

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210428Orig1s000

OTHER REVIEW(S)



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

I. GENERAL INFORMATION

NDA: 210428

Drug: Metoprolol Succinate Extended-Release Capsules, 25 mg, 50 mg, 100 mg and 200 mg

Class: Beta- Blocker

Applicant: Sun Pharmaceutical Industries Limited

Proposed Indications: Hypertension, Angina Pectoris & Heart Failure

Date of submission: March 30, 2017

PDUFA date: January 30, 2018

II. REVIEW TEAM

➤ **Office of New Drugs, Office of Drug Evaluation I:**

Division of Cardiovascular & Renal Product

Norman Stockbridge, MD, PhD, Director

Mary Ross Southworth, PharmD, Deputy Director for Safety

Michael Monteleone, MS, RAC, Assistant Director for Labeling

Martina Sahre, PhD, Cross Discipline Team Leader

Fortunato Senatore, MD, Clinical Reviewer

Albert DeFelice, PhD, Non-Clinical Supervisor

Muriel Saulnier, PhD, Non-Clinical Reviewer

Edward Fromm, RPh, RAC, Chief, Project Management Staff

Maryam Changi, PharmD, Regulatory Project Manager

➤ **Office of Pharmaceutical Quality:**

Wendy Wilson-Lee, PhD, Application Technical Lead

Grafton Adams, Regulatory Business Process Manager

Milton Sloan, PhD, Drug Product Reviewer

Rohit Tiwari, PhD, Drug Substance Reviewer

Ben Stevens, PhD, Drug Substance Team Leader

Kaushal Dave, PhD, Biopharmaceutical Reviewer

Wu, Ta-Chin, PhD, Biopharmaceutical Team Leader

Viviana Matta, PhD, Facility Reviewer

Ruth Moore, PhD, Facility Team Leader

Chunsheng Cai, PhD, Process Reviewer

Akm Khairuzzaman, PhD, Process Team Leader

➤ **Office of Clinical Pharmacology:**

Snehal Samant, PhD, Clinical Pharmacology Reviewer

Sudharshan Hariharan, PhD, Clinical Pharmacology Team Leader

➤ **Office of Surveillance and Epidemiology:**

Darrel Lyons, RN, Safety Regulatory Project Manager

Ashleigh Lowery, PharmD, DMEPA Reviewer

Tu, Chi-Ming, PharmD, DMEPA Team Leader

➤ **Office of Prescription Drug Promotion:**

Zarna Patel, PharmD, OPDP Reviewer

James Dvorsky, OPDP Team Leader

➤ **Division of Pediatric and Maternal Health: (Labeling)**

Christos Mastroyannis, MD

Tamara Johnson, MD, MS, Team Leader

III. **BACKGROUND:**

On March 30, 2017, Sun Pharmaceutical Industries Limited, SPIL, filed a 505(b)(2) application. The applicant referring to ARALEZ PHARMACEUTICALS' NDA 019962 (TOPROL-XL® Tablets) as a Reference Drug List (RLD). SPIL has developed a new dosage form from Extended Release Tablets to Extended-Release Capsules. The application was cleared by the 505(b)(2) committee on January 16, 2018.

The applicant performed a pivotal pharmacokinetic study and extrapolated the effectiveness of new product entirely from existing clinical efficacy studies without the need for additional trials. The Sponsor indicated that the effectiveness of new dosage form maybe assessed based on evidence of bioequivalence.

The Sponsor submitted an IND #127963 for Metoprolol Succinate Extended-Release Capsules 25 mg, 50 mg, 100 mg and 200 mg on June 08, 2016 and further submitted in-vitro alcohol dose dumping studies as "Information Amendment to IND on January 30, 2017 and February 20, 2017, as requested by the Agency.

We received the Agreed iPSP on March 27, 2017. The Sponsor requested the full waiver for management of angina pectoris & heart failure, (b) (4)

[REDACTED]

IV. **APPLICATION REVIEW**

1. **User Fee**

The User fee for this application was paid in full on March 30, 2017. User Fee I.D. Number for this application is PD3016739.

2. Pediatric Review Committee (PeRC)

The Division met with PeRC on November 15, 2017. The Division and Perc agreed to grant applicant's request for a full waiver in pediatric patients from birth to less than 17 years of age for the indications angina pectoris and heart failure because studies are impractical. However, PeRC indicated that, if the follow up internal discussion of the heart failure suggests that this approach be modified, then that would be acceptable. (please refer to PeRC Minutes dated November 28, 2017).

3. Advisory Committee

There was no Advisory Committee meeting for this NDA, because it did not raise any significant safety or efficacy issues.

4. Trade name

On July 13, 2017, Sun Pharmaceutical submitted a request for Proprietary Name Review for (b)(4) DMEPA sent an information request on 7/18/2018 to clarify the applicant's intended proposed name "(b)(4) or (b)(4)

On July 25, 2018, the applicant submitted an amendment to request for proprietary name review. On October 10, 2017, DMEPA found (b)(4) unacceptable.

On November 7, 2017, Sun Pharmaceutical Industries submitted a request for Proprietary Name Review for (b)(4) DMEPA held a t-con with the applicant on November 21, 2017 to discuss DMEPA's preliminary findings for the proposed name and to address the Agency's concerns and to provide the applicant with regulatory options. DMEPA finds the proposed proprietary name, (b)(4) unacceptable.

On November 22, 2017, Sun Pharmaceutical Industries withdrew the proposed proprietary name, (b)(4) and submitted a request for proprietary name review for (b)(4). Later, on January 11, 2018, DMEPA held another t-con with the applicant to discuss their findings on the proposed name and informed that the submitted name is not acceptable.

5. Facilities Inspections

Per the Integrated Quality Assessment dated November 30, 2017, the Office of Process and Facilities has recommended approval for all listed manufacturing facilities for NDA 210428.

