CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204760Orig1s000

CHEMISTRY REVIEW(S)

Memorandum	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research
Date:	12-Sep-2014
To:	CMC Review #1 for NDA 204760
From:	Bogdan Kurtyka, Ph.D. CMC Reviewer, Division II/ONDQA
Through:	Moo-Jhong Rhee, Ph.D. Chief, Branch IV/ Division II/ONDQA
CC:	Marie Kowblansky, Ph.D. CMC Lead, Division II/ONDQA
Subject:	**Final CMC Recommendation**

Previous CMC Review #1, dated 12-Jun-2014, noted the following deficiencies which resulted in a recommendation for "Non Approval".

1. The Office of Compliance did not yet issue an overall "Acceptable" recommendation for the manufacturing establishments.
2. Unresolved label/labeling issues.
3. The Environmental Assessment review was not finalized by the CDER OPS EA team.

Regarding Item #1:
On 23-Jun-2014 the Office of Compliance issued an overall recommendation of "**Acceptable**" for the facilities involved in this application (see the **Attachment 1**).

Regarding Item #2:
Amendment dated 23-June-2014 resolved all issues on PI except for the controlled substance symbol.
Amendment dated 11-Aug-2014 resolved the remaining controlled substance symbol issue.
Amendment dated 23-June-2014 corrected the storage temperature on container and carton labels.
Amendment dated 8-Sep-2014 added salt equivalency statement on the labels.
Amendment dated 11-Sep-3014 added parenthesis on the established name on the labels.

The final PI and container and carton labels were reviewed and found satisfactory (see the **Attachment 2**).

Regarding Item #3:
The review of the Environmental Assessment was documented on 18-Jul-2014, with the determination that the application qualifies for the categorical exclusion claimed by the sponsor.

Other:
On 25-Aug-2014, Method Validation was documented for the following methods:

1. APPEARS THIS WAY test by LC
2. Assay by HPLC
3. Assay by HPLC
4. APPEARS THIS WAY ON by LC

The report found all methods acceptable for the quality control and regulatory purposes.

Recommendation:

Because all issues noted in Review #1 were resolved satisfactorily, from the ONDQA perspective, this NDA is now recommended for **Approval** with an expiration dating period of 24-month for all packaging configurations.

Attachment 1: EES Summary Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204760/000	**Sponsor:**	ASTRAZENECA PHARMS
Org. Code:	180		1800 CONCORD PIKE
Priority:	1		WILMINGTON, DE 198038355
Stamp Date:	16-SEP-2013	**Brand Name:**	NALOXEGOL
PDUFA Date:	16-SEP-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	NALOXEGOL
District Goal:	16-APR-2014	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET; NALOXEGOL OXALATE; 12.5MG 002; TABLET; NALOXEGOL OXALATE; 25MG

FDA Contacts:	B. KURTYKA	Prod Qual Reviewer		3017961431
	S. LANGILLE	Micro Reviewer	(HFD-805)	3017961557
	C. TRAN-ZWANETZ	Product Quality PM	(HFD-800)	3017963877
	M. DEWEY	Regulatory Project Mgr		3017960845
	M. KOWBLANSKY	Team Leader		3017961390

Overall Recommendation:	ACCEPTABLE	on 23-JUN-2014	by C. CAPACCI-DANIEL	()	3017963532
	PENDING	on 23-OCT-2013	by EES_PROD		

Establishment:	**CFN:** 9615999	**FEI:** 3003342394	
	ASTRA ZENECA AB GARTUNAVAGAN		
	SODERTALJE, , SWEDEN		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE OTHER TESTER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-JUN-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 2517100 **FEI:** 2517100 ASTRAZENECA PHARMACEUTICALS LP NEWARK, , UNITED STATES 197021307		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-OCT-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE OTHER TESTER DRUG SUBSTANCE STABILITY TESTER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	05-MAR-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	INTERMEDIATE MANUFACTURER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-DEC-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Attachment 2: Labels/labeling evaluation

1. Package Insert

(a) "Highlights" Section

MOVANTIK (naloxegol) tablets, for oral use, C-II
Initial US Approval: xxxx

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	MOVANTIK (naloxegol) **Satisfactory**
Dosage form, route of administration	Tablets, for oral use **Satisfactory**
Controlled drug substance symbol (if applicable)	C-II **Satisfactory**
Dosage Forms and Strengths (201.57(a)(8))	Tablets: 12.5 mg and 25 mg **Satisfactory**
Whether the drug product is scored	N/A

The "Highlights" section is adequate.

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths

MOVANTIK (naloxegol) is as available in two strenghts:

- Tablets: 12.5 mg supplied as mauve, oval, biconvex, film-coated, intagliated with "nGL" on one side and "12.5" on the other side.
- Tablets: 25 mg supplied as mauve, oval, biconvex, film-coated, intagliated with "nGL" on one side and "25" on the other side.

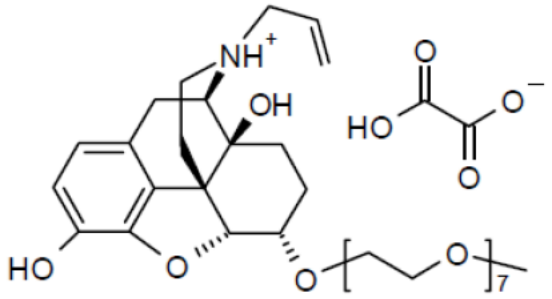
Item	Information Provided in NDA
Available dosage forms	Tablets **Satisfactory**
Strengths: in metric system	25 mg, 12.5 mg **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	None **Satisfactory**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Oval, biconvex, mauve, film-coated tablet intagliated with "nGL" on one side and "12.5" or "12.5" on the other side. **Satisfactory**

The "Dosage Forms and Strengths" section is adequate.

