

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204384Orig1s000**

**CHEMISTRY REVIEW(S)**

# **NDA 204-384**

**Sirturo<sup>TM</sup>**

**(Bedaquiline) 100 mg Tablets**

**Janssen Therapeutics Div Janssen Products LP**

**CMC Review Team**  
**Celia N. Cruz, Ph.D.\***  
**Lin Qi, Ph.D. \***  
**Minerva Hughes, Ph.D. \*\***

**Section**  
**Drug Product**  
**Drug Substance**  
**Biopharmaceutics**

**\*DPA II/Branch V**  
**\*\*Biopharmaceutics**  
**Office of New Drug Quality Assessment**

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# Chemistry Review Data Sheet

1. NDA 204384
2. REVIEW #: 1.0 Amendment 1
3. REVIEW DATE: 21 Dec 2012
4. REVIEWERS:

Primary:

<u>Reviewer</u>	<u>NDA CTD Section</u>
Li Qin, Ph.D.	Drug Substance (DS) DS Method Validation
Celia N. Cruz, Ph.D.	Drug Product (DP) DP Method Validation DP Master Batch Record Labeling

Secondary:

<u>Reviewer</u>	<u>Section</u>
Rapti Madurawe, Ph.D.	All Overall Recommendation

5. PREVIOUS DOCUMENTS:

See Product Quality Review 1.0.

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SDN 016 Quality/Response to Information Request	13-Nov-2012
SDN 026 Labeling	21-Dec-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Janssen Therapeutics, a Division of Janssen Products, LP
-------	--

Address:	1125 Trenton-Harbourton Road Titusville, NJ 08560 USA
Representative:	Gary Lewis 920 Route 202 South Raritan, NJ 08869
Telephone:	908-218-6014

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Sirturo™
- b) Non-Proprietary Name (USAN): Bedaquiline Tablet
- c) Code Name/#: TMC207, R4033232
- d) Chem. Type/Submission Priority:
  - Chem. Type: 1 new molecular entity
  - Submission Priority: P

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

10. PHARMACOLOGICAL CATEGORY: Antimicrobial

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 100 mg per tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

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

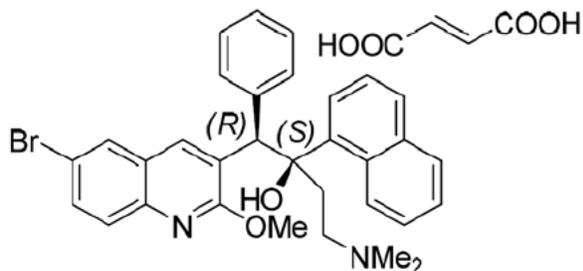
SPOTS product – Form Completed

Not a SPOTS product

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

Name: bedaquiline

(1R,2S)-1-(6-bromo-2-methoxy-3-quinolinyl)-4-(dimethylamino)-2-(1-naphthalenyl)-1-phenyl-2-butanol compound with fumaric acid (1:1)



$C_{32}H_{31}B_4N_2O_2 \cdot C_4H_4O_4$ , 671.58 (555.50+116.07)

## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

See Product Quality Review 1.0.

### B. Other Product Quality Reviews:

See Product Quality Review 1.0.

### C. Consults or Outside CMC Review Team input:

The following consults were updated and finalized since the last review:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	Overall OC Recommendation: Acceptable	17-Dec-2012	Vipul Dholakia
Pharm/Tox	Final Review: "There are no nonclinical pharmacology or toxicology data that preclude the approval of SIRTURO"	05-Dec-2012	Owen McMaster

### D. Other Applications or Submissions Referenced:

See Product Quality Review 1.0.

# The Chemistry Review for NDA 204-384

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA 204384 has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has provided an overall recommendation of "Acceptable" for the establishments filed in this NDA, as of December 17, 2012. Also, the revisions to the container label have been submitted to the NDA. Therefore, from the CMC perspective, this NDA is recommended for approval.

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

None.

### II. Summary of Chemistry Assessments

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

Refer to Product Quality Review 1.0

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

Bedaquiline 100 mg tablets are intended to be taken orally with food. The recommended dosage is 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks. Each bottle contains 188 tablets, which is enough for a complete 24-week dosing regimen. The label recommends that this product be administered by directly observed therapy.

The Bedaquiline 100 mg tablets are available in a 160 ml high density polyethylene bottles, with child resistant polypropylene closure and aluminum induction seal. The bottle is labeled with instructions to store at 25 °C, with excursions permitted to 15 °C - 30 °C. Bedaquiline 100 mg tablets have a 24-month shelf-life in the approved container closure system.