6. Regulatory Timeline

PIND Meeting final written response: November 25, 2015

FDA User Fee Received Date: March 30, 2017

Filing date: May 29, 2017

74-Day letter issued: June 5, 2017

Mid-cycle meeting: August 29, 2017

PeRC Meeting: November 15, 2017

Labeling/PMC-PMR to Sponsor: November 30, 2017
PDUFA Date: January 30, 2018 (Standard, 10-Month)
PDUFA Goal Date: January 30, 2018
Approval letter: January 26, 2018

7. Reviews

a) Divisional Memorandum: (January 26, 2018)

Dr. Stockbridge indicated his concurrence on Dr. Sahre's CDTL memo.

b) Cross-Discipline Team Leader Review : (January 26, 2018)

Dr. Sahre recommends approval. Her review summarizes each disciplines finding including consults. She also provided a detailed regulatory history.

c) Clinical Pharmacology Review: (December 4, 2017)

Dr. Samant recommended approval for this application:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1(OCP/DCP1) has reviewed the NDA submission. The results of the relative BA study and food effect study support approval of METOPROLOL SUCCINATE Extended-Release Capsules for the proposed indications at the doses as approved for the listed drug TOPROL-XL.

She also included:

The food effect study results support administration of METOPROLOL SUCCINATE Extended-Release Capsules by sprinkling the contents on soft food and without regards to meal. The clinical pharmacology section of the proposed label was updated to reflect the current Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products

d) Pharmacology & Toxicology Review: (July 5, 2017)

Dr. Saulnier stated in her review:

No new safety findings of concern were found and this product is approvable from the preclinical development aspect. Furthermore, an extensive clinical experience in adults and children ≥ 6 years old with metoprolol is available.

e) Office of Pharmaceutical Quality Review: (November 30, 2017)

OPQ recommended 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.

8. Consults

Please see the following reviews and their corresponding dates:

- OSE/DMEPA: 10/10/17-10/16/17
- OPDP: 11/30/17
- DPMH: 12/25/17

9. Labeling

Labeling discussions occurred with the applicant. The final agreed-upon labeling will be attached to the approval letter.

V. CONCLUSION

The review team recommended approval.

An Approval letter was signed by Dr. Norman Stockbridge on January 26, 2018.

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

/s/

MARYAM K CHANGI
01/26/2018



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
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Division of Pediatric and Maternal Health Memorandum

Date: December 21, 2017 **Date consulted:** May 16, 2017

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Metoprolol ER Capsules

Drug Class: Beta-Blocker

NDA: 210428

Applicant: Sun Pharmaceutical Industries LTD (SPIL)

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication: Metoprolol succinate extended-release capsules are indicated for:

- Hypertension, to lower blood pressure and thus to reduce cardiovascular morbidity and mortality including stroke and myocardial infarction. It may be administered with other antihypertensive agents.
- The long-term treatment of angina pectoris, to reduce angina attacks and to improve exercise tolerance.
- Heart failure, to reduce the risk of cardiovascular mortality and hospitalization in patients [REDACTED] (b) (4)

Materials Reviewed:

- DPMH consult request dated May 16, 2017 in DARRTS (Reference ID 4098932)
- Applicant's submission for NDA 210428 dated March 30, 2017 and the latest Prescribing Information (PI) for Metoprolol ER Capsules dated June 5 and November 13, 2017
- Applicant's response to information request of May 16, 2017 submitted June 6, 2017

Consult Question:

DCRP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation labeling subsections to comply with PLLR format.

INTRODUCTION

On March 30, 2017, Sun Pharmaceutical Industries Ltd. (SPIL) submitted a 505(b)(2) New Drug Application (NDA) 210428 for Metoprolol Succinate Extended-Release (ER) Capsules 25 mg, 50 mg, 100 mg and 200 mg. The applicant has developed a new dosage form from Extended Release Tablets to Extended-release Capsules. No pharmacology and/or toxicology studies have been conducted by the applicant. For the nonclinical toxicology and safety & efficacy profile, SPIL depends on previous finding of safety and efficacy for the listed drug Toprol XL, and on several published literature and clinical trials references.

The Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Pediatric and Maternal Health (DPMH) on May 16, 2017, to provide input for appropriate labeling of the pregnancy and lactation subsections of Metoprolol ER capsules to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

This review provides recommended revisions and structuring of information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

BACKGROUND

Metoprolol ER capsules are indicated in:

- Hypertension, to lower blood pressure and thus to reduce cardiovascular morbidity and mortality including stroke and myocardial infarction. It may be administered with other antihypertensive agents.
- The long-term treatment of angina pectoris, to reduce angina attacks and to improve exercise tolerance.
- Heart failure, to reduce the risk of cardiovascular mortality and hospitalization in patients (b) (4)

Regulatory History

This 505(b)(2) NDA submission relies on Toprol XL (metoprolol succinate, NDA 019962), the reference listed drug (RLD), approved on January 10, 1992, for use in the following indications:

- Hypertension, to lower blood pressure and thus to reduce cardiovascular morbidity and mortality including stroke and myocardial infarction. It may be administered with other antihypertensive agents.
- The long-term treatment of angina pectoris, to reduce angina attacks and to improve exercise tolerance.
- Heart failure, to reduce the risk of cardiovascular mortality and hospitalization in

Metoprolol Drug Characteristics¹

- Metoprolol succinate, is a beta₁-selective (cardioselective) adrenoceptor blocking agent.
- Metoprolol crosses the blood-brain barrier and has been reported in the cerebrospinal fluid (CSF) in a concentration 78% of the simultaneous plasma concentration.
- The molecular weight of metoprolol succinate is 652.82.
- Plasma half-life ranges from approximately 3 to 7 hours.
- Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity.
- About 12% is bound to human serum albumin.

In the US, metoprolol is currently available from different manufacturers, including SPIL, in different salt forms (such as succinate, fumarate and tartrate) and different dosages [such as immediate release tablets (50 mg, and 100 mg), extended/sustained release tablets (25 mg, 50 mg, 100 mg, and 200 mg) and injectable (1 mg/1 mL)].