#11: Description

MOVANTIK (naloxegol), an opioid antagonist, contains naloxegol oxalate as the active ingredient. (Naloxegol is a PEGylated derivative of naloxone.)

The chemical name for naloxegol oxalate is: (5α,6α)-17-allyl-6-(2,5,8,11,14,17,20-heptaoxadocosan-22-yloxy)-4,5- epoxymorphinan-3,14-diol oxalateepoxymorphinan-3,14-diol oxalate. The structural formula is:



The empirical formula for naloxegol oxalate is $C_{34}H_{53}NO_{11}*C_2H_2O_4$ and the molecular weight is 742.

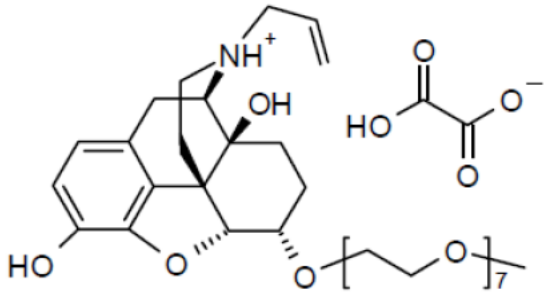
Naloxegol oxalate is a white to off-white powder, with high aqueous solubility across the physiologic pH range.

MOVANTIK (naloxegol) tablets for oral use contain 14.2 mg and 28.5 mg of naloxegol oxalate, respectively equivalent to 12.5 mg and 25 mg of naloxegol.

Excipients in tablet core are: mannitol, cellulose microcrystalline, croscarmellose sodium, magnesium stearate, and propyl gallate.

Excipients in tablet coat are: hypromellose, titanium dioxide, polyethylene glycol, iron oxide red, and iron oxide black.

Item	Information Provided in NDA
Proprietary name and established name	MOVANTIK (naloxegol) **Satisfactory**
Dosage form and route of administration	Tablets **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Contain 14.2 mg and 28.5 mg of naloxegol oxalate, respectively equivalent to 12.5 mg and 25 mg of naloxegol. **Satisfactory**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Excipients in tablet core are: mannitol, cellulose microcrystalline, croscarmellose sodium, magnesium stearate, and propyl gallate. Excipients in tablet coat are: hypromellose, titanium dioxide, polyethylene glycol, iron oxide red, and iron oxide black. **Satisfactory**
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Opioid antagonist **Satisfactory**

Chemical name, structural formula, molecular weight	 (5α,6α)-17-allyl-6-(2,5,8,11,14,17,20-heptaoxadocosan-22-yloxy)-4,5- epoxymorphinan-3,14-diol oxalateepoxymorphinan-3,14-diol oxalate, $C_{34}H_{53}NO_{11}*C_2H_2O_4$, MW: 742 **Satisfactory**
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	High aqueous solubility across the physiologic pH range. **Satisfactory**

The "Description" section is adequate.

#16: How Supplied/Storage and Handling

MOVANTIK (naloxegol oxalate) tablets are supplied as:

- NDC 0310-1969-30: 12.5 mg, bottle of 30 tablets
- NDC 0310-1969-90: 12.5 mg, bottle of 90 tablets
- NDC 0310-1969-39: 12.5 mg, unit dose blister carton of 100 tablets (for HUD only)
- NDC 0310-1970-30: 25 mg, bottle of 30 tablets
- NDC 0310-1970-90: 25 mg, bottle of 90 tablets
- NDC 0310-1970-39: 25 mg, unit dose blister carton of 100 tablets (for HUD only)

Store MOVANTIK at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA
Strength of dosage form	12.5 mg , 25 mg tablets **Satisfactory**
Available units (e.g., bottles of 100 tablets)	bottle of 30 tablets bottle of 90 tablets unit dose blister carton of 100 tablets **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC numbers listed **Satisfactory**
Special handling (e.g., protect from light)	N/A
Storage conditions	Store MOVANTIK at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	None, however it shows at the bottom of the package insert. **Satisfactory**

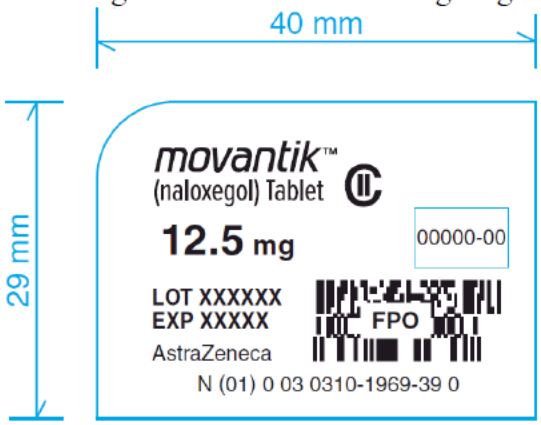
The "How Supplied/Storage and Handling" section is adequate.

Overall PI Evaluation:

The Prescribing Information is **ADEQUATE**.

