CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210428Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 210428
Review #1

Drug Name/Dosage Form	Metoprolol Extended-Release Capsules
Strength	25 mg, 50 mg, 100 mg, 200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Sun Pharmaceutical Industries Limited
US agent, if applicable	Sun Pharmaceutical Industries Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment	22-NOV-2017
Amendment	21-NOV-2017
Amendment	14-NOV-2017
Amendment	13-NOV-2017
Amendment	07-NOV-2017
Amendment	30-OCT-2017
Amendment	14-SEP-2017
Amendment	13-JUL-2017
Amendment	14-JUN-2017
Amendment	05-JUN-2017
Original	30-MAR-2017

Quality Review Team

DISCIPLINE	REVIEWER/SECONDARY	OFFICE
Drug Substance	Rohit Tiwari/Ben Stevens	ONDP
Drug Product	Milton Sloan/Wendy Wilson-Lee	ONDP
Process	Chunsheng Cai/Akm Khairuzzaman	OPF
Facility	Viviana Matta/Ruth Moore	OPF
Biopharmaceutics	Kaushal Dave/Ta-Chen Wu	ONDP
Regulatory Business Process Manager	Grafton Adams	OPRO
Application Technical Lead	Wendy Wilson-Lee	ONDP
Environmental Analysis	Milton Sloan/Wendy Wilson-Lee	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF	Type	Holder	Item Referenced	Status	Review Date	Comments
(b) (4)	Type III		(b) (4)	Not reviewed	N/A	Information in the submission
	Type III			Not reviewed	N/A	Information in the submission
	Type III			Not reviewed	N/A	Information in the submission
	Type IV			Not reviewed	N/A	Information in the submission
	Type III			Not reviewed	N/A	Information in the submission
	Type III			Not reviewed	N/A	Information in the submission
	Type III			Not reviewed	N/A	Information in the submission
	Type III			Not reviewed	N/A	Information in the submission
	Type III			Not reviewed	N/A	Information in the submission
	Type III			Not reviewed	N/A	Information in the submission
	Type II			Adequate	13-NOV-2017	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	127963	Clinical development program for treatment of hypertension, angina pectoris, and heart failure
NDA	19962	Reference Listed Drug

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 210428 for Metoprolol Extended-Release Capsules, 25 mg, 50 mg, 100 mg, 200 mg when packaged in the intended commercial container closure and stored at USP controlled room temperature.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Treatment of hypertension, angina pectoris, and heart failure
Duration of Treatment	Chronic
Maximum Daily Dose	
Alternative Methods of Administration	Sprinkle contents on soft foods; nasogastric tube administration

B. Quality Assessment Overview

The Applicant developed an Extended-Release (ER) Capsule formulation of Metoprolol. Metoprolol succinate, the drug substance used in the ER capsule, has two known polymorphic forms) (b) (4) is the desired polymorphic form. The ER capsule is claimed to be bioequivalent to the Reference Listed drug TOPROL-XL tablets. The presumed advantage of the ER capsule formulation is the ability to administer the capsule contents (film-coated beads) as a sprinkle over soft foods and via nasogastric tube administration. The ER capsule represents the same uses (except the dosage regimen for patients with severe 'Heart Failure' indication as starting dose of 12.5 mg), strengths, and route of administration with the addition of nasogastric tube administration. The target population for the ER capsule is long term care of patients with dysphagia (difficulty swallowing). Key review issues included substantiation of the extended release claim, compatibility of the AR capsule with typical soft foods and nasogastric tubes, potential for dose dumping, and potential for (b) (4)

The Applicant cited DMF (b) (4) for the description of the synthetic scheme and manufacturing process, control of materials, process validation and characterization of Metoprolol Succinate drug substance. The limits and the tests for the assay, identification, loss on drying, and residue on ignition are as per the USP monograph. Additionally, the Sun Pharmaceuticals in house specification for Metoprolol Succinate include X-ray diffraction as identification test, and some of the process derived impurities and residual solvents. The acceptance limits for the impurities described in USP are as per the USP specifications, and for all of the other impurities, the acceptance limits are as per the ICH Q3A identification thresholds (NMT (b) (4) %). The acceptance limits for the residual solvents are as per ICHQ3C limits.