The bottle label contains language to dispense in original container, but also provides special instructions to pharmacists, in case of repackaging to address the intended use.

(b) (4) Dispense in original container. Tablets dispensed outside the original container should be stored in a tight light-resistant container with a 3 month expiration date. Store at 25°C (77°F); Excursions permitted to 15°C-30°C (59°F - 86°F).[See USP Controlled Room Temperature]."

### C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. Final drug substance and drug product specifications as well as the manufacturing process and controls information are adequate. The revisions to the container label have been submitted to the NDA and are acceptable. CMC revisions to the prescribing information have been accepted by the Sponsor. Finally, The Office of Compliance has provided an “Overall Acceptable” recommendation for the establishments in this NDA. Therefore, from the CMC perspective, this NDA is recommended for approval.

### III. Administrative

#### A. Reviewer’s Signature\*

Celia N. Cruz

*On file*

#### B. Endorsement Block

Rapti Madurawe

*On file*

#### C. CC Block

*On file*

\*Dr. Lin Qi’s signature was not included in this amendment, because she was on Annual Leave on 21-Dec-2012. There are no drug substance-related updates included in this amendment.

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/s/  
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CELIA CRUZ

12/21/2012

Dr. Lin Qi's signature was not included in this amendment, because she is on Annual Leave as of 21-Dec-2012. From CMC perspective, NDA 204384 is recommended for approval.

RAPTI D MADURawe

12/21/2012

## MEMORANDUM

**Date:** December 21, 2012

**To:** NDA 204-384

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

**Subject:** Tertiary review of ONDQA recommendation for NDA 204-384, bedaquiline, 100 mg tablets, Sirturo™. Bedaquiline is a new molecular entity (NME).

I have assessed the combined ONDQA reviews of NDA 204-384 by Celia N. Cruz, Ph.D. (Drug Product), Lin Qi, Ph.D. (Drug Substance) and Minerva Hughes, Ph.D. (Biopharmaceutics).

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 commercial product when it is stored not store above 30 °C.

The initial ONDQA review was entered into DARRTS on November 16, 2012, with a recommendation for a Complete Response due to an absence of a recommendation from the Office of Compliance on the manufacturing and testing sites acceptability and pending labeling issues. A separate Biopharmaceutics review was into DARRTS on November 16, 2012. The dissolution method and acceptance criterion were found to be acceptable and the Bioequivalence Waiver (BE) for the Kemwell site was granted. The request for an alternate approach for similarity f2 testing was not accepted. However, this does not affect the approvability of the NDA. In response to the f2 testing, the following comment should be conveyed to the Applicant after the NDA action is taken:

*FDA recommends that future in vitro dissolution comparability data submitted to the NDA in support of manufacturing changes include the 5 minutes sampling time point to characterize the complete profile. Note that the 5 minutes dissolution data may be omitted from the similarity f2 test, if the RSDs exceed 20%. Otherwise, FDA considers the 5 minutes dissolution data appropriate for the f2 statistical analysis.*

All CMC related label/labeling issues were satisfactorily resolved through an amendment dated December 20, 2012. On December 17, 2012 the Office of Compliance entered an Overall Recommendation of "Acceptable" into EES. A second CMC review was entered into DARRTS on December 21, 2012 following the updating of the status of the recommendation from the Office of Compliance and resolution of the CMC related labeling issues.

A Method Validation Consult Request was generated to evaluate the test methods for Assay and Impurities for drug substance and drug product (Janssen, Bedaquiline Fumarate Tablets, HPLC Method ID: LC-005327-V1). The Method Validation Report Summary was entered into

DARRTS on October 26, 2012, stating the methods are acceptable for quality control and regulatory purposes.

The Product Quality Microbiology Review was entered into DARRTS on November 02, 2012 with a recommendation of Approval.

Sirturo (bedaquiline) Tablets, 100 mg, is an uncoated, immediate release tablet, containing 120.89 mg of bedaquiline fumarate drug substance, equivalent to 100 mg bedaquiline free base. The tablet is white round biconvex, with a diameter of 11 mm. It is debossed with "T" over "207" on one side and "100" on the other side. The maximum daily dose is 400 mg per day. The tablet formulation contains (b) (4) % loading of bedaquiline fumarate drug substance and the following compendial excipients: lactose monohydrate, corn starch, hypromellose 2910 15 mPa.s, polysorbate 20, purified water, microcrystalline cellulose, croscarmellose sodium, colloidal silicone dioxide, and magnesium stearate

A quality by design approach was used in development of bedaquiline tablets which included full scale design of experiments for (b) (4) to establish the operating ranges that would ensure equivalent dissolution (via profile f2 comparisons) and other drug product critical quality attributes (CQAs). (b) (4)

The stability data also supports an alternative label of "Do not store above 30 °C", as per WHO guidelines for products used in Zone IV countries with supporting data. The long term storage condition for stability commitment batches is 30 °C/ 75% RH.

