Cross-Discipline Team Leader Review

Date	January 23, 2018
From	Martina Sahre, PhD
Subject	Cross-Discipline Team Leader Review
NDA#	210,428
Applicant	Sun Pharmaceutical Industries, Ltd.
Date of Submission	March 30, 2017
PDUFA Goal Date	January 30, 2018
Proprietary Name / Established (USAN) names	Metoprolol succinate Extended-Release Capsules (metoprolol succinate)
Dosage forms / Strength	25, 50, 100, and 200 mg extended-release capsules
Proposed Indication(s)	1. Hypertension (including pediatric hypertension in children 6 years and older) 2. Angina pectoris 3. Heart failure
Recommended:	Approval

1. Introduction

On March 30, 2017, Sun Pharma Industries Ltd, submitted NDA 210428 for Metoprolol extended release capsules under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The application relies on the finding of safety and efficacy of the reference listed drug (RLD) Toprol-XL® (metoprolol succinate), NDA 19,962, which is approved for the following indications:

1. Hypertension,
2. Angina Pectoris, and
3. Heart Failure.

The applicant is seeking the same indications for their product as the RLD, with the exception of the initiation of therapy in patients with more severe heart failure, because the applicant did not develop a 12.5 mg dosage form, which the RLD provides (the 25 mg tablet is scored) and which is the indicated dose to initiate treatment in that population. The applicant had discussed with the Agency their proposal to not produce a 12.5-mg dose strength during the development of their product and it was found to be acceptable.

The following primary and consult reviews were used for this CDTL review:

Office of Product Quality review (November 30, 2017)	Rohit Tiwari, Ben Stephens, Milton Sloan, Chunsheng Cai, Akm Khairuzzaman, Viviana Matta, Ruth Moore, Kaushal Dave, Ta-Chen Wu, Grafton Adams, Milton Sloan, Wendy Wilson-Lee (Application Technical Lead),

Pharmacology/Toxicology review (July 4, 2017)	Muriel Saulnier
Clinical Pharmacology review (December 4, 2017)	Snehal Samant, Martina Sahre
Label and Labeling Review (DMEPA) (October 13, 2017)	Ashleigh Lowery, Chi-Ming (Alice) Tu
OPDP Labeling Review (November 30, 2017)	Zarna Patel, James Dvorsky
Proprietary Name Review (October 10, 2017)	Ashleigh Lowery, Chi-Ming (Alice) Tu, Danielle Harris
DPMH Review (December 21, 2017)	Christos Mastroyannis, Tamara Johnson, Lynne P. Yao

2. Background

Metoprolol belongs to the class of selective beta1-receptor antagonists. The succinate salt form of metoprolol is only available as an extended-release product. Metoprolol lowers heart rate and cardiac output as well as blood pressure.

The RLD, Toprol-XL®, is marketed as film coated tablets. The application under review is for extended-release capsules that can either be swallowed whole, or if a patient has difficulty swallowing, opened and the content administered after mixing with on soft food or via a nasogastric tube.

3. CMC/Device

OPQ recommends approval from a quality perspective. There are no recommended post-marketing commitments (b) (4)

Drug Substance:

Metoprolol succinate is a non-hygroscopic, white to off-white powder. Given one stereoisomeric center, there are two enantiomers and the final product is an even racemic mixture. Metoprolol succinate exists in two polymorphic forms, with (b) (4) being the form manufactured for this product. Relevant information on the synthesis and manufacturing of the drug substance is contained in DMF (b) (4). Acceptance limits for impurities and residual solvents were found to be acceptable. One genotoxic impurity, (b) (4) is controlled per ICH M7 guidance, and that control was found to be acceptable by both the drug substance and the pharmacology/toxicology reviewers. The (b) (4) impurity was not found in ranges outside the previously mentioned specifications in drug substance batches, where (b) (4) levels were below the level of quantification.

The sponsor is currently using USP specifications for metoprolol succinate drug substance that include a test for heavy metals per a monograph (USP 231) that will be retired from USP in January 2018. The sponsor commits to switching to a different USP monograph to test for heavy metals (USP 232/233) before January 2018 or on marketing of the product.

Drug Product:

Metoprolol succinate extended release capsules will be provided in dose strengths of 25, 50, 100, and 200 mg. The RLD is also available in these strengths as film-coated scored tablets. Therefore, the RLD provides the option for one additional dose, if needed, of 12.5 mg, which will not be an option for the extended-release capsules.

The 25 and 50 mg strengths are available in size 4 capsules, with tan and yellow caps, respectively. The 100 and 200 mg strengths are provided as size 2, white and size 0, yellow capsules, respectively.

Stability and Shelf-life:

The data to support an expiration period of two years for all strengths was found acceptable. The supported storage temperature is between 20 and 25°C (68-77° F).