The only genotoxic impurity described in the application was the [redacted], the process related impurity. [redacted] is controlled with limit "NMT [redacted] ppm" by [redacted] in Metoprolol succinate. This limit is as per the ICH M7 guidance option 1 (1.5 µg/day for a lifetime oral exposure and the maximum daily dose for Metoprolol Succinate is 0.4 gm). No out of specifications results were observed in any of the drug substance batches described and the level of epoxide impurity in all of these batches were below the quantification level.

The current USP specifications for Metoprolol Succinate drug substance include the test for heavy metals as per USP<231> and this test will be deleted from USP from January 2018. The Sun Pharmaceuticals is also the DMF holder for this drug substance and they committed that for the heavy metals test in the Metoprolol Succinate specification the switch from USP<231> to USP <232>/<233> will be made on starting or before January 1, 2018.

The re-test period of Metoprolol Succinate, USP drug substance is [redacted] when stored under the recommended storage conditions described in DMF [redacted] The data submitted in the DMF supports this re-test period of Metoprolol Succinate USP drug substance. **The proposed storage condition for the drug substance i** [redacted]

The proposed drug product is manufactured in four dose strengths (same as RLD). The applicant states a quality by design approach was used to develop the formulation and manufacturing process to ensure the quality, safety and efficacy of Metoprolol Succinate Extended-Release Capsules 25 mg, 50 mg, 100 mg and 200 mg. However, no regulatory flexibilities are apparent or were mentioned as result of their approach. The different strengths are manufactured from the [redacted]

The target batch size for the final blend is [redacted] kg. The Applicant provided data on three exhibit batches at commercial scale along with the process validation reports to demonstrate the viability of the proposed commercial manufacturing process. Stability data for [redacted]

All manufacturing, testing, and packaging facilities associated with NDA 210428 are in good compliance standing and acceptable to support this application.

The dosage forms strengths appear to be easily distinguished by capsule size, capsule color, and imprinted markings (monogram). Only the 25 and 50 mg have the same capsule size. One cap is light yellow (25 mg) and the other is a dark yellow cap (50 mg). Please see labeling review for further comments and refer to the life cycle section of the drug product review for comments on potential concerns for adequate distinction of the two capsules.

Each excipient is of compendial grade with exception of the [redacted] (b) (4) The in-house analytical procedures are provided and appropriate for their intended use. The general HPLC method is modified for use in identification, average fill weight, uniformity of dosage, assay, related substances, and dissolution. The proposed analytical procedures to be used for the batch release and stability testing of the drug product are per the current USP general chapters and in-house methods.

The container closure for the Metoprolol succinate extended release capsules is a 30's count HDPE bottle pack. The suitability of packaging has been demonstrated by the applicant. The finished drug product release and stability specifications for this product include the tests that are commonly applicable for an extended-release solid oral dosage form. Attributes used to confirm the quality of the finished drug product on batch release were evaluated during stability testing, except for Identification (by HPLC and IR), Average Fill Weight, Uniformity of Dosage Units and Residual Solvents which are not expected to change over time. [redacted] (b) (4)

Sun Pharmaceutical Industries Limited is proposing a **two-year expiration-dating period for Metoprolol Succinate Extended-Release Capsules, 25 mg, 50 mg, 100 mg and 200 mg packed in HDPE bottle packs when stored at: Store 20°C - 25°C (68 – 77°F); (See USP Controlled Room Temperature).** The proposed expiration dating for this product is supported by initial, three (3) and six (6) months accelerated stability data (40 ± 2 °C / 75 ± 5% relative humidity) and initial, three (3), six (6), nine (9) and twelve (12) months controlled room temperature data (25 ± 2 °C / 60 ± 5 % relative humidity) in container/closure system (30's count bottle pack) proposed for marketing. The proposed two-year expiration period is acceptable.