The drug substance (DS), bedaquiline fumarate, is a white to almost white powder, (b) (4). It is practically insoluble in aqueous media over a wide pH range. (b) (4) It is a single enantiomer containing two asymmetric carbon atoms with R- and S- configurations respectively for the (b) (4). The specific (b) (4) polymorphic forms of bedaquiline are identified. Form (b) (4) is obtained by the manufacturing process. No form conversion occurs during manufacture and storage. Stability data support a retest period of (b) (4) months at all climatic zones for the drug substance packaged (b) (4). The drug substance should be protected from light.

Secondary reviews of the CMC reviews were performed by Rapti Madurawe, Ph.D.

Secondary review of the Biopharmaceutics review was performed by Angelica Dorantes, Ph.D.

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/s/  
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TERRANCE W OCHELTREE  
12/21/2012

# **NDA 204-384**

**Sirturo<sup>TM</sup>**

**(Bedaquiline) 100 mg Tablets**

**Janssen Therapeutics Div Janssen Products LP**

**CMC Review Team**  
**Celia N. Cruz, Ph.D.\***  
**Lin Qi, Ph.D. \***  
**Minerva Hughes, Ph.D. \*\***

**Section**  
**Drug Product**  
**Drug Substance**  
**Biopharmaceutics**

**\*DPA II/Branch V**  
**\*\*Biopharmaceutics**  
**Office of New Drug Quality Assessment**

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# Chemistry Review Data Sheet

1. NDA 204384
2. REVIEW #: 1.0
3. REVIEW DATE: 16 Nov 2012
4. REVIEWERS:

Primary:

<u>Reviewer</u>	<u>NDA CTD Section</u>
Li Qin, Ph.D.	Drug Substance (DS) DS Method Validation
Celia N. Cruz, Ph.D.	Drug Product (DP) DP Method Validation DP Master Batch Record Labeling

Secondary:

<u>Reviewer</u>	<u>Section</u>
Rapti Madurawe, Ph.D.	All Overall Recommendation

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Type A meeting preliminary comments for 21-May-2012	17-May-2012
Pre NDA meeting minutes, 05-Oct-2011	04-Nov-2011
EoP2b CMC meeting minutes 05-Nov-2009	04-Dec-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SDN 000 New/NDA	29-June-2012
SDN 005 Quality/Response to Information Request	14-Aug-2012

SDN 006 Biometrics/Response to Information Request	24-Aug-2012 (Biopharmaceutics)
SDN 008 Quality/Response To Information Request	12-Sept-2012 (Quality Micro)
SDN 009 Quality/Response To Information Request	19-Sept-2012 (Quality Micro)
SDN 013 Quality/Response to Information Request	25-Oct-2012
SDN 015 Quality/Response to Information Request	13-Nov-2012
SDN 017 Quality/Response to Information Request	13-Nov-2012

1. NAME & ADDRESS OF APPLICANT:

Name:	Janssen Therapeutics, a Division of Janssen Products, LP
Address:	1125 Trenton-Harbourton Road Titusville, NJ 08560 USA
Representative:	Gary Lewis 920 Route 202 South Raritan, NJ 08869
Telephone:	908-218-6014

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Sirturo™
- b) Non-Proprietary Name (USAN): Bedaquiline Tablet
- c) Code Name/#: TMC207, R4033232
- d) Chem. Type/Submission Priority:
  - Chem. Type: 1 new molecular entity
  - Submission Priority: P

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

10. PHARMACOLOGICAL CATEGORY: Antimicrobial

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 100 mg per tablet

13. ROUTE OF ADMINISTRATION: Oral

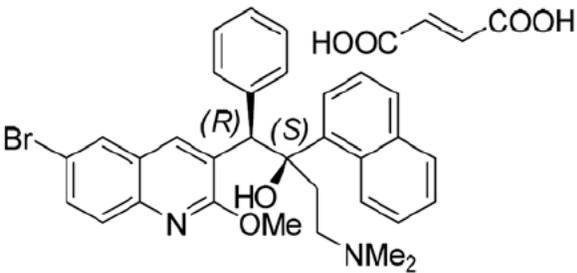
14. Rx/OTC DISPENSED:  X  Rx      \_\_\_ OTC