Hypertension and Pregnancy

Chronic hypertension occurs in up to 5% of pregnant women. Pregnant women with hypertension are at an increased risk for preeclampsia (occurs in 13-40% of pregnant women with chronic hypertension), gestational diabetes (OR 1.8; 95% CI 1.4-2.0), cesarean delivery (OR 2.7; 95% CI 2.4-3.0), post-partum hemorrhage (OR 2.2, 95% CI 1.4-3.7), placental abruption, premature delivery, intrauterine growth restriction, and intrauterine death.²

³

Ischemic Heart Disease and Pregnancy

Ischemic heart disease (IHD) in pregnancy, particularly myocardial infarction (MI), is a rare yet potentially fatal condition for the mother and the fetus. Females of reproductive potential are considered low risk for the development of coronary artery disease and myocardial infarction (MI). Pregnancy increases the risk of MI by 3–4 times.^{4,5,6} and maternal mortality can be as high as 7-11%.^{7,8} Fetal loss rate is primarily the result of the maternal outcome. Overall the fetal loss rate with MI in pregnancy was 37% in early reports⁹

¹ Metoprolol applicant's proposed labeling, Sections 11 and 12

² The American College of Obstetrics and Gynecologist. Hypertension in Pregnancy. 2013. <http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy>. Accessed 1/29/2016.

³ NIH: National Heart, Lung, and Blood Institute. High Blood Pressure in Pregnancy. <http://www.nhlbi.nih.gov/health/resources/heart/hbp-pregnancy>. Accessed 1/29/2016.

⁴ James A.H., Jamison M.G. Acute myocardial infarction in pregnancy: a United States population-based study. *Circulation*. 2006;113:1564–1571.

⁵ Bondagji NS Ischaemic heart disease in pregnancy. *J Saudi Heart Assoc*. 2012; 24(2): 89–97

⁶ Naderi S, Raymond R. Pregnancy and Heart Disease.

www.clevelandclinicmeded.com/medicalpubs/.../pregnancy-and-heart-disease/

⁷ Roth A., Elkayam U. Acute myocardial infarction associated with pregnancy an update. *Ann Intern Med*. 1996;125:751–762.

⁸ Ladner H.E., Danielson B. Acute myocardial infarction in pregnancy and the puerperium: a population-based study. *Obstet Gynecol*. 2005;105:480–484

⁹ Hankins G.D.V., Wendel G.V. Myocardial infarction during pregnancy. A review. *Obstet Gynecol*. 1985;65:139–146.

which decreased to 9% in more recent reviews.¹⁰ In general IHD is classified into angina pectoris (transient myocardial ischemia) and MI (fixed myocardial ischemia/necrosis).

Angina pectoris is rare in pregnancy with only a few reported cases. Most women who have MI in pregnancy present with sudden infarction that is not preceded by angina pectoris. Despite the rarity of angina pectoris in pregnancy, patients with angina pectoris in pregnancy should be considered at high risk of developing subsequent MI and should be managed accordingly.^{4,5}

Heart Failure and Pregnancy

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the appropriate function of the heart. Severely depressed systemic ventricular function (EF <30%) constitutes a contraindication for pregnancy.^{11,12} Women with heart failure or a condition leading to heart failure should undergo pre-conception counseling and be under the care of a team (cardiologist and maternal fetal medicine specialist). Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester.

Current RLD Labeling

The current labeling for RLD, Toprol XL as of May 6, 2014, is in Physician Labeling Rule format (PLR), but has not yet complied with PLLR and still has letter category. It states¹³:

HIGHLIGHTS OF PRESCRIBING INFORMATION

USE IN SPECIFIC POPULATIONS -----

- Pregnancy: There are no adequate and well-controlled studies in pregnant women. Use this drug during pregnancy only if clearly needed. (8.1)
- Nursing Mothers: Consider possible infant exposure. (8.3)

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease

¹⁰ Roth A., Elkayam U. Acute myocardial infarction associated with pregnancy. J Am Coll Cardiol. 2008;52:171-180.

¹¹ Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BG, et al. Cardiac Disease in Pregnancy (CARPREG) Investigators. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001;104:515-21

¹² Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. Heart 2006;92:1520-5

¹³ Toprol XL labeling last approved on May 6, 2014

neonatal survival in rats at doses up to 22 times, on a mg/m² basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

8.3 Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Consider possible infant exposure when TOPROL-XL is administered to a nursing woman.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor. All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella*/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m² basis, the daily dose of 200 mg in a 60-kg patient.

REVIEW

As per applicant, SPIL has not performed any nonclinical studies on the potential effects of Metoprolol succinate ER capsules on pregnancy, lactation, and females and males of reproductive potential. There is no pharmacovigilance database nor pregnancy registry by

(b) (4)

PREGNANCY

Animal Data

No new information was provided by the applicant. As per the nonclinical reviewer Muriel Saulnier, Ph.D., “the extensive review of the updated nonclinical literature revealed that

there are no new safety issues. Systemic effects of metoprolol have been well characterized and long clinical experience supports the safety of metoprolol”.

Review of Literature

Applicant’s Review

On June 5, 2017, the applicant provided a review of the literature and summary of the available information in response to FDA’s information request of May 16, 2017, to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential (PLLR) subsections of labeling. The literature search for clinical data was carried out regardless of indication, dosage form or dose level. Online search of published biomedical literature was performed on PubMed database on May 12, 2017 and May 22, 2017 using the search term “Metoprolol” and applying the limit “Humans”. Terms used included metoprolol and pregnancy, pregnancy exposure, pregnant, gestation, gravida, postpartum, delivery, labor, antenatal, birth defects, congenital, congenital malformations, developmental effects, cardiovascular abnormalities, embryopathy etc. which resulted in a total of 2153 citations. After initial review, 723 unique publications (removal of duplicate publications) were identified of which 18 were relevant including clinical studies, meta-analysis, systemic reviews and 8 case reports/series. No serious adverse events were reported except of fetal growth restriction which can be confounded by the underlying disease.

A study was carried out to evaluate the steady-state pharmacokinetics of metoprolol during pregnancy and lactation. Serial plasma and urine, concentrations of metoprolol and its metabolite, α -hydroxymetoprolol, were measured over 1 dosing interval in women treated with metoprolol (25-750 mg/day) during early pregnancy, mid-pregnancy, and late pregnancy, as well as postpartum. Mean metoprolol apparent oral clearance was significantly higher in mid-pregnancy (361 ± 223 L/h, $P < 0.05$) and late pregnancy (568 ± 273 L/h, $P < 0.05$) compared with ≥ 3 months postpartum (200 ± 131 and 192 ± 98 L/h, respectively). When the comparison was limited to extensive metabolizers (EMs), metoprolol apparent oral clearance was significantly higher during both mid and late pregnancy ($P < 0.05$). From these results, it was concluded that, because of the large, pregnancy-induced changes in metoprolol pharmacokinetics, if inadequate clinical responses are encountered, clinicians who prescribe metoprolol during pregnancy should be prepared to make aggressive changes in dosage (dose and frequency) or consider using an alternate beta-blocker.¹⁴

The most noteworthy publications are summarized below (See the Table 1 in the Appendix for further details). Fetal growth restriction was the major finding from the literature review by the applicant.