The Biopharmaceutics review focused on data supporting: 1) approval of the proposed dissolution method and acceptance criteria, 2) request of biowaiver for 25 mg, 50 mg and 100 mg capsule strengths, 3) effects of alcohol on in vitro dissolution of the proposed product, and 4) effects of food (apple sauce, pudding and yogurt) and exposure to nasogastric (NG) tube on dissolution performance of the proposed product. Based on the review of the provided information/data, Division of Biopharmaceutics has the following conclusions and recommendations:

Dissolution Method: The proposed dissolution method for the proposed product is the same as the Dissolution Test 1 (USP Apparatus 2 (paddle) @50 rpm; 500 ml of pH 6.8 phosphate buffer at 37°C) described in the USP Monograph for the Listed Drug (LD) product, Toprol-XL® [Metoprolol Succinate Extended-Release (ER)] Oral Tablets approved under NDA 19962. The Applicant investigated the discriminating ability of the proposed dissolution method by [redacted] (b) (4) Results of the study, supported by the similarity factor (*f*2) calculation, indicate that the proposed dissolution method can discriminate between quality and sub-quality products in terms of [redacted] (b) (4) and is ACCPETABLE.

Dissolution Acceptance Criteria: The originally proposed dissolution acceptance criteria of 'Not more than (NMT) (b) (4) and not less than (NLT) (b) (4) were permissive and not supported by their data. The agreement was reached during the review cycle on the recommended dissolution acceptance criteria of 'NMT (b) (4) (b) (4)

Alcohol-Induced Dose-Dumping Potential: Increases in the rates of drug release were observed as the alcohol concentration were increased (5, 10, 20 and 40% v/v alcohol in 0.1 N HCl medium) in in-vitro alcohol-induced dose dumping studies with all strengths of the proposed product. Significant drug release at 2 hours in the presence of 20% and 40% alcohol concentrations suggest the potential of dose-dumping from the proposed ER drug product in patients with consumption of alcohol. The proposed labeling states that consumption of alcohol with the proposed ER drug product is not recommended.

In Vitro Soft-Food Interaction Study: No significant differences in rate of drug release from the pellets were observed between any of the studies groups after sprinkling the pellets on apple sauce, pudding and yogurt (including the control group) for 60 minutes for any of the two studied strengths (25 mg Capsules and 200 mg Capsules).

Administration via NG Tube: In-vitro studies using NG tube with the lowest and the highest strengths of the proposed product show that exposure of the drug-loaded pellets to NG tube for 60 minutes has no significant effect on the release of metoprolol succinate from the pellets. Results support the administration of the proposed drug product via NG tube.

Biowaiver Request: The provided data/information with regards to similarity in design, composition and release mechanism among different strengths of the proposed product, similar dissolution profiles in multi-media pH conditions (0.1N HCI, pH 4.5 and 6.8), bioequivalence between the highest proposed strength and the Toprol-XL® 200-mg strength, and PK linearity over the proposed dose range (25-200 mg) support the requested biowaiver for 25 mg, 50 mg and 100 mg capsules of the proposed product.

C. Special Product Quality Labeling Recommendations (NDA only)

There are no special labeling recommendations.

D. Final Risk Assessment (see Attachment)

ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment – NDA 210428 Metoprolol Succinate Extended Release Capsules, 25 mg, 50 mg, 100 mg, 200 mg

a) Drug Product

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Raw Materials/Formulation Process/Equipment/Scale/Site Container Closure	Low	End product testing	Acceptable	
Solid State	Raw Materials/Formulation Process/Equipment/Scale/Site Container Closure	Low	(b) (4)	Acceptable	
Content Uniformity	Raw Materials/Formulation Process/Equipment/Scale/Site	Low		Acceptable	
Microbial Limits	Raw Materials/Formulation Process/Equipment/Scale/Site Container Closure	Low		Acceptable	
Dissolution	Raw Materials/Formulation Process/Equipment/Scale/Site Container Closure	Medium	Revised dissolution method	Acceptable	Commitment to reassess post-approval
Alcohol Dose Dumping	Formulation Process/Equipment/Scale/Site Container Closure	Medium	Labeled to not administer with alcohol	Acceptable	
Bead size (sprinkles)	Raw Materials/Formulation Process/Equipment/Scale/Site Container Closure	Low	In-process controls ensure bead size	Acceptable	

