

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202611Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: May 25, 2012

To: NDA 202-611

From: Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 202-611, mirabegron extended release tablets, 25 mg and 50 mg, (b) (4)™.

I have assessed the ONDQA reviews of NDA 202-611 by Bogdan Kurtyka, Ph.D. and John Duan, Ph.D. The ONDQA Biopharmaceutics review was entered into DARRTS on April 24, 2012, with a recommendation of Approval from the ONDQA Biopharmaceutics perspective. The review focused on the evaluation of the proposed in vitro release method, dose dumping and in vitro in vivo correlation (IVIVC). Three ONDQA CMC reviews were entered into DARRTS by Dr. Kurtyka. The initial ONDQA CMC review was entered into DARRTS on April 26, 2012, with a recommendation for a Complete Response due to the blister pack label not containing appropriate information. All other ONDQA related labeling issues were resolved prior to April 26, 2012. The second CMC review was entered into DARRTS on May 16, 2012. The ONDQA recommendation was changed from Complete Response to Approval based on labeling data submitted by the applicant on May 11, 2012. Dr. Kurtyka entered a third review into DARRTS on May 22, 2012 summarized the results of a Method Validation Request submitted for this product (for more information see report entered in to DARRTS by Michael Trehy on May 18, 2012). The results of this method validation did not affect the approvability of this NDA. Therefore, the ONDQA recommendation for NDA 202-611 remains, Approval.

On April 19, 2012 the Office of Compliance entered an Overall Recommendation of “Acceptable” into EES. This recommendation was confirmed in EES on May 25, 2012.

Through evaluation of the submitted biopharmaceutics related information, Dr. Duan determined that: 1) the proposed in vitro release method, using USO Apparatus 1 at 100 rpm and 3 sample points is acceptable, 2) the drug product does not demonstrate a potential for dose dumping in alcohol and 3) the provided data supported a “Level C” IVIVC.

The drug substance, manufactured by Astellas Pharma Tech Co., Ltd., Takahagi Technology Center, 160-2, Akahama, Takahagi-shi, Ibaraki 318-0001, Japan. A (b) (4) retest period of is granted based on the submitted stability data.

The proposed drug products, (b) (4) (mirabegron) extended release tablets, 25 mg and 50 mg, are brown or yellow, debossed with “325” or “355” and the Astellas logo, respectively. The proposed dose is one tablet daily.

I concur with the determination that the information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support the recommendation of a drug product shelf life of 24 months for the proposed 25 mg tablets in bottles and 36-months for the proposed 50 mg tablets in bottles, and both the 25 mg and 50 mg strengths in blisters packs when stored at controlled room temperature.

Secondary review of the ONDQA CMC reviews was performed by Moo-Jhong Rhee, Ph.D.
Secondary review of the ONDQA Biopharmaceutics review was performed by Angelica Dorantes, Ph.D.

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/s/

TERRANCE W OCHELTREE
05/25/2012

Memorandum

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 22-May-2012

From: Bogdan Kurtyka, Ph.D.
CMC Reviewer

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

To: Memorandum, dated 16-May-2012, to CMC Review #1 for NDA 202-611

CC: Donna Christner, Ph.D.

Subject: Method Validation

Methods Validation Consult Request to evaluate selected analytical procedures submitted in NDA 202-611 was sent to the Division of Pharmaceutical Analysis on November 1, 2011. The Methods Validation Report Summary dated 18-May-2012 indicated that the methods are acceptable for the regulatory purposes.

During the validation process, the FDA laboratory noted that the amount of BHT in the drug product samples was out of specification. However, this is expected result as discussed below, and this observation would not affect our previous "Approval" recommendation.

Attachment

Review Notes on the Method Validation Reports

The report includes the following statement:

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to this method.

- Drug Product BHT

(Astellas Pharma Global Development, CTD Module 3.2.S.4.2, Drug Substance, page 12)

Duplicate analyses of the sample confirmed the BHT amount in the Tablets was out of specification.