¹⁴ Ryu RJ et al (2016). Pharmacokinetics of metoprolol during pregnancy and lactation. J Clin Pharmacol. 56(5):581-9.

DPMH Review

In addition to the search by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for metoprolol and use in pregnancy. No publications were identified stating any additional safety issues. GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation report that: “no fetal malformations attributable to metoprolol have been reported, but experience during the 1st trimester is limited”.

Reprotox¹⁵ concludes, based on experimental animal studies and human experience, that metoprolol therapy is not anticipated to increase the risk of congenital anomalies.^{16,17} In one study, it may have caused intrauterine growth restriction when given early in pregnancy (in the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities, the use of metoprolol during gestation was associated with a decrease in birth weight but not in gestational age at delivery).¹⁸ Metoprolol crosses the placenta and maternal and fetal blood concentrations are about equal.^{19,20} Human studies indicated that metoprolol administration might impair intervillous blood flow.²¹

In general, beta-blockers are commonly used to treat hypertension during pregnancy.^{22,23,24} While some studies that have evaluated the use of beta-blockers during pregnancy, have demonstrated an increased risk of intrauterine growth restriction, bradycardia, hypotension, hypoglycemia, respiratory distress and feeding problems,^{25,26,27} other studies have failed to demonstrate an increased risk for adverse fetal outcomes.^{28,29} Labeling for beta-blockers, such as atenolol and labetalol, notes that infants born to mothers taking these beta-blockers are at risk for hypotension, bradycardia, hypoglycemia and respiratory depression.³⁰

Reviewer comment

The published literature has reported inconsistent findings of intrauterine growth restriction, with maternal use of metoprolol during pregnancy; however, these studies have methodological limitations hindering interpretation. Methodological limitations include retrospective design, concomitant use of other medications, and other unadjusted

¹⁵ Reprotox. A Truven health analytics, Micromedex solutions

¹⁶ Hogstedt S et al.: A prospective controlled trial of metoprolol-hydralazine treatment of hypertension during pregnancy. Acta Obstet Gynecol Scand 664:505-510, 1985

¹⁷ Jannet D, Carbonne B, Sebban E, Milliez J. Nicardipine versus metoprolol in the treatment of hypertension during pregnancy: a randomized comparative trial. Obstet Gynecol 1994;84:354-9.

¹⁸ Redmond GP: Propranolol and fetal growth retardation. Semin Perinatol 6:142-7, 1982

¹⁹ AHFS: Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; Jan 2009.

²⁰ Sandström B (1978). Antihypertensive treatment with the adrenergic beta-receptor. Gynecol Invest. 9(4):195-204.

²¹ Suonio S et al.: Acute effects of dihydralazine mesylate, furosemide, and metoprolol on maternal hemodynamics in pregnancy-induced hypertension. Am J Obstet Gynecol 155:122-5, 1986

²² Mothertobaby

²³ <https://www.escardio.org/Journals/E-Journal-of.../Tachyarrhythmias-and-Pregnancy>. May 20, 2011

²⁴ www.medscape.com/viewarticle/878881

²⁵ Lydakis, et al. Atenolol and fetal growth in pregnancies complicated by hypertension. Am J Hypertension. 1999; 12(6): 541-547.

²⁶ Magee, et al. Oral beta-blockers for mild to moderate hypertension during pregnancy. Cochrane Database Sys Reve. 2003; 3.

²⁷ Davis, et al. Risk of congenital malformations and perinatal among infants exposed to calcium channel and beta blockers during Pregnancy. Pharmacoepidemiology and Drug Safety. 2011; 20: 138-145.

²⁸ Magee, et al. Fortnightly review: management of hypertension during pregnancy. Br Med J. 1999; 318 (7194): 1332-1336

²⁹ Easterling, et al. Prevention of preeclampsia: a randomized trial of atenolol in hyperdynamic patients before the onset of hypertension. Obstet Gynecol. 1993; 3 (5): 725-733.

³⁰ Drugs@FDA. Tenormin (atenolol) and Trandate (labetalol). Accessed 12/12/2017.

confounders that may account for the study findings including the underlying disease in the mother. These observational studies cannot definitely establish or exclude any drug-associated risk during pregnancy.

Pharmacovigilance Review

The applicant performed a search in company's Argus Safety database to identify cases relevant to the use of metoprolol during pregnancy. Cases of hypoglycemia, bradycardia, fetal growth restriction, congenital anomalies (congenital hypothyroidism, atrial septal defects) and premature birth have been reported following *in utero* exposure of metoprolol (peripartum and during the first trimester and sometimes in the second and third trimesters). Respiratory distress syndrome, cerebral infarction and renal infarct have also been reported following *in utero* exposure of metoprolol.

Reviewer comment

The reports in the safety data base refer to women who were had multiple medical conditions, many required hospitalizations and were exposed to multiple medications. Infants developed multiple conditions that evaluators considered as possibly related to use of metoprolol during pregnancy. No patterns of adverse developmental outcomes were identified; therefore, information from the applicant's pharmacovigilance should not be contributing to the labeling.

Summary

Review of the literature and applicant's pharmacovigilance have not demonstrated an association of adverse developmental outcomes with maternal use of metoprolol during pregnancy. Animal reproduction studies have shown an increase in post-implantation loss and decreased neonatal survival in rats with metoprolol use of 500mg/kg/d, approximately 24 times the daily dose of 200 mg. The underlying disease that requires treatment with metoprolol plays a significant role to the adverse developmental outcomes, if untreated. Because metoprolol crosses the placenta, neonates born to mothers who are receiving metoprolol during pregnancy, may be at risk for hypotension, hypoglycemia, bradycardia, and respiratory depression.