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LABELING

{For NDA only}

R Regional Information

1.14 Labeling

Highlights of Prescribing Information

----------**DOSAGE FORMS AND STRENGTHS**----------

- Extended-release capsules: 25 mg, 50 mg, 100 mg and 200 mg. (3)

FULL PRESCRIBING INFORMATION: CONTENTS

3 DOSAGE FORMS AND STRENGTHS

25 mg capsule: Light (b) (4) opaque cap and white opaque body both imprinted with '**RL14**' in black ink containing white to off-white pellets.

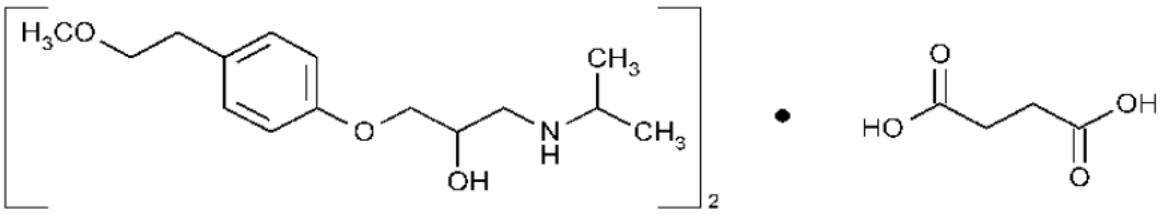
50 mg capsule: Yellow opaque cap and white opaque body both imprinted with '**RL15**' in black ink containing white to off-white pellets.

100 mg capsule: White opaque cap and white opaque body both imprinted with '**RL16**' in black ink containing white to off-white pellets.

200 mg capsule: Yellow opaque cap and yellow opaque body both imprinted with '**RL17'** in black ink containing white to off-white pellets.

11 DESCRIPTION

Metoprolol succinate, is a beta$_1$-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended-release capsules. (b) (4) has been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. The extended-release capsules comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. (b) (4) Its chemical name is (±)-1-(Isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol succinate (2:1) (salt). Its structural formula is:



Metoprolol succinate, USP is a white to off-white powder with a molecular weight of 652.82. It is freely soluble in water, soluble in methanol, sparingly soluble in alcohol, slightly soluble in isopropyl alcohol. Inactive ingredients: ethyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 6000, sugar spheres (corn starch and sucrose), talc and triethyl citrate. The capsule shell and imprinting ink has the following composition: ferric oxide yellow (25 mg, 50 mg and 200 mg), ferrosoferric oxide, gelatin, potassium hydroxide, propylene glycol, shellac and titanium dioxide.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each extended-release capsule contains 23.75 mg, 47.5 mg, 95 mg, and 190 mg of metoprolol succinate equivalent to 25 mg, 50 mg, 100 mg, and 200 mg of metoprolol tartrate, USP respectively and are supplied as follows:

25 mg capsule: Light (b) (4) opaque cap and white opaque body both imprinted with '**RL14**' in black ink containing white to off-white pellets.

NDC 10631-008-30 Bottle of 30

50 mg capsule: Yellow opaque cap and white opaque body both imprinted with '**RL15**' in black ink containing white to off-white pellets.

NDC 10631-009-30 Bottles of 30

100 mg capsule: White opaque cap and white opaque body both imprinted with '**RL16**' in black ink containing white to off-white pellets.

NDC 10631-010-30 Bottles of 30

200 mg capsule: Yellow opaque cap and yellow opaque body both imprinted with '**RL17**' in black ink containing white to off-white pellets.

NDC 10631-011-30 Bottles of 30

Store at 20° C - 25° C (68° F - 77° F). [See USP Controlled Room Temperature].