2. Immediate container labels

The image of the label for 12.5 mg single unit blister is shown below:



Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Movantic™ (naloxegol) Tablet **Satisfactory**
Dosage strength	12.5 mg. **Satisfactory**
Net contents	None **Satisfactory**
"Rx only" displayed prominently on the main panel	None **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Yes **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Yes **Satisfactory**
Storage conditions	None **Satisfactory**
Bar code (21CFR 201.25)	Yes **Satisfactory**
Name of manufacturer/distributor	Yes **Satisfactory**
And others, if space is available	N/A

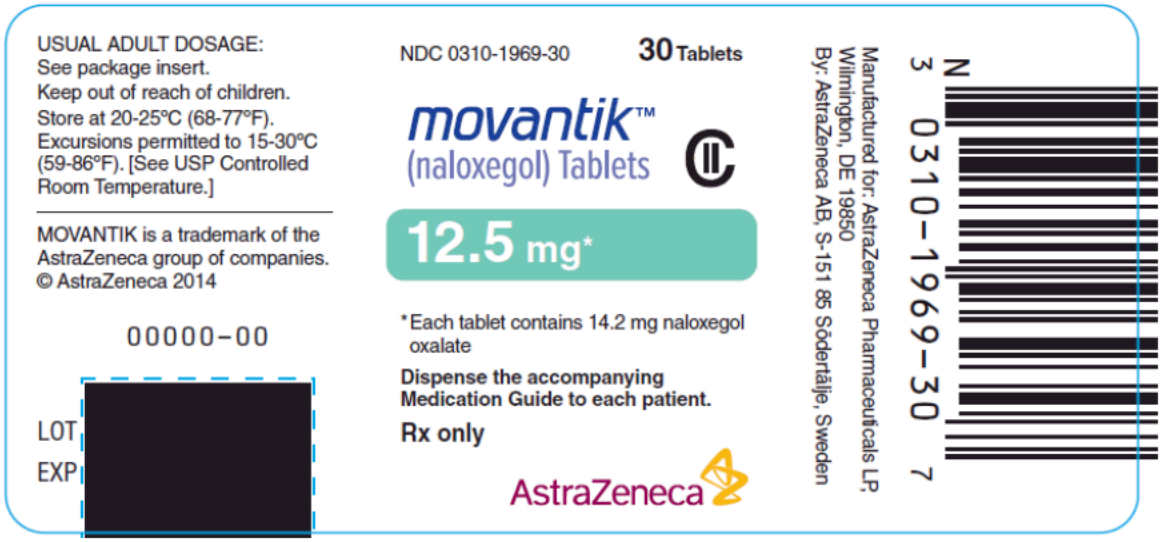
Blister label for 25 mg tablets includes the same information, except for strength 25 mg.

Evaluation:

- It is noted that "Rx only" and storage conditions are not present on the blister label. It is considered acceptable since, according to 21 CRF 210.10 (i) these items can be omitted from the small container label as long as they appear on the carton.
- Net content is not specified, however it is deemed acceptable for a single tablet

blister. Moreover, the name implies a single tablet.

The image of the label for bottle of 30 counts of 12.5 mg tablets is shown below:



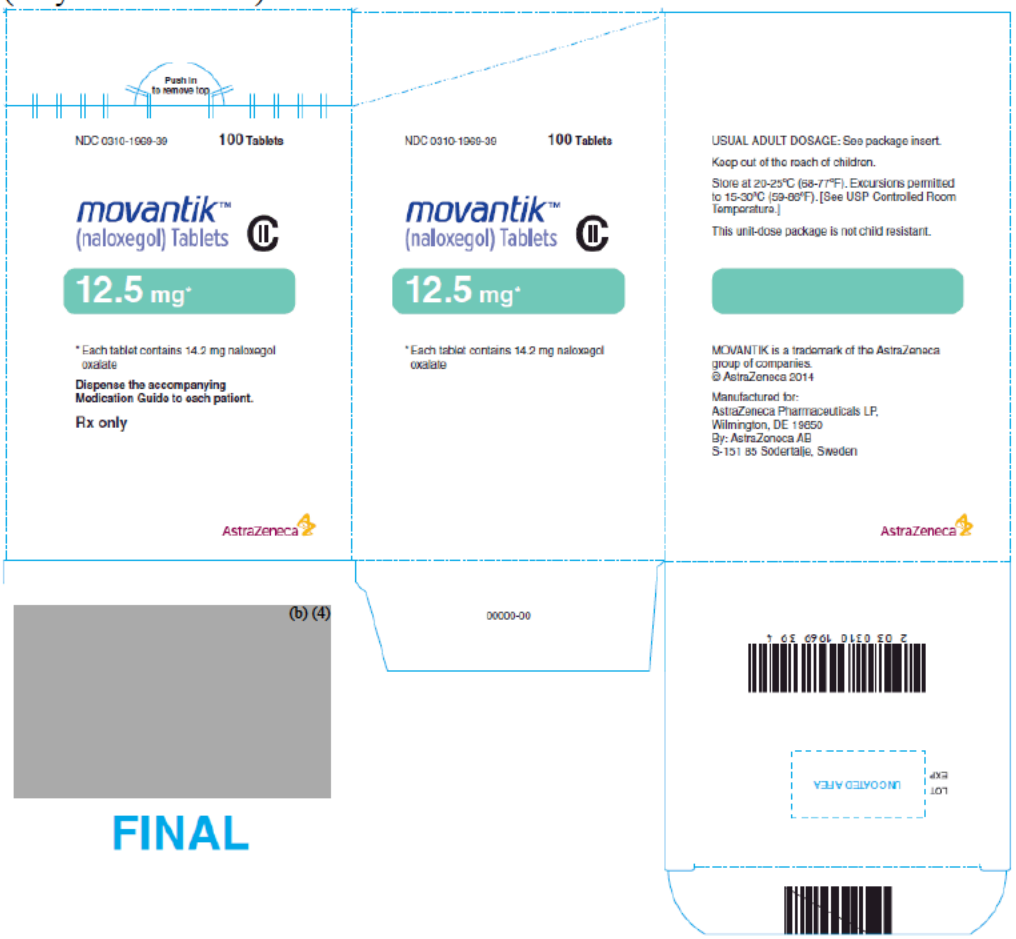
Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Movantic™ (naloxegol) Tablet **Satisfactory**
Dosage strength	12.5 mg, with appropriate equivalence statement **Satisfactory**
Net contents	30 tablets **Satisfactory**
"Rx only" displayed prominently on the main panel	Yes **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Yes **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Yes **Satisfactory**
Storage conditions	Store at 20-25°C (68-77 °F). Excursions permitted to 15-30°C (59- 86°F) [see USP Controlled Room Temperature]. **Satisfactory**
Bar code (21CFR 201.25)	Yes **Satisfactory**
Name of manufacturer/distributor	AstraZeneca **Satisfactory**
And others, if space is available	Usual adult dosage see package insert. Keep out of reach of children. **Satisfactory**