The comment is based on the following results obtained during evaluation:

	BHT (mg), Run#1	BHT (mg), Run#2
Amount	(b) (4)	
Limit		

Pass/Fail: Fail

Evaluation:

Butylated Hydroxytoluene (BHT) specification limit was defined only for release. It is expected that during storage of drug product level of BHT will decrease. Therefore the result obtained by the Division of Pharmaceutical Analysis is expected and acceptable.

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/s/

BOGDAN KURTYKA
05/22/2012

MOO JHONG RHEE
05/22/2012
Chief, Branch IV

Memorandum

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 16-May-2012

From: Bogdan Kurtyka, Ph.D.
CMC Reviewer

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

To: CMC Review #1 for NDA 202-611

CC: Donna Christner, Ph.D.

Subject: Final Recommendation

Previous CMC Review #1 dated 23-Apr-2012 noted the following deficiency with a recommendation of “Non Approval” action.

The blister pack labels do not have the required name of the manufacturer, packer, or distributor.

The sponsor addressed above issue satisfactorily in the submission dated 11-May-2012 (see the **Attachment**).

Recommendation:

This NDA is now recommended for “**Approval**” from the ONDQA perspective.

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/s/

BOGDAN KURTYKA
05/16/2012

MOO JHONG RHEE
05/16/2012
Chief, Branch IV

NDA 202-611

(b) (4)

**(mirabegron) extended release tablets
25 mg and 50 mg**

Astellas Pharma US, Inc.

Bogdan Kurtyka, Ph.D.
Review Chemist

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

**CMC REVIEW OF NDA 202-611
For the Division of Reproductive and Urologic Products (HFD-580)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202-611
2. REVIEW #: 1
3. REVIEW DATE: 23-Apr-2012
4. REVIEWER: Bogdan Kurtyka, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>EDR Document Date</u>
Original Submission	29-Aug-2011
Amendment – Stability update	22-Dec-2011
Amendment – Responses to IR	17-Jan-2012
Amendment – Specification and stability update	07-Mar-2012
Amendment – Responses to IR	20-Mar-2012
Amendment – Responses to IR	11-Apr-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Astellas Pharma US, Inc.
Address: Three Parkway North
Deerfield, IL 60015-2548
Representative: Judy Kannenberg, Associate Director, Regulatory Affairs
Telephone: (847) 317-1277

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: (b) (4)
a) Non-Proprietary Name: mirabegron
b) Code Name/# (ONDQA only): None
c) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: A selective agonist for human beta 3-adrenoceptor is indicated for the treatment of overactive bladder.
11. DOSAGE FORM: Tablet, film coated, extended release CODE: 511
12. STRENGTH/POTENCY: 25 mg and 50 mg
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

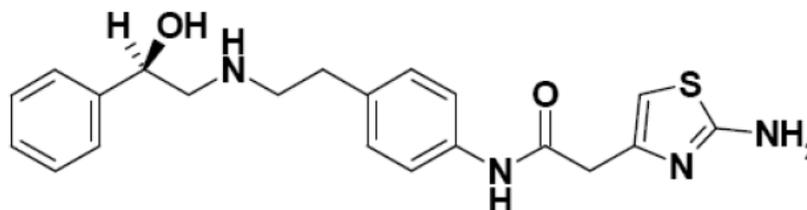
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2-(2-aminothiazol-4-yl)-N-[4-(2-{{(2R)-2-hydroxy-2-phenylethyl}amino}ethyl)phenyl]acetamide

USAN Name: Mirabegron

CAS Number: 5223673-61-8

Structural Formula:



Molecular Formula: C₂₁H₂₄N₄O₂S

Molecular Weight: 396.51

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	[REDACTED]	(b) (4)	3	Adequate	15-Sep-2000	Reviewed by Dr. Donald Klein
	III			1	Adequate	16-Apr-2012	
	III			3	Adequate	15-Jun-2010	Reviewed by Dr. George Lunn
	III			1	Adequate	21-Mar-2012	
	III			3	Adequate	28-Jan-2010	Reviewed by Dr. Rajiv Agarwal
	IV			4	N/A	N/A	N/A

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")

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	Acceptable	19-Apr-2012	Bogdan Kurtyka, Ph.D.
Pharm/Tox	N/A		
Biopharm	Acceptable	24-Apr-2012	John Duan, Ph.D.
LNC	N/A		
Methods Validation	Pending		
DMEPA	N/A		
EA	Categorical exclusion is granted (see review)	14-APR-2012	Bogdan Kurtyka, Ph.D.
Microbiology	Acceptable	09-Mar-2012	Bryan S. Riley, Ph.D.