LACTATION

Review of Literature

Applicant's Review

Online search of published biomedical literature was performed on PubMed database on May 12, 2017 and May 22, 2017 using the search term "Metoprolol" and applying the limit "Humans". Terms used included metoprolol and breast milk, nursing, milk, lactation, breastfeeding, milk production, milk excretion. A study was carried out to evaluate the steady-state pharmacokinetics of metoprolol during lactation. Serial plasma and breast milk concentrations of metoprolol and its metabolite, α -hydroxymetoprolol, were measured over 1 dosing interval in women treated with metoprolol (25-750 mg/day) postpartum with and without lactation. Relative infant exposure to metoprolol through breast milk was <1.0% of maternal weight-adjusted dose.⁶ Possible infant exposure should be considered when metoprolol succinate extended release is administered to a lactating woman (USPI of TOPROL-XL, AstraZeneca, May 2014).¹³.

The following 6 publications were identified and are summarized below in Table 2.(See the Table 2 in the Appendix for further details). Liedholm *et al* studied three women 4-6 months postpartum who received 100 mg twice daily for 4 days. The mean milk to plasma ratio was about 3. The authors calculated that an infant who ingests 75 ml of milk, will ingest about

0.05 mg of metoprolol with first feeding and less at subsequent feedings.³¹ Sandstrom *et al* calculated from a study in 9 women receiving 50-100 mg of metoprolol twice daily that the mean milk to plasma ratio was 3.72. TW Hale postulates that although milk/plasma ratio is high, the maternal plasma levels are quite small and therefore the absolute amount transferred to the fetus is small. He further states “these levels are probably too low to be clinically relevant” and estimates the relative infant dose to be 1.4%³². GG Briggs and RK Freeman state that metoprolol is concentrated in breast milk at approximately 3 times higher than the maternal plasma and agrees with Hale that the metoprolol amount ingested by the infant is probably clinically insignificant. Despite the low amounts ingested by the breastfed infant, infants should be observed for signs and symptoms of β -blockade.³³ The American Academy of Pediatrics classifies metoprolol as compatible with breastfeeding.³⁴

Summary

Metoprolol is present in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

There are nine (9) clinical studies on metoprolol use in fertility/reproduction referring to the treatment of coronary artery bypass graft (CABG), arterial, essential or untreated hypertension, elective coronary angioplasty and erectile dysfunction. The safety data reported in these publications is summarized below in Table 3 (See the Table 3 in the Appendix for further details).

Summary

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m² basis, the daily dose of 200 mg in a 60-kg patient.

In animal fertility studies, metoprolol has been associated with reversible adverse effects on spermatogenesis starting at oral dose level of 3.5 mg/kg in rats, which would correspond to a dose of 34 mg/kg/day in humans in mg/m² equivalent, although other studies have shown no effect of metoprolol on reproductive performance in male rats.

Cases of impotence have been reported in patients receiving metoprolol and inhibit sperm motility in animal studies.

Because there is no need for contraception and pregnancy testing while someone takes metoprolol, pregnancy testing and contraception are omitted from the labeling.

CONCLUSIONS

Metoprolol Succinate Extended-Release Capsules labeling has been edited to comply with the PLLR. There is no identified association between metoprolol use during the 1st trimester and adverse developmental outcomes or adverse lactation-related outcomes.

DPMH revised subsections 8.1, 8.2, and 8.3 and section 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

³¹ Liedholm H, Melander A, Bitzen PO et al. Accumulation of atenolol and metoprolol in human breast milk. *Eur J Clin Pharmacol* ;20(3):229-31, 1981

³² Hale TW Medications and Mother's Milk. Springer Publishing Company, LLC. New York, NY, 2017

³³ Briggs GG and Freeman RK, Drugs in Pregnancy and Lactation, Wolters Kluwer, Philadelphia, PA. 2015

³⁴ Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 108:776-89;2001

The *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections of Metoprolol Succinate Extended-Release Capsules labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Subsection 8.1**
 - The “Pregnancy” subsection of metoprolol labeling was formatted in the PLLR format to include: “Risk Summary”, “Clinical Considerations” and “Data” headings.
- **Lactation, Subsection 8.2**
 - The “Lactation” subsection of metoprolol labeling was formatted in the PLLR format to include the “Risk Summary”, “Clinical Considerations” and “Data” headings.
- **Females and Males of Reproductive Potential, Subsection 8.3**
 - Females and Males of Reproductive Potential subsection of metoprolol labeling was formatted in the PLLR format to include the “Risk Summary”.
- **Section 17 PATIENT COUNSELING INFORMATION**

RECOMMENDATIONS

DPMH has the following recommendations for Metoprolol Succinate Extended-Release Capsules labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

(b) (4)

FULL PRESCRIBING INFORMATION: CONTENTS

USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published observational studies have not demonstrated an association of adverse developmental outcomes with maternal use of metoprolol during pregnancy (*see Data*). Untreated hypertension and heart failure during pregnancy can lead to adverse outcomes for the mother and the fetus (*see Clinical Considerations*). In animal reproduction studies, metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at oral dosages of 500 mg/kg/day, approximately 24 times the daily dose of 200 mg in a 60-kg patient on a mg/m² basis

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical consideration

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester.

Fetal/Neonatal adverse reactions

Metoprolol crosses the placenta. Neonates born to mothers who are receiving metoprolol prior to delivery, may be at risk for hypotension, hypoglycemia, bradycardia, and respiratory depression. Observe neonates for symptoms of hypotension, bradycardia, hypoglycemia and respiratory depression and manage accordingly.

Data

Human Data

Data from published observational studies did not demonstrate an association of major congenital malformations and use of metoprolol in pregnancy. (b) (4)

Animal Data

Metoprolol has been shown to increase post-implantation loss and decrease neonatal survival in rats at oral dosages of 500 mg/kg/day, i.e., 24 times, on a mg/m² basis, the daily dose of 200 mg in a 60-kg patient

No fetal abnormalities were observed when pregnant rats received metoprolol orally up to a dose of 200 mg/kg/day, i.e. 10 times, the daily dose of 200 mg in a 60-kg patient.