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

\_\_\_ SPOTS product – Form Completed

X  Not a SPOTS product

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

<p><u>Name:</u> bedaquiline</p> <p>(1R,2S)-1-(6-bromo-2-methoxy-3-quinolinyl)-4-(dimethylamino)-2-(1-naphthalenyl)-1-phenyl-2-butanol compound with fumaric acid (1:1)</p>	 <p><math>C_{32}H_{31}B_4N_2O_2 \cdot C_4H_4O_4</math>, 671.58 (555.50+116.07)</p>
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**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	REVIEW DATE	COMMENT
(b) (4)	III			4	N/A		LoA confirmed, 21-Nov-2011
	III			4	N/A		LoA confirmed. 21-Nov-2011
	III			4	N/A		LoA confirmed. 06-Dec-2011
	III			4	N/A		LoA confirmed. 06-Dec-2011
	III			4	N/A		LoA confirmed. 25-Aug-2011

<sup>1</sup> 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")

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

**B. Other Product Quality Reviews:**

REVIEW	RECOMMENDATION	DATE	REVIEWER
Biopharmaceutics	<b>Method:</b> Apparatus: USP 1 Paddle Speed: 150 rpm Medium: 0.01M HCl, 900 ml Temperature: 37.0 ± 0.5 °C <b>Dissolution acceptance criterion:</b> Q= $\frac{(b)}{(4)}$ % at 30 minutes	15-Nov-2012	Minerva Hughes, Ph.D. Angelica Dorantes, Ph.D. (secondary reviewer)

**C. Consults or Outside CMC Review Team input:**

<b>CONSULTS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
EES	Pending Sites: Kemwell Biopharma	15-Nov-2012	Vipul Dholakia
Pharm/Tox	Pending final review	15-Nov-2012	Owen McMaster
Methods Validation	Drug Product Method for Assay and Impurities is acceptable for quality control and regulatory purposes.	26-Oct-2012	Wei Ye
Environmental Analysis	N/A		
Quality Microbiology	“Recommend Approval”;	02-Nov-2012	Jessica Cole

**D. Other Applications or Submissions Referenced:**

<b>DOCUMENT Referenced</b>	<b>APPLICATION NUMBER</b>	<b>DESCRIPTION</b>
All	IND 69-600	TMC 207 (bedaquiline)

# The Chemistry Review for NDA 204-384

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. Labeling is pending team review and CMC revisions to the package insert will be communicated to the Applicant through label review team communications. In addition, the drug product manufacturing site has inspection issues and an overall site recommendation has not yet been made by the Office of Compliance. Therefore, from the CMC perspective, this NDA is not recommended for approval until the overall site recommendation and final labeling are found satisfactory.

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

None.

### II. Summary of Chemistry Assessments

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

##### Drug Product

###### Description

Situro™ (bedaquiline) Tablets, 100 mg, is an uncoated, immediate release tablet for oral administration, containing 120.89 mg of bedaquiline fumarate drug substance, equivalent to 100 mg bedaquiline free base. The tablet is white round biconvex, with a diameter of 11 mm. It is debossed with “T” over “207” on one side and “100” on the other side. The maximum daily dose is 400 mg per day.

The tablet formulation contains (b) (4) % loading of bedaquiline fumarate drug substance and the following compendial excipients: lactose monohydrate, corn starch, hypromellose 2910 15 mPa.s, polysorbate 20, purified water, microcrystalline cellulose, croscarmellose sodium, colloidal silicone dioxide, and magnesium stearate

###### Manufacturing and Control Strategy

Bedaquiline tablets are manufactured

(b) (4)

The quality by design approach used in development included full scale

design of experiments for [REDACTED] (b) (4) to establish the operating ranges that would ensure equivalent dissolution (via profile f2 comparisons) and other drug product critical quality attributes (CQAs). Development also incorporated statistical analysis of relevant parameters and properties for tablet performance.

Tablet dissolution is sensitive to drug substance particle size distribution, [REDACTED] (b) (4). The manufacturing control strategy is based on the capability to operate and manage within the ranges of a design space for [REDACTED] (b) (4).

The drug product quality is also assured by the following final specifications: appearance, identification, assay, chromatographic purity (any unspecified and total sum of degradation products), uniformity of dosage form by content uniformity, dissolution, water content, and microbiological purity. All methods have been adequately validated and the specification criteria limits justified appropriately.