Reviewer's Assessment: Adequate

Although the established name "metoprolol succinate" does not comply with the current salt policy in the USP <1121>, we are not recommending removing the "succinate". Typically, USP General Chapters titled with numbers above <1000> are considered to be recommendations

and not requirements, unless the chapter is cited in a product-specific monograph or another General Chapter titled with a number below <1000>.
We are thus recommending including an equivalency for both the tartrate products as well as for the metoprolol free base as provided by the OPPO as follows:

Highlights of Prescribing Information
----DOSAGE FORMS AND STRENGTHS-

Extended-release capsules: 25 mg, 50 mg, 100 mg and 200 mg.

11 DESCRIPTION:
The extended-release capsules contain 10.24 mg, 20.48 mg, 40.96 mg, and 81.92 mg of metoprolol free base, present as 23.75 mg, 47.5 mg, 95 mg, and 190 mg of metoprolol succinate and are equivalent to 25 mg, 50 mg, 100 mg, and 200 mg of metoprolol tartrate, USP, respectively.

16 HOW SUPPLIED:
Each extended-release capsule contains 10.24 mg, 20.48 mg, 40.96 mg, and 81.92 mg of metoprolol free base, present as 23.75 mg, 47.5 mg, 95 mg, and 190 mg of metoprolol succinate and equivalent to 25 mg, 50 mg, 100 mg, and 200 mg of metoprolol tartrate, USP respectively and are supplied as follows:

The above sections in the Package Insert are acceptable with the recommended changes. The applicant has not chosen to include the child resistant cap statement in the "How supplied" section of the labeling. Minor changes may be made on the Word document itself at the designated labeling meetings of the review team (or in SHAREPOINT location).

The applicant has accepted our recommendations in the amendment dated 11/13/17 and has provided a current version. The recommendation for revision based on team labeling meeting is as follows:

1. Revise the descriptions of the 25 mg and 50 mg capsules in all relevant sections of the submission – including the description (P.1), product specification (P.5), and SPL data elements – to include the following:

- For 25 mg Strength – Capsule with light yellow opaque cap and white opaque body both imprinted with RL14 in black ink containing white to off-white pellets
- For 50 mg Strength – Capsule with dark yellow opaque cap and white opaque body both imprinted with RL15 in black ink containing white to off-white pellets

2. We do not agree with the use of (b) (4) to describe the capsule cap color for the 25 mg strength as it does not reflect the actual color of the capsules. We recommend describing the color of the 25mg strength capsule cap as "light yellow." In order to ensure distinction between the 25 mg and 50 mg strength capsules based on the new

"light yellow" color for the 25 mg capsule, we recommend revising the color description for the 50 mg capsule cap to "dark yellow."

SPIL Response:

Sun Pharmaceutical Industries Limited (SPIL) acknowledges the FDA's comment and as per recommendation the description of the drug product is revised.

Current and revised description is provided below for ready reference.

Description Test	Existing specifications	Revision Specifications
For 25 mg Strength	Capsule with **light** (b) (4) opaque cap and white opaque body both imprinted with RL14 in black ink containing white to off-white pellets	Capsule with **light yellow** opaque cap and white opaque body both imprinted with RL14 in black ink containing white to off-white pellets
For 50 mg Strength	Capsule with **yellow** opaque cap and white opaque body both imprinted with RL15 in black ink containing white to off-white pellets	Capsule with **dark yellow** opaque cap and white opaque body both imprinted with RL15 in black ink containing white to off-white pellets

The following documents are revised and documents are provided in the corresponding sections.

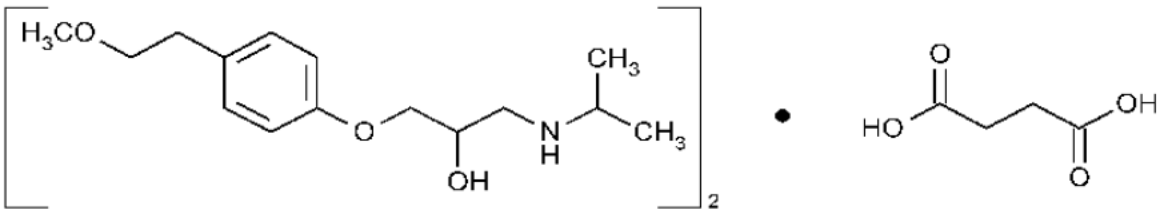
Documents	Section of module
Unit composition	32p1-description-and-composition
Drug product specification	32p51-specifications
Labeling and SPL	1-14-labeling