Facilities review/inspection

Facilities associated with this substance and product were found to be acceptable based on results from previous inspections and new inspections were not conducted.

Other notable issues (resolved or outstanding)

The applicant commits to performing post-approval studies on the first three post-approval production batches for stability at controlled room temperature and for one of these batches until the end of the approved shelf-live. (b) (4)

4. Nonclinical Pharmacology/Toxicology

The submission included a review of recent non-clinical literature about the drug substance. No new safety issues were identified by the pharmacology/toxicology reviewer.

5. Clinical Pharmacology/Biopharmaceutics

An inspection of study site and analytical facilities was deemed not necessary by the Office of Study Integrity and Surveillance (OSIS), given that recent inspections did not show problems. OSIS recommends accepting the data from study MPL_200C_0179_16 without inspection. Review of financial disclosure information from the principal investigator of the relative bioavailability studies did not raise concerns.

The applicant conducted a relative bioavailability study comparing 200 mg Toprol-XL tablets to 200 mg Metoprolol succinate extended-release capsules. The geometric mean ratio of Cmax and AUCinf (90% confidence interval) was 95.6 (91.3, 100) and 88.3 (80.9, 96.4), respectively. The results show that exposure after administration of metoprolol succinate extended-release capsules is similar to that after administration of Toprol-XL tablets. A food-effect study showed that a high-fat, high-calorie meal does not change the exposure of Metoprolol succinate extended-release capsules. Likewise, administering the contents of the

opened capsule with soft food did not alter the exposure compared to administering an intact capsule.

The OPQ/Biopharmaceutics reviewer concluded that the submitted data on composition of drug product, release-mechanisms between capsule dose-strength and design, in addition to the establishment of bioequivalence in study MPL_200C_0179_16, support the biowaiver for the lower strengths of 25, 50 and 100 mg metoprolol succinate extended-release capsules.

Given that the proposed product is an extended-release formulation, in vitro assessment of release rates in the presence of various concentrations of alcohol (5, 10, 20, and 40% V/V in 0.1 N HCl) was performed. Results show that drug was released faster in the presence of 20 and 40% alcohol, which shows a potential for dose-dumping. Language to avoid alcohol use when taking metoprolol succinate extended-release capsules was included in labeling.

The applicant also conducted assessments to show that capsule contents, when sprinkled on soft food with various pH, did not degrade for at least 60 minutes. When administered through a nasogastric tube, the sponsor showed that no drug is retained on tubing material. An in vivo study to show relative bioavailability of administration of whole capsules vs administration via an NG tube was therefore not deemed necessary.

6. Clinical/Statistical- Efficacy

As discussed under section 5 (Clinical Pharmacology/Biopharmaceutics), the relative BA study provides the bridge to the efficacy findings of the listed drug, Toprol-XL.

7. Safety

This application primarily relies on the Agency’s previous determination of safety for the listed drug.

8. Advisory Committee Meeting

The application does not raise new significant issues regarding the safety or effectiveness of the drug. Therefore, no Advisory Committee Meeting was held.

9. Pediatrics

Since the product represents a new formulation, PREA requirements apply.

The applicant is seeking the following waivers for pediatric studies:

- Angina (all pediatric age groups): On the basis that are impossible or highly impractical in the age group.
- Heart Failure (all pediatric age groups): On the basis that are impossible or highly impractical in the age group.

The applicant is seeking the following deferral for pediatric studies:

- Hypertension (Younger than 6 years and birth weight greater than 7 kg): On the basis that an age-appropriate formulation is not yet available and juvenile animal studies are still outstanding.

Metoprolol succinate labeling supports hypertension in pediatric patients six years old or older; therefore, studies are not needed to establish safety and efficacy in this population.

The Division and PeRC agreed to the proposed deferral and waivers.

10. Other Relevant Regulatory Issues

To date, none of the names submitted to the Agency was found to be acceptable by DMEPA. This should not preclude approval, however.

11. Labeling

The label was revised to conform to PLLR format and the new Section 12 Labeling Guidance. The Toprol-XL label contains a boxed warning about the risk for ischemic disease on abrupt termination of beta-blocker therapy. This box will be not be included in the label for Metoprolol Succinate Extended-Release Capsules for the following reasons: because the information relayed in the boxed warning is not so severe that is merits a boxed warning and in other labels for beta blockers, the information about this risk is addressed in Section 5 alone. Further, it is current medical practice not to abruptly cease use of beta-blockers. (b) (4)

(b) (4)

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval

Risk Benefit Assessment

The risk-benefit relationship of this product is not expected to differ from that of the reference product.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

Recommendation for other Postmarketing Requirements and Commitments

None

Recommended Comments to Applicant

None

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

/s/

MARTINA D SAHRE
01/26/2018

NORMAN L STOCKBRIDGE
01/26/2018