CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213330Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	03-November-2020
From	Mohan Sapru, M.S., Ph.D. CMC Lead, Division of Cardiology and Nephrology
Through	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiology and Nephrology
Subject	CDTL Review
NDA	213330; Labetalol Hydrochloride in Sodium Chloride Injection, and Labetalol Hydrochloride in Dextrose Injection
Type of Application	505(b)(2)
Applicant	Hikma Pharmaceuticals International Limited
Date of Receipt	10-January-2020
PDUFA Goal Date	10-November-2020
Established/Proper Name	Labetalol Hydrochloride in Sodium Chloride Injection, and Labetalol Hydrochloride in Dextrose Injection
Dosage forms; Strength	Injection; Labetalol HCl in Sodium Chloride Injection in a single dose bag: • 100 mg/100 mL (1 mg/mL) • 200 mg/200 mL (1 mg/mL) • 300 mg/300 mL (1 mg/mL) Labetalol HCl in Dextrose Injection in a single-dose bag: • 200 mg/200 mL (1 mg/mL)
Route of Administration	Intravenous (IV)
Proposed Indication(s)	Indicated for control of blood pressure in severe hypertension
Regulatory Action	**Approval**

This CDTL review is based on the primary reviews, memos and documented review input, as listed below:

Material Reviewed/Consulted	Review Team
OPQ's Integrated Quality Review (DARRTS, dated 21-September-2020)	Daniel Jansen, Rao Kambhampati, Xia Xu, Allison Aldridge, Min Sung Suh, and Mohan Sapru (ATL)
DMEPA Review (DARRTS, dated 30-September-2020 and 24-June-2020)	Mariette Aidoo, and Chi-Ming (Alice) Tu
OPDP Labeling Consult Review (DARRTS, dated 03-September-2020)	Zarna Patel, James Dvorsky
DPMH Labeling Consult Review (DARRTS, dated 25-June-2020)	Jeanine Best, Tamara Johnson

OPQ: Office of Pharmaceutical Quality; DPMH: Division of Pediatric and Maternal Health; DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion.

1. Background

The Applicant, Hikma Pharmaceuticals International Limited, has sought U.S. marketing approval for ready-to-use, preservative-free, Labetalol Hydrochloride in Sodium Chloride Injection, and Labetalol Hydrochloride in Dextrose Injection, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Labetalol combines both selective, competitive, alpha1-adrenergic blocking and nonselective, competitive, beta-adrenergic blocking activity in a single substance. The ratio of alpha-to-beta-blockade has been estimated to be approximately 1:7 following intravenous administration. The proposed drug products, intended solely for slow continuous infusion at a rate of 2 mL/minute (2 mg/minute), are indicated for control of blood pressure in severe hypertension. The Applicant has listed TRANDATE® (labetalol hydrochloride) Injection as the as the Listed Drug (LD), which is a discontinued product; but not discontinued or withdrawn for safety or efficacy reasons.

2. Product Quality

2.1. Drug Substance (Labetalol hydrochloride)

The drug substance (Labetalol hydrochloride), a racemate, is water-soluble white or off-white crystalline powder. The Applicant has cross-referenced CMC information about the drug substance to DMF (b) (4), which has been previously reviewed and found adequate. The additional information provided in the NDA about general properties of the drug substance, specification, and certificates of analysis for drug substance batches used to produce the drug product is adequate. The identity, quality, and purity of each batch of the drug substance are assessed and confirmed as per the specification, which appropriately involves release testing of the critical quality attributes (CQAs) of the drug substance.

2.2. Drug Product (Labetalol Hydrochloride in Sodium Chloride Injection, USP, and Labetalol Hydrochloride in Dextrose Injection, USP)

2.2.1. Product Design, and Specification: Labetalol HCl in Sodium Chloride Injection, and Labetalol HCl in Dextrose Injection are two preservative-free, ready-to-use aqueous, sterile, isotonic formulations of labetalol for intravenous injection. Each of these products are made available in a single-dose, single-port bag with an aluminum overwrap. All the excipients proposed are compendial grade and their proposed levels are lower than those present in the FDA-approved IV Injection formulations. Adequate formulation development studies have been conducted. All the product critical quality attributes such as identification, pH, volume in container, particulate matter, assay of dextrose or sodium chloride, levels of degradants and (b) (4), osmolality, leak testing, bacterial endotoxins, and sterility, and elemental impurities (per USP < 232>, ICH Q3D Option 2) are controlled by product release specification. The proposed specifications comply with the USP monograph for Labetalol Injection. The proposed impurity limits have been adequately justified. The method validation details provided for all non-compendial methods are adequate. From product quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, sterility, and stability.