Remaining bottle labels for 30 counts of 25 mg tablets, 90 counts of 12,5 mg tablets, and 90 counts of 25 mg tablets list the same information except for the different net contents and strength.

Container labels are adequate.

3. Carton labeling

The image of the proposed carton for 100 counts of 12.5 mg tablets stored in blisters (only relevant faces) is shown below:



Item	Information Provided in NDA
Proprietary name, established name (font size, prominence)	Movantic™ (naloxegol) Tablet **Satisfactory**
Dosage strength	12.5 mg, with appropriate equivalence statement **Satisfactory**
Net quantity of dosage form	100 tablets **Satisfactory**
"Rx only" displayed prominently on the main panel	Yes **Satisfactory**
Lot number and expiration date	Yes **Satisfactory**
Storage conditions	Store at 20-25°C (68-77 °F). Excursions permitted to 15-30°C (59- 86°F) [see USP Controlled Room Temperature]. **Satisfactory**
Bar code (21CFR 201.25)	Yes **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Yes **Satisfactory**

Manufacturer/distributor's name	AstraZeneca **Satisfactory**
Quantitative ingredient information (injectables)	N/A
Statement of being sterile (if applicable)	N/A
"See package insert for dosage information"	The following statement provided: "Usual adult dosage: See package insert **Satisfactory**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Yes **Satisfactory**

Remaining carton labeling for:

- 100 (25 mg) tablets stored in blisters
- bottle, 30 of 12.5 mg tablets,
- bottle, 30 of 25 mg tablets,
- bottle, 90 of 12.5 mg tablets,
- bottle, 90 of 25 mg tablets

lists the same information except for the different net contents and strength.

Carton labeling is adequate.

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/s/

BOGDAN KURTYKA
09/12/2014

MOO JHONG RHEE
09/12/2014
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Bogdan Kurtyka, CMC Reviewer

Office of New Drug Quality Assessment (ONDQA)
E-mail Address: bogdan.kurtyka@fda.hhs.gov
Phone: (301)-796-796-1390
Fax: (301)-796-796-9745

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3815

Through: John Kauffman, Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 204760

Name of Product: Movantik (Naloxegol) tablets 12.5 mg and 25 mg

Applicant: Asta Zeneca

Applicant's Contact Person: Barry Sickels

Address: 1800 Concord Pike, PO Box 8355, Wilmington, DE 19803-8355

Telephone: (302) 886-5895 Fax: (302) 886-2822

Date Methods Validation Consult Request Form Received by DPA: Nov-8-2013

Date Methods Validation Package Received by DPA: Nov-8-2013

Date Samples Received by DPA: Jun-11-2014

Date Analytical Completed by DPA: Aug-25-2014

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments: See attached memo for analysts' comments, summary of results and link to data sheets.

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63110
Tel. (314) 539-3874

Date: August 25, 2014

To: Bogdan Kurtyka, Reviewer, Office of New Drug Quality Assessment

Through: John Kauffman, Deputy Director, Division of Pharmaceutical Analysis

From: Anna Wokovich, Chemist, Division of Pharmaceutical Analysis

Subject: NDA 204760, Naloxegol

Data: Data package available at
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f88079bfa1

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. S.4.2A Analytical Procedure for (b) (4) test by LC; (b) (4)
2. S.4.2A Analytical Procedure for Assay by UHPLC; (b) (4)
3. S.4.2A Analytical Procedure for Assay by HPLC; (b) (4)
4. P.5.2A Analytical procedure for (b) (4) LC; (b) (4)