Executive Summary Section

The CMC Review for NDA 202-611

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

The office of Compliance has issued an overall recommendation of “Acceptable” for the facilities involved in this application (see the Attachment, p. 86).

However, an issue on the blister labels is still pending as of the date of this review.

Therefore, from the ONDQA perspective, this NDA is *not* recommended for approval per 21CFR 314.125(b)(6) in its present form until the issue delineated in the “List of Deficiencies” (see p. 85) is 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 Product(s) and Drug Substance(s)

(1) Drug Substance

The proposed drug substance, mirabegron, is a new molecular entity. It is a white (b) (4) powder practically insoluble in water and soluble in ethanol.

Drug substance is manufactured (b) (4)

Structure of drug substance was confirmed by multiple techniques including elemental analysis, mass spectroscopy, NMR, UV, and IR spectroscopy, but the ultimate confirmation of the structure was done by single crystal x-ray crystallography. (b) (4)

Executive Summary Section

(b) (4)

The proposed specification is deemed adequate to assure identity, strength, purity, and quality. Particularly, tests for (b) (4) genotoxic impurities, and (b) (4), which are potentially present in drug substance, are placed with appropriate acceptance limits. (b) (4)

(b) (4) All the analytical procedures and their validations are satisfactory.

Stability data support the proposed (b) (4) retest period.

(2) Drug Product

The drug product is in the form of oval, extended release, film coated tablets in the dosage strength of 25 mg or 50 mg. The tablets, developed for the treatment of overactive bladder, are brown or yellow, debossed with “325” or “355” and the Astellas logo, respectively. The application refers to the proposed drug product as Oral Controlled Absorption System (OCAS). OCAS is an extended release system developed by Astellas Pharma Inc., that allows the release of drug substance from the tablets for an extended period.

The main components of mirabegron tablets are the drug substance, polyethylene oxide (b) (4) and polyethylene glycol (b) (4) (PEG). (b) (4)

The extended release tablets are manufactured through: (b) (4)
(b) (4). The parameters for the processes were investigated in the DoE optimization study to optimize parameter ranges for each process.

(b) (4)

The final drug product is controlled by the specification which includes description, identification, impurities, assays, content uniformity, dissolution, (b) (4) tests. Analytical methods and acceptance criteria for all the tests are deemed satisfactory for assuring the identity, strength, purity, and quality.

Based on Microbiologist’s recommendation and applicant agreement, microbial test is to be done only in stability studies at initial and final time points.

The proposed container/closure systems consist of high density polyethylene bottles

Executive Summary Section

with child resistant enclosures and blisters with push-through lidding, both of which are considered adequate to protect the drug product during the expiration dating period.

The applicant provided the stability data up to 36 months under the long-term conditions, and proposed a 24-month (for 25 mg tablets in bottles) and 36-months (for 50 mg tablets in bottles, and both strengths in blisters) of expiration dating period under the controlled room temperature. The proposed expiration dating periods are granted.

The applicant claimed categorical exclusion from the Environmental Assessment based on 21CFR 25.31(b).

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

The intended dosage is one extended release tablet daily.

C. Basis for Not-Approval Recommendation

21CFR 314.125(b)(6)

- Labels for blister packs do not have the required information (see the **List of Deficiencies** on p.85).

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
04/26/2012

MOO JHONG RHEE
04/26/2012
Chief, Branch IV

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

OND Division: Division of Reproductive and Urologic Products
NDA: 202611
Applicant: Astellas
Stamp Date: 29-Aug-2011
PDUFA Date: 29-Jun-2012
Trademark: Mirbetan
Established Name: Mirabegron
Dosage Form: 25 and 50 mg tablets
Route of Administration: Oral
Indication: Treatment of overactive bladder

CMC Lead: Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	X

Summary and Critical Issues:

A. Summary

Mirabegron is a selective agonist for human beta 3-adrenoceptor (beta 3-AR) that is indicated for the treatment of overactive bladder. It is a New Molecular Entity.