2.2.2. Manufacturing: Labetalol Hydrochloride in Dextrose and in Sodium Chloride Injection are (b) (4). The drug products are preservative-free, and the packaging is (b) (4) bags, which are controlled effectively with (b) (4) checks. Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

2.2.3. Microbiological Aspects: The bulk drug product solution is (b) (4) (b) (4), filled into single port IV bags, closed with Twist-Off closures, and (b) (4) sterilized. The product sterility is the key critical quality attribute of the proposed product. Manufacturing of the drug product is adequately controlled for microbiological attributes at various stages of the process. Specifically, the (b) (4) sterilization process for the finished drug products, and the container closure integrity testing have been adequately validated. The product release specification includes testing for bacterial endotoxins and sterility per USP <85> and USP <71>, respectively.

2.2.4. Biopharmaceutics Aspects: The Applicant has provided comparative *in vitro* study results for demonstrating bridging with the LD (Trandate®, 5 mg/mL vial dosage, NDA 019425), and the Reference Standard (RS; Hospira's Labetalol Hydrochloride Injection, 5mg/mL vial dosage, ANDA 075239). The proposed single-dose, ready-to-use Labetalol Hydrochloride in Sodium Chloride Injection, and Labetalol Hydrochloride in Dextrose Injection drug products are equivalent to the post-diluted RLD or RS solution for intravenous infusion administration at a final concentration of 1 mg/mL of Labetalol Hydrochloride, except that the parabens preservatives are present in the RLD or RS, but not in the proposed formulations. The intravenous infusion administration rate and dose remain the same between the RLD, RS and the proposed products. The Applicant has demonstrated that removing preservatives from the proposed formulations has no impact on CQAs such as the pH, assay, and degradation products. The route of administration of the proposed products is identical to that of the LD and RS, post-dilution. Given that intravenous solutions are 100% bioavailable, the active ingredient in Hikma's proposed products is 100% bioavailable in the same manner as the slow infusion preparation of the LD or RS. To support formulation bridging, the Applicant has provided information regarding the comparative composition and physicochemical (pH, osmolality) properties to demonstrate equivalency between the diluted LD/RS and proposed ready-to-use drug products. Additionally, the Applicant has included references to support that the removal of parabens from the formulation is unlikely to impact the PK properties of labetalol in the proposed drug products. Thus, a bridging information/data to demonstrate equivalence of the proposed product to the diluted LD/RS is acceptable, and formulation bridging under CFR 320.23 (b)(6) is deemed established.

2.3. Assessment of the Manufacturing Facilities: Regarding the listed manufacturing and testing facilities for this NDA, there are no outstanding cGMP issues and are deemed acceptable. Specifically, both the drug product and drug substance facilities have been approved based on inspection history and manufacturing experience of the concerned facilities.

2.4. Integrated Quality Assessment Conclusion: From the chemistry, manufacturing, and controls (CMC)/quality perspective, the NDA is recommended for approval.

3. Non-Clinical Pharmacology/Toxicology

No pivotal Pharmacology/Toxicology studies have been submitted and are not required for this NDA. The nonclinical information is mainly referred to the findings from the LD. Previously, long-term oral dosing studies with labetalol for 18 months in mice and for 2 years in rats have shown no evidence of carcinogenesis. Studies with labetalol, using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests, has shown no evidence of mutagenesis.

4. Clinical Pharmacology

N/A

5. Statistical-Evaluation

N/A

6. Clinical Studies/Financial Certification Disclosure

No clinical studies have been performed in support of this 505(b)(2) NDA. Hence, there is no financial information to disclose.

7. Advisory Committee Meeting

N/A

8. Pediatrics, and Other Relevant Regulatory Issues

None of the PREA criteria apply to this application. Hence, the Applicant is exempt from this requirement.

9. Labeling

The USP salt policy is not applicable for this NDA per the product monograph. This is because the drug product monograph specifically expresses the name and strength of the drug product in terms of the salt form. Based on multidisciplinary review, the Division's labeling recommendations have been accepted by the Applicant and are reflected in the most recent version of the product labeling.

10. Risk Benefit Assessment, and Recommendations

- **Risk Benefit Assessment**

  The current NDA relies on FDA's previous finding of safety and efficacy for the LD i.e., TRANDATE® (labetalol hydrochloride) Injection. The proposed indication for the proposed drug product has been previously approved for the LD. The Applicant's proposed to-be-marketed drug products are essentially similar to the LD as these have the same active

moiety, dosage form, dose, dosing regimen, and route of administration as the LD. The minor differences in inactive ingredients between the proposed product and the LD have been adequately justified by the Applicant and are not expected to impact disposition, safety, or efficacy of the proposed drug products. Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for the previously approved LD. The non-clinical, and clinical information concerning clinical efficacy and safety available in published literature does not warrant any change in current assessment of the risk-benefit profile of labetalol hydrochloride.

- **Recommended Regulatory Action**

All the review teams for this application recommended approval, and I concur with the review teams. Based on the OPQ's Integrated Quality Review, an expiration period of 24 months is granted for the product when stored at 20°C - 25°C (68°F - 77°F) in the commercial container closure system. Product excursions are permitted to 15°C -30°C (59°F -86°F).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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