8.2 Lactation

Risk Summary

Limited available data from published literature report that metoprolol is present in human milk. The estimated daily infant dose of metoprolol received from breastmilk range from 0.05 mg to less than 1 mg. The estimated relative infant dosage was 0.5% to 2% of the mother's weight-adjusted dosage (*see Data*). No adverse reactions of metoprolol on the breastfed infant have been identified. There is no information regarding the effects of metoprolol on milk production.

Clinical consideration

Monitoring for adverse reactions

(b) (4)
In a report of 6 mothers taking metoprolol, none reported adverse effects in her breastfed infant.

Data

(b) (4)
Limited published cases estimate the infant daily dose of metoprolol received from breastmilk range from 0.05 mg to less than 1 mg.

In 2 women who were taking unspecified amount of metoprolol, milk samples were taken after one dose of metoprolol. The estimated amount of metoprolol and alpha-hydroxymetoprolol in breastmilk is reported to be less than 2% of the mother's weight-adjusted dosage.

In a small study, breast milk was collected every 2 to 3 hours over one dosage interval, in three mothers (at least 3 months postpartum) who took metoprolol of unspecified amount. The average amount of metoprolol present in breast milk was 71.5 mcg/day (range 17.0 to 158.7). The average relative infant dosage was 0.5% of the mother's weight-adjusted dosage.

8.3 Females and Males of Reproductive Potential

Infertility

Based on the published literature, beta blockers (including metoprolol) may cause erectile dysfunction and inhibit sperm motility. In animal fertility studies, metoprolol has been associated with reversible adverse effects on spermatogenesis starting at oral dose level of 3.5 mg/kg in rats, which would correspond to a dose of 34 mg/kg/day in humans in mg/m² equivalent, although other studies have shown no effect of metoprolol on reproductive performance in male rats. No evidence of impaired fertility due to metoprolol was observed in rats [*see Nonclinical Toxicology (13.1)*]

17 PATIENT COUNSELING INFORMATION

Advise patients who are breastfeeding to monitor the infant for bradycardia, dry mouth, skin or eyes, and diarrhea or constipation [*see Use in Specific Population (8.2)*].

Appendix

Table 1: Metoprolol and Pregnancy

Study	Treatment and Study Population (N)	Safety reported/comments
<p>Tanaka K et al (2016)³⁵ Beta-Blockers and Fetal Growth Restriction (FGR) in Pregnant Women With Cardiovascular Disease. [Retrospective study]</p>	<ul style="list-style-type: none"> • α/β group: [Carvedilol (2.5 – 20 mg per day)] [n=13] • β-adrenergic blocker group: [Atenolol (25–50 mg/day), Propranolol (15–60 mg/day), Bisoprolol (5–10 mg/day), and metoprolol (20–120 mg/day)] [n=45] <p>[Exposure to metoprolol (n=12)]</p> <ul style="list-style-type: none"> • Control (n=100) <p>[Not treated with an oral α/β- or β-adrenergic blocker over the same period]</p> <p>[N =158 pregnancies in women]</p>	<ul style="list-style-type: none"> • In the metoprolol group, Fetal Growth Restriction (FGR) was observed in 17% of patients. • The use of β-adrenergic blockers was associated with an elevated risk of fetal growth restriction. • Cardiovascular events occurred in 54% of the α/β (carvedilol) group and in 66% of the β group. • There was 1 case (7%) of fetal growth restriction in the α/β group, 12 (26%) in the β group, and 3 (3%) in the control group. • There were no neonatal deaths in any of the groups. • Longer treatment duration increased the probability of giving birth to an infant with fetal growth restriction. The reason why β-adrenergic blockers can cause fetal growth restriction may be based on their ability to increase vascular resistance in both the mother and fetus. <p>It was concluded that as a group, β-adrenergic blocker treatment was found to be significantly associated with fetal growth restriction in pregnant women with cardiovascular disease.</p>
<p>Ryu RJ et al (2016)³⁶ Pharmacokinetics of metoprolol during pregnancy and lactation. [Pharmacokinetic study]</p>	<ul style="list-style-type: none"> • Metoprolol (25 – 750 mg/day) [N=22 pregnant women] 	<ul style="list-style-type: none"> • Metoprolol apparent oral clearance was significantly higher during both mid- and late pregnancy ($P < 0.05$). • Metoprolol was present in umbilical cord blood collected at delivery. • Relative infant exposure to metoprolol through breast milk was $<1.0\%$ of maternal weight-adjusted dose ($n = 3$).
<p>Laivuori HM et al (1999)³⁷ Short-term metabolic effects of isradipine and metoprolol in pre-eclampsia. [Single Centre, Prospective, Randomized, Double Blind,</p>	<ul style="list-style-type: none"> • Metoprolol 50 mg BID ($n = 8$) • Isradipine 2.5 mg BID ($n = 9$) <p>[N=24 previously healthy pregnant women, who were hospitalized for pre-eclampsia]</p>	<p>Isradipine or metoprolol did not affect insulin sensitivity, degree of proteinuria, blood pressure, or the umbilical artery resistance index. Serum uric acid increased in both groups ($P < 0.05$). High-density lipoprotein2 cholesterol increased 15.6% in the isradipine group ($P < 0.05$), but no significant changes appeared in other lipids and lipoproteins in either group.</p>

³⁵ Tanaka K et al. Beta-Blockers and Fetal Growth Restriction in Pregnant Women with Cardiovascular Disease. *Circ J.*2016; 80(10):2221-6.

³⁶ Ryu RJ et al Pharmacokinetics of metoprolol during pregnancy and lactation. *J Clin Pharmacol.* 2016;56(5):581-9.

³⁷ Laivuori HM et al. Short-term metabolic effects of isradipine and metoprolol in pre-eclampsia. *J Hypertens.* 1999;17(8):1189-94.