Mirabegron OCAS (Oral Controlled Absorption System) tablets are oval, modified release, film-coated tablets. Tablets are available in 25 mg and 50 mg strengths and are packaged either in HDPE bottles of 30 or 90 tablets, and blister strips for institutional use and Physician Samples.

The applicant states that the OCAS formulation was developed with a systematic approach, in addition to conventional empirical approach. They used methods of design of experiments, quality risk management, and systematic evaluations of the formulations and manufacturing processes, in addition to prior knowledge and experiences from manufacturing. They created a pharmaceutical quality target product profile to identify critical quality attributes. Their goal was to make a product that was safe, efficacious and in a convenient dosage form that would facilitate patient compliance. They also sought a tablet of an appropriate size, with a single tablet per dose.

In developing the dosage form, the applicant designed the OCAS system (b) (4)



B. Critical issues for review

Information for drug substance is provided in the NDA. The specification appears typical for drug substances. Footnote 3 proposes that the specification for (b) (4) be deleted after 10 commercial batches. This proposal will need to be carefully evaluated during the review.

For drug substance, Sponsor has provided multivariate analysis information on particle size of the drug substance and its relationship to Critical Quality Attributes (CQAs) of the drug product, and has provided information on the compatibility of excipients with mirabegron (b) (4). The sponsor has extensive discussion in the application on the importance of (b) (4) specifications accordingly.

For the drug product, the sponsor has identified CQAs and has performed a number of DoEs on material quantities and material attributes. Although the applicant has used principles of Quality by Design in their development of the drug product, they have not proposed a Design Space or requested regulatory relief. This information will require careful review.

The applicant notes that (b) (4) are determined only at release. It is a review issue on whether this plan is adequate. Microbial limits will also only be tested on every tenth batch. This will also require careful evaluation.

The applicant has submitted a Comparability Protocol in Module 3.2.R.2 for addition of an alternate manufacturing site for the API. API is currently manufactured at Astellas Pharma Tech. Co., Ltd. Takahagi Technology Center. The CP seeks to add Astellas Ireland Co., Ltd. The applicant has provided information following the **Guidance for Industry: Comparability Protocols-Chemistry, Manufacturing, and Controls information (February 2003)**. The applicant is requesting a CBE-30. The Comparability Protocol will require careful review.

As an NME, a Methods Validation Request will be submitted.

ONDQA BIOPHARM-RELATED ISSUES

The applicant has provided information to support their determination of a BCS 3 classification for mirabegron. ONDQA BioPharm should evaluate whether the BCS 3 classification is supported by the data..

The sponsor has provided information to support a Level C IVIVC (in Section M.5.3) and information to support that alcohol-induced dose dumping does not occur.

Dissolution will be reviewed by ONDQA BioPharm. During development, the sponsor was advised to change their dissolution method from (b) (4) to Apparatus 1 @ 100 rpm (refer to EOP2 meeting held on 14-Nov-2007 and preNDA teleconference held on 01-Mar-2010). Sponsor has provided a comparison of these methods and states that the two methods have adequate discriminating power both in vitro (quality control aspect) and in vivo (the same level correlations on in vitro and in vivo).

During the filing meeting, the Clinical Pharmacology reviewer, Sayed Al Habet, Ph.D. had a question about (b) (4) and a possible

difference in the in vivo performance. Agreement was reached between Dr. Al Habet and Dr. John Duane to discuss the issue during the review cycle.

C. Comments for 74-Day Letter

There are no comments to be conveyed to the sponsor at this time.

D. Recommendation:

This NDA is fileable from a CMC perspective. Critical issues for review are outlined above. Bogdan Kurtyka, Ph.D. has been assigned as the primary CMC reviewer. John Duane, Ph.D. has been assigned as the ONDQA BioPharm reviewer.

REGULATORY BRIEFING RECOMMENDATION: As an NME and a modified-release dosage form which uses a novel technology, this is recommended for an Office Level Briefing.

Donna F. Christner, Ph.D.

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/s/

DONNA F CHRISTNER
11/01/2011

MOO JHONG RHEE
11/01/2011
Chief, Branch IV