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/s/

MICHAEL L TREHY
08/25/2014

JOHN F KAUFFMAN
08/25/2014

NDA 204760

Movantik (naloxegol) tablets
12.5 mg and 25 mg

AstraZeneca Pharmaceuticals LP

Bogdan Kurtyka, Ph.D.
Review Chemist

Office of New Drug Quality Assessment
Division New Drug Quality Assessment II
Branch IV

CMC REVIEW OF NDA 204760
For the Division of Gastroenterology and Inborn Errors Products
(HFD-180)

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CMC Review Data Sheet

1. NDA 204760

2. REVIEW #: 1

3. REVIEW DATE: 12-Jun-2014

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	16-Sep-2013
Update of analytical methods	17-Jan-2014
Response to Information Request	14-Apr-2014
Response to Information Request	15-May-2014

7. NAME & ADDRESS OF SPONSOR:

Name:	AstraZeneca Pharmaceuticals LP
Address:	1800 Concord Pike P.O. Box 8355 Wilmington, DE, USA
Telephone:	302-886-5895
Fax:	302-886-2822

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Movantic
b) Non-Proprietary Name (USAN): Naloxegol oxalate
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Mu-opioid receptor antagonist

CMC Review Data Sheet

11. DOSAGE FORM: Tablet, coated CODE: 502

12. STRENGTH/POTENCY: 12.5 and 25 mg (as free base)

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

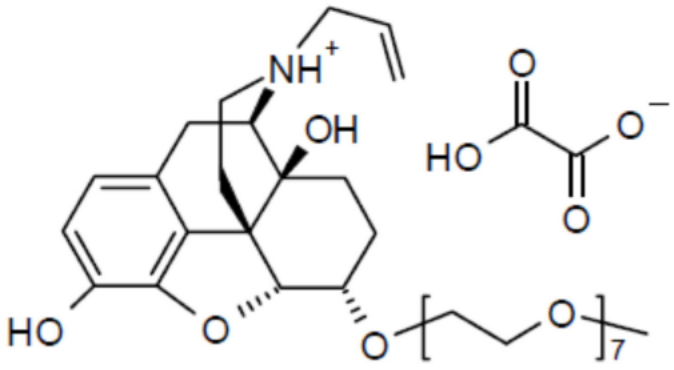
14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

_____SPOTS product – Form Completed
__√__Not a SPOTS product

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

Chemical Name: (5α,6α)-17-allyl-6-(2,5,8,11,14,17,20-heptaoxadocosan-22-yloxy)-4,5-epoxymorphinan-3,14-diol oxalate
USAN Name: Naloxegol oxalate
CAS Number: 1354744-91-4
Structural Formula:



Molecular Formula: $C_{34}H_{53}NO_{11}*C_2H_2O_4$
Molecular weight: 741.8

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	N/A	N/A	
	III			4	N/A	N/A	

(b) (4)		(b) (4)	(b) (4)				
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	
	III			4	N/A	N/A	

on 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")
[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: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Approval	15-May-2014	Yuk Chow Ng
Biopharm	Approval	16-May-2014	Kareen Riviere
LNC	N/A		
Methods Validation	Pending		
DMEPA	N/A		
EA	Pending		
Microbiology	Approval	06-Jun-2014	Stephen Langille

The CMC Review for NDA 204399

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The office of Compliance has ***not*** issued an overall recommendation of "Acceptable" for the facilities involved in this application.

The label/labeling issues are ***not*** fully resolved (see the **List of Deficiencies**, page 93).

Therefore, from the ONDQA perspective, this NDA is ***not*** ready for approval per 21CFR 314.125(b)(6) and (13) in its present form until the issues delineated in the **List of Deficiencies** (page 93) are satisfactorily resolved.

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

N/A

II. Summary of CMC Assessments

A. Description of the Drug Substance and Drug Product

(1) Drug Substance

The proposed drug substance naloxegol oxalate is a new molecular entity. It is a white to off-white (b) (4) powder, highly soluble in water in pH range 1 to 7.5. It is manufactured in a (b) (4). The sponsor proposed to control multiple potential and observed impurities through in-process controls and specification. The sponsor proposed not to control some impurities and polymorphic forms. Based on the knowledge of manufacturing process and batch data obtained so far the sponsor demonstrated that the risk of such impurities being present in drug substance is negligible. This approach is acceptable.

The drug substance specification includes description, identification, assay, organic impurities, a specified genotoxic impurity (b) (4), and residue on ignition. The limits for organic and genotoxic impurities were found adequate by toxicology reviewer and

the specification is deemed satisfactory.

Drug substance is packaged in [redacted] The container system is deemed satisfactory.

The sponsor provided the results of up to 12 months long-term stability studies, and proposed an [redacted] retest period, which is justified by the submitted data.

(2) Drug Product

Naloxegol oxalate tablets 12.5 and 25 mg (as free base) are indicated for treatment of opioid-induced constipation in adults with chronic non-cancer pain. Drug product is an immediate release tablet.

The inactive ingredients of the formulation are commonly used in oral drug products. The drug product is manufactured by [redacted] The sponsor proposed its establishment in Södertälje, Sweden as the manufacturing site.

The drug product specification includes: description, identification, assays of drug substance and [redacted] degradation products, dissolution, uniformity of dosage units, and [redacted]. [redacted] content is tested on the annual bases. The test attributes, acceptance criteria, analytical methods and their validation are deemed satisfactory.