Study	Treatment and Study Population (N)	Safety reported/comments
Double Dummy and Parallel Group Study]		It was concluded that short-term antihypertensive treatment with isradipine or metoprolol in preeclampsia had no detrimental effect on serum lipid and lipoprotein levels or insulin sensitivity.
Jannet D et al (1994) ³⁸ Nicardipine Versus Metoprolol in the Treatment of Hypertension During Pregnancy [Randomized Comparative Trial]	<ul style="list-style-type: none"> •Metoprolol slow-release 200 mg, po (OD in morning) for 9.1 weeks [n=50] •Nicardipine 20 mg oral (TID) for 8 weeks[n=50] [N=100 pregnant patients with mild or moderate hypertension]	<ul style="list-style-type: none"> • No perinatal deaths occurred in the nicardipine group, but one patient had a medical abortion at 33 weeks after the diagnosis of fetal trisomy 9. • One neonatal death occurred in the metoprolol group (difference not significant). The infant was transferred to the neonatal care unit and died 5 days later with uninterrupted seizures. <p>The incidence of associated threatened premature labor was reported in 6 cases in nicardipine and 4 cases in metoprolol group.</p> <p>Other reported safety information Proteinuria appeared during treatment in three patients in the nicardipine group and in eight in the metoprolol group (not significant).</p> <p>Three patients in the metoprolol group reported fatigue and one felt breathless.</p> <p>Two patients receiving nicardipine and three patients treated with metoprolol developed the syndrome of hemolysis, elevated liver enzymes, and low platelet count.</p>
Oumachigui A et al (1992) ³⁹ A comparative evaluation of metoprolol and methyldopa in the management of pregnancy induced hypertension (PIH). [Randomized clinical study]	<ul style="list-style-type: none"> •Metoprolol 25 mg bid (n=15) •Methyldopa 250 mg tid (n=15) <p>Maximum dose: Metoprolol: up to 300 mg/24 hours Methyldopa: up to 2000 mg/24 hours</p> <p>[N=30 patients matched for age, parity, socioeconomic status and severity of pregnancy induced hypertension (PIH)]</p>	<ul style="list-style-type: none"> •There were 2 still births due to severe PIH, one in each group (metoprolol and methyldopa). •There were two neonatal deaths due to respiratory distress syndrome in preterm babies in methyldopa group. •The mean birth weight of the babies was higher in cases treated with metoprolol. •There were no adverse effects on labor or on the fetal cardiac status.
Resch BA et al (1990) ⁴⁰	Metoprolol 3 x 100 mg (3 x 1 tab) oral doses	•Notable fetal bradycardia was not observed; in the course of

³⁸ Jannet D et al Nicardipine versus metoprolol in the treatment of hypertension during pregnancy: a randomized comparative trial. *Obstet Gynecol.* 1994;84(3):354-9.

³⁹ Oumachigui A et al A comparative evaluation of metoprolol and methyldopa in the management of pregnancy induced hypertension. *Indian Heart J.* 1992;44(1):39-41.

⁴⁰ Resch BA et al Betaloc therapy in pregnancy-associated mild and moderately severe hypertension. *Ther Hung.* 1990;38(1):30-6.

Study	Treatment and Study Population (N)	Safety reported/comments
Betoloc (metoprolol) therapy in pregnancy associated mild and moderately severe hypertension. [Prospective Study]	[30 pregnant women with pregnancy associated mild and moderately severe hypertension]	metoprolol administration the decrease of fetal heart rate did not surpass the normal limit values. •During the therapy no side-effect attributable to the drug was observed.
Björkstén B et al (1988) ⁴¹ Intrauterine exposure to the beta-adrenergic receptor- blocking agent metoprolol and allergy. [Placebo Controlled]	<ul style="list-style-type: none"> •Metoprolol 50 mg BID (n=26) •Placebo (n=26) Hydralazine 25 mg BID Maximum dose: Metoprolol 100 mg BID Hydralazine 50 mg BID (only for two mothers) [Children born by 52 mothers who had been treated with the metoprolol or by placebo during the pregnancy]	<ul style="list-style-type: none"> • Twenty nine (29) children born by mothers who had been treated with metoprolol and 23 children of placebo-treated mothers during the pregnancy. • It was reported from the previous observations that many children with elevated serum IgE levels at birth develop allergic disease. • In this study, 13 (45%) of the metoprolol and 3 (15%) of the placebo group had elevated cord blood IgE levels and/or obvious or probable allergy developed (p=0.03). It was concluded from experimental observations mentioned in this publication that beta-blocking agents may enhance IgE antibody formation.
Lindeberg S et al (1987) ⁴² Disposition of the adrenergic blocker metoprolol and its metabolite OH metoprolol in maternal plasma, amniotic fluid and capillary blood of the neonate. [Pharmacokinetic study]	Metoprolol (50 – 100 mg) bid and Hydralazine (25 – 50 mg) bid Duration: 2 – 20 weeks [N= 7 women with hypertension in pregnancy]	<ul style="list-style-type: none"> • In this study, none of the newborns suffered any complications that could be definitely ascribed to the therapy. There are, however, reports of neonatal distress after maternal beta blocker administration when the fetus is compromised, and fetal heart rate has also been shown to be affected. • All infants had measurable concentrations of metoprolol in cord blood. • It was recommended that if possible the drug should be withdrawn before delivery, especially when the fetal compromise is suspected.
Olofsson P et al (1986) ⁴³ Effects of beta 1 adrenoceptor blockade in the treatment of hypertension during pregnancy in diabetic women. [Clinical study]	<ul style="list-style-type: none"> •Metoprolol (n=1) •Atenolol >>>> Metoprolol (n=1) •Atenolol (n=16) [N=18 hypertensive pregnant diabetic women]	<ul style="list-style-type: none"> • The study included 18 hypertensive pregnant diabetic women, out of which 2 were exposed to metoprolol. • There was 1 stillbirth in atenolol group but no neonatal deaths. All survivors (17) were healthy at follow-up till 1 to 4 years. • A depressive effect on fetal heart was found during therapy. Except for respiratory problems, the incidence of neonatal complications was low.

⁴¹ Björkstén B et al Intrauterine exposure to the beta-adrenergic receptor blocking agent metoprolol and allergy. Int Arch Allergy Appl Immunol.1988; 87(1):5962.

⁴² Lindeberg S et al Disposition of the adrenergic blocker metoprolol and its metabolite OH-metoprolol in maternal plasma, amniotic fluid and capillary blood of the neonate. Eur J Clin Pharmacol.1987;33(4):363-8.

⁴³ Olofsson P et al Effects of beta 1-adrenoceptor blockade in the treatment of hypertension during pregnancy in diabetic women. Acta Med Scand. 1986;220(4):321-8.