----------**DOSAGE FORMS AND STRENGTHS**----------

- (b) (4) extended-release capsules: 25 mg, 50 mg, 100 mg and 200 mg. (3)

11 DESCRIPTION

Metoprolol succinate, is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended-release capsules. (b) (4) has been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. The extended-release capsules comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. (b) (4) Its chemical name is (±)-1-(Isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol succinate (2:1) (salt). Its structural formula is:



Metoprolol succinate, USP is a white to off-white powder with a molecular weight of 652.82. It is freely soluble in water, soluble in methanol, sparingly soluble in alcohol, slightly soluble in isopropyl alcohol. Inactive ingredients: ethyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 6000, sugar spheres (corn starch and sucrose), talc and triethyl citrate. The capsule shell and imprinting ink has the following composition: ferric oxide yellow (25 mg, 50 mg and 200 mg), ferrosoferric oxide, gelatin, potassium hydroxide, propylene glycol, shellac and titanium dioxide.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each extended-release capsule contains 23.75 mg, 47.5 mg, 95 mg and 190 mg of metoprolol succinate equivalent to 25 mg, 50 mg, 100 mg and 200 mg of metoprolol tartrate, USP respectively and are supplied as follows:

25 mg capsule: [redacted] (b) (4) light yellow opaque cap and white opaque body both imprinted with '**RL14**' in black ink containing white to off-white pellets.
NDC 10631-008-30 Bottle of 30

50 mg capsule: [redacted] (b) (4) dark yellow opaque cap and white opaque body both imprinted with '**RL15**' in black ink containing white to off-white pellets.
NDC 10631-009-30 Bottles of 30

100 mg capsule: White opaque cap and white opaque body both imprinted with '**RL16**' in black ink containing white to off-white pellets.
NDC 10631-010-30 Bottles of 30 22

200 mg capsule: Yellow opaque cap and yellow opaque body both imprinted with '**RL17**' in black ink containing white to off-white pellets.
NDC 10631-011-30 Bottles of 30

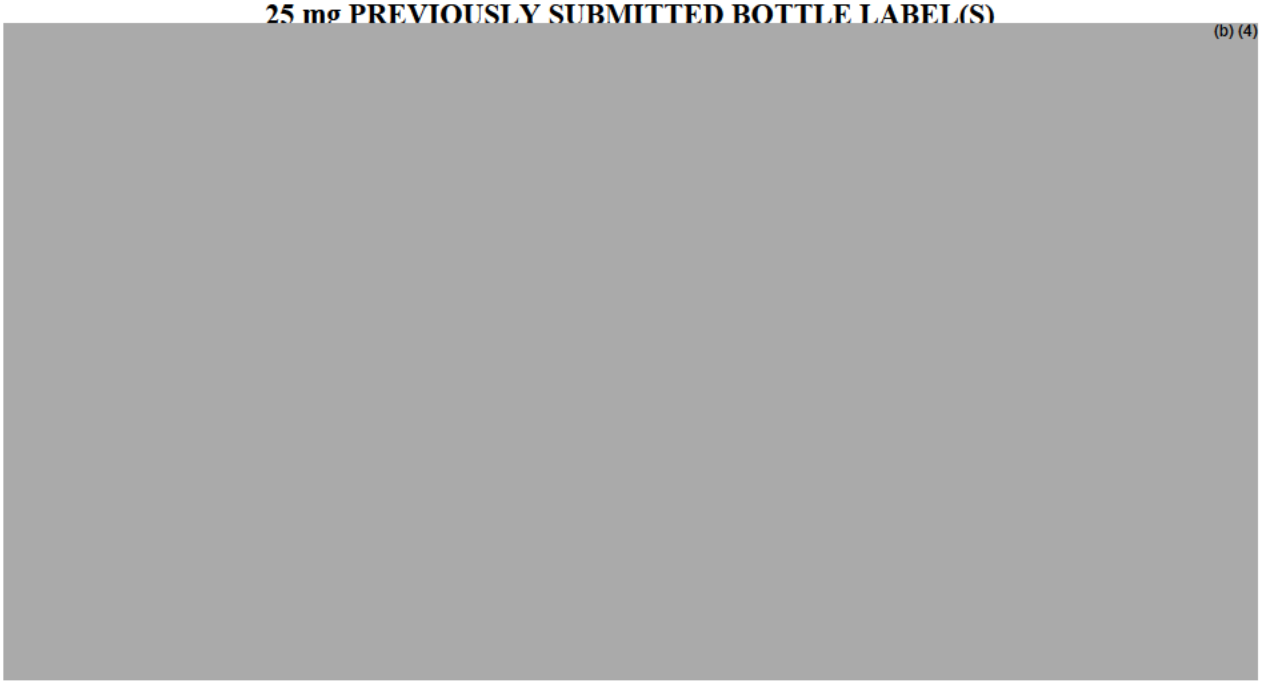
Store at 20° C - 25° C (68° F - 77° F). [See USP Controlled Room Temperature