Three container closure systems are proposed: HDPE bottle, aluminum/aluminum blister, and [redacted] for bulk storage. The information included in the application demonstrates that the proposed container/closure systems are suitable for drug product.

The sponsor provided the results of up to 12 months long-term stability studies, and proposed a 24-month expiration dating period for all packaging presentations under the controlled room temperature conditions. The requested expiration dating periods are granted for all the packaging configurations.

The applicant claimed categorical exclusion from the Environmental Assessment based on 21CFR 25.31(a) or (b). This claim is pending the review of Environmental Review staff.

Method validation request has been sent to DPA for assay and selected impurities procedures. By the time this review is written, the validation report was not completed.

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

Drug product (25 mg) should be taken once daily in the morning on an empty stomach

at least (b) (4) prior to the first meal of the day or 2 hours post meal.

C. Basis for Not-Approval Recommendation

21 CFR 314.125(b)(13)

- No final "Acceptable" recommendation has been made from the Office of Compliance.

21CFR 314.125(b)(6)

- Labels and labeling issues are not finalized.

(see the **List of Deficiencies** on page 93).

III. Administrative

A. Reviewer's Signature: *(See appended electronic signature page)*

Bogdan Kurtyka, Ph.D.
CMC Reviewer, Branch IV/Division II/ONDQA

B. Endorsement Block: *(See appended electronic signature page)*

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV/Division II/ONDQA

C. CC Block: Entered electronically in DARRTS

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/s/

BOGDAN KURTYKA
06/12/2014

MOO JHONG RHEE
06/12/2014
Chief, Branch IV

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **204760**
2. DATES AND GOALS:

Letter Date: 9/16/2013	Submission Received Date : 9/16/2013
PDUFA Goal Date: 9/16/2014	Filing Date: **11/15/2013**

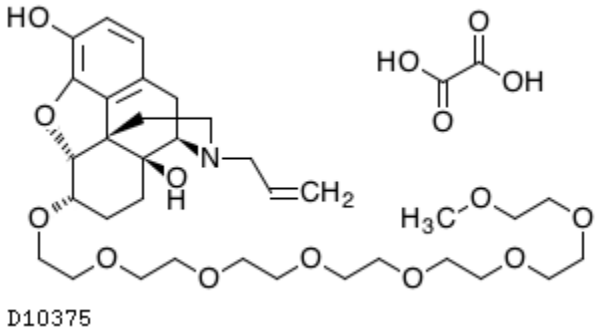
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Movantig
Established or Non-Proprietary Name (USAN):	**naloxegol (USAN)** **naloxegol oxalate (USAN)**
Dosage Form:	**tablets**
Route of Administration	**oral**
Strength/Potency	**25mg and 12.5mg**
Rx/OTC Dispensed:	**Rx**

4. INDICATION: treatment of opioid-induced constipation in adults with chronic non-cancer pain

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Naloxegol Oxalate: $C_{34}H_{53}NO_{11}\cdot C_2H_2O_4$. 741.80



Naloxegol: $C_{34}H_{53}NO_{11}$. 651.78

(Naloxegol is the PEGylated derivative of naloxone)

6. NAME OF APPLICANT (as indicated on Form 356h): AstraZeneca

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 1 (NME)
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Gastrointestinal and Inborn Error Products (HFD-180)

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Establishment Evaluation Request (EER)	x		
Methods Validation	x		
Environmental Assessment	x		Request for categorical exclusion
CDRH		x	
Other		x	

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?
Yes √ No

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?
Yes No √
CMC Comments for 74-Day Letter: **none**

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
Yes √ No

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?
Yes √ No
Biopharmaceutics Comments for 74-Day Letter:
1. Submit a SAS transport file of the plasma concentration data from the BE study (D3820C00018). This data should also include the first and last time points used to estimate the elimination constant (Kel) for each subject/period as shown. Please submit the data in the following format: SUBJ SEQ PER TRT C1 C2 C3...Cn KE_FIRST KE_LAST T1 T2 T3…Tn 2. In addition, submit a SAS transport file of the pharmacokinetic data from the BE study. The data should include AUC0-t, AUC0-inf, Cmax, Tmax, Kel, and T1/2 as shown. Please submit the data in the following format: SUBJ SEQ PER TRT AUC AUCINF CMAX TMAX KE Thalf

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?
Yes √ No
Microbiology Filing Issues:
See Microbiology Filing Review for details and for any potential Microbiology review issues.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	no	no	no

Is a team review recommended?	Yes
Reviewers already assigned:	NDA: Bogdan Kurtyka, PhD Biopharmaceutics: Kareen Riviere, PhD Micro: Stephen Langille

Summary of Critical Issues and Complexities

Naloxegol is a PEGylated derivative of naloxone, where the PEG chain is comprised of seven monomer units (PEG-7). Specified impurities include a [(b) (4)] [(b) (4)], with proposed limits, respectively at [(b) (4)] While these limits exceed ICH recommendations, it is not anticipated that these impurities pose any more of a safety risk than the PEG-7 drug substance itself, and the proposed limits should be acceptable. However, this should be confirmed with the toxicology reviewer.

[(b) (4)] are genotoxic impurities that are reported to be formed [(b) (4)] The review will need particular attention to this issue to ensure that proper controls are in place.

The limit for unspecified impurities in the drug product is specified at [(b) (4)]%, which exceeds the ICH identification limit is 0.2%. This should be further evaluated.