#### Stability

Overall, there are no drug product changes in assay, appearance, polymorph, enantiomeric content, or microbiological purity upon storage in the primary container system. Stress studies (in solution) show drug product can degrade [REDACTED] (b) (4). However, no growth of synthesis impurities or degradation is observed in the drug product upon storage. The [REDACTED] (b) (4) of the tablet has no apparent impact on degradation, assay, appearance or microbiological purity. [REDACTED] (b) (4) with no impact to quality of the tablets. Photostability studies were conducted for all the primary and supportive stability batches, and no degradation due to light was detected in the formulated drug product, though the drug substance is shown to be photosensitive.

[REDACTED] (b) (4)

The stability results support a 24 month shelf life for the drug product in the current 160 ml HDPE bottle for all climatic zones and the proposed product label statement of “Store at [REDACTED] (b) (4) 25°C ([REDACTED] (b) (4) 77°F); excursions permitted to 15-30 °C (59-86 °F).” The stability data also supports an alternative label of “Do not store above 30 °C”, as per WHO guidelines for products used in Zone IV countries with supporting data. The long term storage condition for stability commitment batches is 30 °C/ 75% RH.

## **Biowaiver**

A bioequivalence (BE) study waiver was requested for Sirturo™ tablets manufactured at (b) (4) the proposed manufacturer for Phase 3/commercial product. In support of the BE-waiver request, the Applicant provided comparative in vitro dissolution data, using an appropriately discriminating method, for tablets used in the Phase 2 clinical studies (manufactured at Janssen) and tablets manufactured at (b) (4) using the proposed commercial manufacturing process. (b) (4)

The provided comparative in vitro dissolution data and manufacturing controls support approval of the BE-waiver request and it is granted.

## **Dissolution Specification**

The proposed dissolution method and acceptance criterion  $Q = (b) (4)\%$  at (b) (4) minutes is acceptable for product quality control.

## **Drug Substance**

### **Description**

The drug substance (DS), bedaquiline fumarate, is a white to almost white powder, (b) (4) (b) (4). It is practically insoluble in aqueous media over a wide pH range. (b) (4). It is a single enantiomer containing two asymmetric carbon atoms with R- and S- configurations respectively for the (b) (4) (b) (4) polymorphic forms of Bedaquiline are identified. Form (b) (4) is obtained by the manufacturing process. No form conversion occurs during manufacture and storage.

### **Manufacturing and Control Strategy**

Bedaquiline fumarate is made from (b) (4) starting materials through (b) (4)

Critical Process Parameters (CPPs) and Proven Acceptable Ranges (PARs) establish an overall process control, in combination with normal GMP controls and release testing. (b) (4)

(b) (4)

### Stability

Forced degradation study show the drug substance degrades significantly (b) (4). The drug substance is slightly photosensitive, but not heat sensitive. Primary stability data at long-term (25°C/60% RH & 30°C/75% RH) and at accelerated (40°C/75% RH) storage conditions show no significant changes or trends. The data support a retest period of (b) (4) months at all climatic zones for the drug substance packaged (b) (4). The drug substance should be protected from light.

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

Bedaquiline 100 mg tablets are intended to be taken orally with food. The recommended dosage is 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks. Each bottle contains 188 tablets, which is enough for a complete 24-week dosing regimen. The label recommends that this product be administered by directly observed therapy.

The Bedaquiline 100 mg tablets are available in a 160 ml high density polyethylene bottles, with child resistant polypropylene closure and aluminum induction seal. Each bottle is labeled instructions to store at (b) (4) 25 °C, with excursions permitted to 15 - 30 °C. The label also contains language to store in original container to protect from light.

### **C. Basis for Approvability or Not-Approval Recommendation**

As of this review, an overall recommendation on facilities is pending, due to ongoing review of inspection findings at the drug product manufacturing site. In addition, labeling is pending team review. CMC revisions to the package insert will be communicated to the Applicant through label review team communications. Therefore, from the CMC perspective, this NDA is not recommended for approval until the overall site recommendation and final labeling are found satisfactory.

## **III. Administrative**

### **A. Reviewer's Signature**

Celia N. Cruz, Li Qin

*On file*

### **B. Endorsement Block**

Rapti Madurawe

*On file*

### **C. CC Block**

*On file*

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/s/  
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CELIA CRUZ  
11/16/2012

LIN QI  
11/16/2012

RAPTI D MADURawe  
11/16/2012