to 77°F), excursions permitted between 15° and 30°C (59° and 86°F).

B. Description of How the Drug Product is Intended to be Used

FARYDAK hard gelatin capsules are intended for oral administration.

B. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels/labeling are under discussion with the Review Team. From a CMC perspective, this NDA is recommended for "Approval" pending an "Acceptable" recommendation from the Office of

Reference ID: 3617102

Compliance and an "Adequate" recommendation from the Biopharmaceutics' reviewer.

Initial Risk assessment

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment	Risk
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	4	2	Release (1) Stability (3)	Release (8) stability (24)	Poorly Stable Drug: Single impurity > (b) (4)% Total impurities > (b) (4)%	L
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3 (Crystalline)	3	4	36	Per biopharm: No BCS classification. The aqueous solubility is low, and the permeability is moderate, so it could be a BCS class II or IV.	L
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3 (b) (4)	3	4	36		M
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Finished product (b) (4) • Release/stability testing	1	2	3	6	OPS Micro will assess	L
Dissolution	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipment • Site	4	2	4	32	ONDQA BioPharm will assess	M

Risk Assessment

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations / Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Analytical methodology	L	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Polymorphism studies	L	
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	Robust manufacturing process	L	

Reference ID: 3617102

Executive Summary Section

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations / Comments**
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site Finished product (b) (4) Release/stability testing	L	See the Quality microbiology review in DARRTS		

Conclusion:

Adequate controls for drug substance and raw materials are in place, manufacturing processes are robust and adequately controlled, specifications ensure the identity, strength, quality, and purity of the drug product. The container/closure system is adequate to protect the drug product. Stability data assure that the product will be stable through the expiration date. Based on provided stability data and statistical analysis the expiration dating period of 36 months is granted for the for the FARYDAK capsules packages in PVC/PCTFE when stored @25°C (77°F); excursions permitted to 15-30°C (59-86°F). For details, please refer to the Biometrics Consult in DARRTS dated 06-Jun-2014, prepared by Dr. Sutan Wu, both at

Labeling has been under discussion with the Review Team. The EES Report indicates a "Pending" recommendation for Novartis Farmaceutica, Barcelona, Spain.

From the CMC perspective, NDA 205 353 has provided sufficient information to assure the identity, strength, purity, and quality of FARYDAK over the proposed shelf life when stored as prescribed in labeling.

This NDA is recommended for "Approval" from the CMC perspective pending an "Acceptable " recommendation from the Office of Compliance and an "Adequate" recommendation from the Biopharmaceutics reviewer.

Reference ID: 3617102

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Danuta Gromek-Woods, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

Ali Al Hakim, Ph.D., Branch Chief, Branch 2, ONDQA

C. CC Block: entered electronically in DFS

130 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 3617102

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

/s/

DANUTA E GROMEK-WOODS
08/27/2014

JANICE T BROWN
08/27/2014
Janice Brown, MS for Ali Al-Hakim, Ph.D.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205353/000	**Sponsor:**	NOVARTIS PHARMS CORP
Office:	161		1 HEALTH PLAZA BLDG 339 RM 1113
Priority:	1		EAST HANOVER, NJ 079361080
Stamp Date:	24-MAR-2014	**Brand Name:**	PANOBINOSTAT (LBH589)
PDUFA Date:	24-NOV-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	24-JUL-2014	**Product Number; Dosage Form; Ingredient; Strengths**	001; CAPSULE; PANOBINOSTAT HYDRATE; 10MG 002; CAPSULE; PANOBINOSTAT HYDRATE; 15MG 003; CAPSULE; PANOBINOSTAT HYDRATE; 20MG

FDA Contacts:				
	D. GROMEK-WOODS	Prod Qual Reviewer		3017961217
	E. PFEILER	Micro Reviewer	(HF-22)	3017960642
	T. AGOSTO	Product Quality PM		2404023777
	D. HANNER	Regulatory Project Mgr	(HFD-006)	3017964058

Overall Recommendation:	ACCEPTABLE	on 11-SEP-2014	by R. MOORE	()	2404029988
	PENDING	on 08-APR-2014	by EES_PROD		

Establishment: **CFN:** 9617362 **FEI:** 3002910506

NOVARTIS FARMACEUTICA SA
RONDA SANTA MARIA 158

BARBERA DE VALLES, BARCELONA, BARCELONA, SPAIN

DMF No: **AADA:**

Responsibilities:
- FINISHED DOSAGE MANUFACTURER
- FINISHED DOSAGE PACKAGER
- FINISHED DOSAGE RELEASE TESTER
- FINISHED DOSAGE STABILITY TESTER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-SEP-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Reference ID: 3709088

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 9692042 **FEI:** 3002865753

NOVARTIS PHARMA STEIN AG
ROTHAUSWEG

SCHWEIZERHALLE, BASEL-LANDSCHAFT, SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE OTHER TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-APR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9692043 **FEI:** 3002653483

NOVARTIS PHARMA STEIN AG
SCHAFFHAUSERSTRASSE 101

STEIN, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

M Date: 01-AUG-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9611204 **FEI:** 3002807772

NOVARTIS RINGASKIDDY PHARMA LTD.
LICHTSRASSE 35

BASEL, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-MAY-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Reference ID: 3709088

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-APR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

M Date: 11-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Reference ID: 3709088