Reviewer's Assessment: Adequate
The response is acceptable and should provide adequate and clear distinction between the two capsule strengths. The applicant has also provided a updated Package insert. The updated label is included with the recommended revisions. The proprietary name (highlighted in yellow) is usually not included as part of the Highlights of Prescribing Information of Dosage Form and Strengths section.

Immediate Container Label

25 mg PREVIOUSLY SUBMITTED BOTTLE LABEL(S)

(b) (4)



25 mg CURRENT PROPOSED BOTTLE LABEL

(b) (4)

Reviewer's Assessment:
The previous proposed proprietary name (b) (4) was not found acceptable by DMEPA review. The applicant has withdrawn the subsequently proposed proprietary name (b) (4) and has currently proposed (b) (4)

Recommended revision:
25mg:
*Each extended-release capsule contains 10.24 mg of metoprolol free base, present as 23.75 mg of metoprolol succinate and equivalent to 25 mg of metoprolol tartrate, USP.

The applicant has accepted our recommendations in the amendment dated 11/13/17

Proposed recommended revision:
25mg:
(b) (4)

50 mg PREVIOUSLY SUBMITTED BOTTLE LABEL(S)

(b) (4)

50 mg CURRENT PROPOSED BOTTLE LABEL

Reviewer's Assessment:
The current proposed proprietary name (b) (4) was not found acceptable by DMEPA review. The applicant has withdrawn the subsequently proposed proprietary name (b) (4) and has currently proposed (b) (4)