Initial Quality Assessment

Movantik (naloxegol oxalate) Tablets is intended for once daily administration in the treatment of opiod-induced constipation. This product was developed under IND 78781. Phase 3 clinical trials were conducted with naloxegol free base, but the naloxegol oxalate salt will be used in the proposed commercial product. Bioequivalence studies have been conducted to link the two formulations. The commercial product will be formulated as an immediate release, film-coated tablet. It will come in two strengths, 12.5 mg, 25 mg (or 14.2 mg, 28.5 mg, expressed as naloxegol oxalate). Both tablet strengths will be marketed in 30 and 90 count bottles and in blister packs. A matrixing design was used in the stability studies; the stability protocol that was used for these studies was agreed to by the Agency in 2012..

Because naloxegol is a new molecular entity, according to the Chemical Classification Code this is a Type 1 application.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			Synthetic drug substance

ONDQA Initial Quality Assessment (IQA) and Filing Review

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	√		
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	√		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	√		Claim of categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	√		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		
14.	Does the section contain information regarding the characterization of the DS?	√		
15.	Does the section contain controls for the DS?	√		
16.	Has stability data and analysis been provided for the drug substance?	√		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		BE studies were conducted to link the phase 3 clinical formulations with the proposed commercial formulation
23.	Have any biowaivers been requested?		√	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	√		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			A micro biology reviewer has been assigned

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		All drug substance information has been included directly in the NDA; DMF references are provided for all container/closures and components

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

ONDQA Initial Quality Assessment (IQA) and Filing Review

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	204-760
Submission Date	9/16/2013
Product name, generic name of the active	Movantik (naloxegol oxalate)
Dosage form and strength	IR Tablets/ 12.5 mg and 25 mg
Applicant	AstraZeneca
Clinical Division	DGIEP
Indication	Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain
Type of Submission	505(b)(1) Original
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.
Biopharmaceutics Supervisor (acting)	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
34.	Does the application contain dissolution data?	x		
35.	Is the dissolution test part of the DP specifications?	x		See the Initial Assessment section for the proposed dissolution method and acceptance criterion.
36.	Does the application contain the dissolution method development report?	x		
37.	Is there a validation package for the analytical method and dissolution methodology?	x		
38.	Does the application include a biowaiver request?	x		The Applicant is requesting a biowaiver for the 12.5 mg strength product.
39.	Is there information provided to support the biowaiver request?	x		
40.	Does the application include a IVIVC model?		x	Not Applicable.
41.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant reports that naloxegol oxalate is a BCS Class 3 compound.
42.	Is information on mixing the product with foods or liquids included?		x	Not Applicable.

43.	Is there any in *vivo* BA or BE information in the submission?	x		BA studies 08-PNL-04 and D3820C00025 will be evaluated by the OCP Reviewer. BE study D3820C00018 to demonstrate bioequivalence between the phase 3 formulation and the commercial formulation will be reviewed by ONDQA/ Biopharmaceutics.
44.	Is there a complete bio-analytical method development and validation report?	x		

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
45.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
46.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	
47.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		IR comments will be sent to the Applicant in the 74 day letter. The comments are outlined in the Initial Assessment.

INITIAL BIOPHARMACEUTICS ASSESSMENT

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method, the proposed dissolution acceptance criterion, BE and dissolution data bridging the Phase 3 formulation and the commercial formulation, and dissolution data supporting a biowaiver for the 12.5 mg strength tablet.

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	500 mL	37 °C	0.1 M HCl

The proposed acceptance criterion is:

Acceptance Criteria
Q = (b)(4)% at 30 minutes

The Biopharmaceutics review will focus on the evaluation and acceptability of:

1) the proposed dissolution methodology,

2) the proposed dissolution acceptance criterion,
3) the BE and dissolution data bridging the Phase 3 formulation and the commercial formulation, and
4) the dissolution data supporting a biowaiver for the 12.5 mg strength tablet.

RECOMMENDATION:

The ONDQA Biopharmaceutics team has reviewed NDA 204-760 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

To aid the review of this NDA submission, the following comment will be conveyed to the Applicant:

3. Submit a SAS transport file of the plasma concentration data from the BE study (D3820C00018). This data should also include the first and last time points used to estimate the elimination constant (Kel) for each subject/period as shown. Please submit the data in the following format:

   SUBJ SEQ PER TRT C1 C2 C3...Cn KE_FIRST KE_LAST T1 T2 T3…Tn

4. In addition, submit a SAS transport file of the pharmacokinetic data from the BE study. The data should include AUC0-t, AUC0-inf, Cmax, Tmax, Kel, and T1/2 as shown. Please submit the data in the following format:

   SUBJ SEQ PER TRT AUC AUCINF CMAX TMAX KE Thalf

ONDQA Initial Quality Assessment (IQA) and Filing Review

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Marie Kowblansky, PhD
CMC-Lead
Division II
Office of New Drug Quality Assessment

{See appended electronic signature page}
Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

{See appended electronic signature page}
Moo-Jhong Rhee, PhD
Branch Chief
Division II
Office of New Drug Quality Assessment

ONDQA Initial Quality Assessment (IQA) and Filing Review

APPEARS THIS WAY ON ORIGINAL

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/s/

MARIE KOWBLANSKY
11/15/2013

KAREEN RIVIERE
11/15/2013

TAPASH K GHOSH
11/15/2013

MOO JHONG RHEE
11/15/2013
Chief, Branch IV

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet
II. Application Detail
III. Filing Checklist
IV. Manufacturing Summary
V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. DMPQ Reviewer: Christina Capacci-Daniel

2. NDA/BLA Number: NDA 204760
   Submission Date: Sept 16, 2013
   21st C. Review Goal Date: July 16, 2013
   PDUFA Goal Date: Sept 16, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Movantik
Established or Non-Proprietary Name (USAN) and strength:	Naloxegol oxalate, 12.5mg and 25mg
Dosage Form:	Tablet, film-coated

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Astrazeneca Pharmaceuticals LP
Responsible Organization (OND Division):	DGIEP

II. Application Detail

1. INDICATION: Treatment of opioid-induced constipation in adult patients with chronic non-cancer pain

2. ROUTE OF ADMINISTRATION: Oral

3. STRENGTH/POTENCY: 12.5mg and 25mg

4. Rx/OTC DISPENSED: ☒Rx ☐OTC

5. ELECTRONIC SUBMISSION (yes/no)? YES

6. PRIORITY CONSIDERATIONS: NONE

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	☑			NME reviewed under the Program
2.	Breakthrough Therapy Designation		☑		
3.	Orphan Drug Designation		☑		
4.	Unapproved New Drug		☑		
5.	Medically Necessary Determination		☑		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		☑		
7.	Rolling Submission		☑		
8.	Drug/device combination product with consult		☑		
9.	Complex manufacturing		☑		
10.	Other (e.g., expedited for an unlisted reason)		☑		

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	☑		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	☑		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	☑		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	-	-	All testing performed at drug substance and drug product manufacturing sites
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	☑		
		☑		(b) (4) planned for (b) (4) facilities and possibly the TCM site.
			☑	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?	☑		(b) (4) [redacted]

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?	☑		NME
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	☑		EERs have been cross referenced against 356h Initial OC recommendation has been made; EERs are being processed
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	☑		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	☑		(b) (4) [redacted]

(b) (4) [redacted]

(b) (4)

2.

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		☑	(b) (4)

COMPONENTS	PROCESS/EQUIPMENTS	IPC
(b) (4)		

3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

- There are no issues at this time. All facilities have NAI inspectional histories.

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

- There are no issues. Recent inspectional history is NAI.

Additional information not covered above

Manufacturing Facilities Chart (generated from 602A DARRTS report and OMPQ macro):

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Comment
[redacted]								(b) (4)
ASTRAZENECA PHARMACEUTIC (b) (4)	2517100	PHI	USA	Packing and batch release	TCM	07/05/2011 VAI covering TCM	OC RECOMMENDATION	
ASTRAZENECA SWEDEN OPERATIONS (TABLET PRODUCTION SWEDEN)	3003342394	WEU	SWE	Drug product manufacturing, quality control testing, packing, batch release and stability testing	TCM	05/29/2012 NAI for (b) (4) 03/25/2010 NAI for (b) (4)	ASSIGNED INSPECTION TO IB (PS&GMP)	(b) (4)

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no) **YES**
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. (b) (4) • **Astrazeneca Sweden Operations (TCM)** – CGMP inspection needed, PAI to focus o (b) (4)
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no)
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL
(DARRTS)

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

/s/

CHRISTINA A CAPACCI-DANIEL
11/15/2013

TARA R GOOEN
11/15/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Bogdan Kurtyka, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: bogdan.kurtyka@fda.hhs.gov
Phone: (301)-796-1431
Fax.: (301)-796-9745

Through: Moo-Jhong Rhee, Branch Chief
Phone: (301)-796-1390
and Youbang Liu
ONDQA Methods Validation Project Manager
Phone: 301-796-1926:

SUBJECT: Methods Validation Request

Application Number: NDA 204760

Name of Product: Movantik (Naloxegol) tablets 12.5 mg and 25 mg

Applicant: Astra Zeneca

Applicant's Contact Person: Barry Sickels

Address: 1800 Concord Pike, PO Box 8355, Wilmington, DE 19803-8355

Telephone: 302-886-5895 Fax: 302-886-2822

Date NDA Received by CDER: **16-Sep-2013**

Date of Amendment(s) containing the MVP: **N/A**

DATE of Request: **07-Nov-2013**

Requested Completion Date: **16-Aug-2013**

PDUFA User Fee Goal Date: **16-Sep-2013**

Submission Classification/Chemical Class: NME

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

☐ Paper **X** Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as descr bed in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA # 204760

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	3.2.P.1
Specifications/Methods for New Drug Substance(s)	3.2.S.4
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5
Supporting Data for Accuracy, Specificity, etc.	N/A
Applicant's Test Results on NDS and Dosage Forms	3.2.S.4.4, 3.2.P.5.4
Other: N/A	

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
N/A	Assay by UHPLC, drug substance	3.2.S.4.2	**0**	N/A
N/A	Assay by HPLC, drug substance	3.2.S.4.2	**0**	N/A
N/A	(b) (4) test by LC, drug substance	3.2.S.4.2	**0**	N/A
N/A	(b) (4) by LC, drug product	3.2.P.5.2	**0**	N/A

Additional Comments: **N/A**

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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

/s/

BOGDAN KURTYKA
11/08/2013

MOO JHONG RHEE
11/08/2013

YOUBANG LIU
11/08/2013