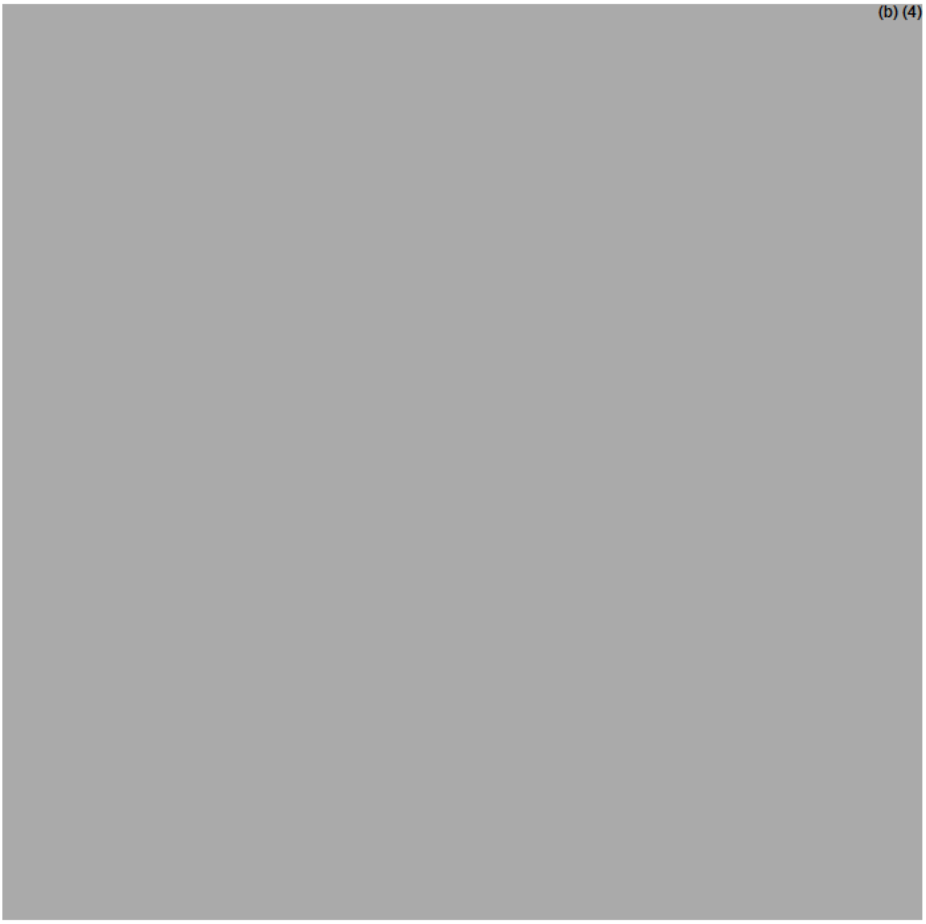
Recommended revision:
50mg:
*Each extended-release capsule contains 20.48 mg of metoprolol free base, present as 47.5 mg of metoprolol succinate and equivalent to 50 mg of metoprolol tartrate, USP.

The applicant has accepted our recommendations in the amendment dated 11/13/17. The (b) (4) ***mg number was inadvertently provided as a typo the correct number should be 47.5mg and is correctly revised in the label.***

Proposed recommended revision:
50mg:
(b) (4)

100 mg PREVIOUSLY SUBMITTED BOTTLE LABEL(S)

(b) (4)



100 mg CURRENT PROPOSED BOTTLE LABEL

(b) (4)

Reviewer's Assessment:

The current proposed proprietary name (b) (4) was not found acceptable by DMEPA review. The applicant has withdrawn the subsequently proposed proprietary name (b) (4) and has currently proposed (b) (4)

Recommended revision:
100mg:
*Each extended-release capsule contains 40.96 mg of metoprolol free base, present as 95 mg of metoprolol succinate and equivalent to 100 mg of metoprolol tartrate, USP.

The applicant has accepted our recommendations in the amendment dated 11/13/17

Proposed recommended revision:
100mg:
(b) (4)

200 mg PREVIOUSLY SUBMITTED BOTTLE LABEL(S)

200 mg CURRENT PROPOSED BOTTLE LABEL

(b) (4)

Reviewer's Assessment:

The current proposed proprietary name (b) (4) was not found acceptable by DMEPA review. The applicant has withdrawn the subsequently proposed proprietary name (b) (4) and has currently proposed (b) (4)

Recommended revision:
200mg:
*Each extended-release capsule contains 81.92 mg of metoprolol free base, present as 190 mg of metoprolol succinate and equivalent to 200 mg of metoprolol tartrate, USP.

The applicant has accepted our recommendations in the amendment dated 11/13/17 and has proposed the current version.

Proposed recommended revision:
200mg:
(b) (4)

Carton Labeling

Reviewer's Assessment:

The carton label complies with all regulatory requirements from a CMC perspective. The same editorial comment applies.

Proposed recommended revision:
25, 50, 100, and 200mg:

(b) (4)

List of Deficiencies:

1. (b) (4)

Primary Labeling Reviewer Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
11/03/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Wendy Wilson-Lee, PhD
(Acting) Branch Chief
OPQ/ONDP/Div1/Branch I
11/03/2017

Milton Sloan

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Wendy Wilson- Lee

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