Study	Treatment and Study Population (N)	Safety reported/comments
		<ul style="list-style-type: none"> • Beta 1 blockade found to be effective and safe in this study.
Högstedt S et al (1985) ⁴⁴ Pregnancy-induced increase in metoprolol metabolism. [Clinical study]	<ul style="list-style-type: none"> •Metoprolol, 10 mg iv; 3 days later metoprolol, 100 mg by mouth. [N= 5 women 20 to 36 years old, 3rd trimester of pregnancy]	<ul style="list-style-type: none"> •No subject reported any adverse effects. •All infants were healthy and had normal birth-weights. Other information <ul style="list-style-type: none"> •Oral bioavailability of metoprolol increased by a factor of 1.3 to 3.7 after pregnancy.
Högstedt S et al (1985) ⁴⁵ Metoprolol hydralazine treatment in hypertension during pregnancy. [Open, Prospective Controlled Trial]	<ul style="list-style-type: none"> •Treatment group: Metoprolol (50 – 200 mg/day) + Hydralazine (25 – 150 mg/day) po, (n=82) •Control group (n=79) [N=161 women with non-pharmacological management of mild and moderate hypertension in pregnancy]	<ul style="list-style-type: none"> • Nine women in the treatment group and 5 in the control group developed albuminuria. • Three infants in the treatment group died (one due to placental abruption and 2 due to unknown causes) perinatally, and one in the control group (due to placental abruption). • Bradycardia was seen in 5 infants (1 in treatment group and 4 in control group). • Respiratory distress syndrome was seen in 4 infants (1 in treatment group and 3 in control group) • The outcome for the newborns was similar in both groups concerning birth weight, head circumference and APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score and in the frequencies of respiratory distress, bradycardia and hypoglycemia. • All patients tolerated the treatment well and no patient was excluded because of adverse drug effect.
Wichman K et al (1984) ⁴⁶ A placebo controlled trial of metoprolol in the treatment of hypertension in pregnancy. [Placebo controlled study]	<ul style="list-style-type: none"> •Metoprolol, 50 – 100 mg twice daily, oral (n=26) •Hydralazine, 25 – 50 mg twice daily (n=26) and 6.25 mg, iv, during labor [N=52 women with hypertension in pregnancy]	<ul style="list-style-type: none"> •There were no difference in the birth weight, umbilical arterial and venous pH and venous hypoxanthine concentration at delivery. •There was two codes had to be broken in metoprolol group (one because of bad BP control and other due to allergy). •No adverse effects on the newborn in the dose of metoprolol used were observed.
Finnström O et al (1984) ⁴⁷ Neonatal effects of beta-blocking drugs in pregnancy	<ul style="list-style-type: none"> •Metoprolol 200 mg daily (or placebo) •Hydralazine 100 mg daily [N=45 pregnant women in whom hypertension appears before the 36 th completed week]	<ul style="list-style-type: none"> •One infant died due to a complicated heart defect. The study was still in progress, the codes have not been broken. No further information is available in this publication.
Ross MG et al (1983) ⁴⁸	<ul style="list-style-type: none"> •Metoprolol (n = 7) po, 100 mg followed by 50 mg every 12 	<ul style="list-style-type: none"> • There were a total of 19 infants; nine were diagnosed having

⁴⁴ Högstedt S et al A prospective controlled trial of metoprolol-hydralazine treatment in hypertension during pregnancy. Acta Obstet Gynecol Scand. 1985;64(6):505-10.

⁴⁵ Högstedt S et al Pregnancy-induced increase in metoprolol metabolism. Clin Pharmacol Ther. 1985;37(6):688-92.

⁴⁶ Wichman K et al A placebo controlled trial of metoprolol in the treatment of hypertension in pregnancy. Scand J Clin Lab Invest Suppl. 1984;169:90-5.

⁴⁷ Finnström O et al Neonatal effects of beta-blocking drugs in pregnancy. Acta Obstet Gynecol Scand Suppl. 1984;118:91-3.

⁴⁸ Ross MG et al . Intravenous terbutaline and simultaneous beta 1-blockade for advanced premature labor. Am J Obstet Gynecol. 1983;147(8):897-902.

Study	Treatment and Study Population (N)	Safety reported/comments
<p>Intravenous terbutaline and simultaneous beta 1 blockade For advanced premature labor. [Randomized, Double Blind placebo controlled study]</p>	<p>hours</p> <ul style="list-style-type: none"> •Placebo (n = 10) •In both groups: <ul style="list-style-type: none"> -Terbutaline iv (0.25 mg as slow IV bolus) and continuous infusion of 10 mcg/min with infusion doses increased by 10 mcg/min every 15 minutes before the end of iv therapy oral terbutaline (5 mg every 4 hours) -Dexamethasone IM injection (4 mg, tid) for six doses -5% glucose in Ringers lactate at 100 mL/hour <p>[N=17 patients in advanced premature labor]</p>	<p>respiratory distress syndrome (RDS). RDS developed infants have birth weight of 1,143 grams and non-RDS infants have 1,900 grams.</p> <ul style="list-style-type: none"> • All infants discharged alive from nursery. <p>Other safety information</p> <ul style="list-style-type: none"> • Both metoprolol and placebo groups experienced blood pressure and heart rate changes in response to increasing doses of terbutaline. • There were no significant differences in the cardiovascular or metabolic responses to terbutaline between the metoprolol and placebo patients. • Laboratory studies revealed significant hyperglycemia, hypokalemia, hypocalcemia, and acidosis during the intravenous terbutaline infusion, all of which normalized during oral terbutaline therapy. • There were no cases of maternal pulmonary edema.
<p>Steyer M et al (1981)⁴⁹ Combined use of beta-sympathomimetic drugs and beta-blockers during labor. [Active, combination clinical study]</p>	<p>Fenoterol (4 - 5 micrograms/min) infused iv was given to complete inhibition of labor. To reduce cardiac side effects, a primarily cardiac beta- blocker given:</p> <ul style="list-style-type: none"> • Metoprolol iv (dose was increased 0.03-0.1-0.4-1.0-2.0 mg/min and each dose was given for 5 min) The total dose was approximately 20 mg in 30 min (n=5) • Atenolol (single i.v. injection of 5 mg) (n=8) <p>[N=12 healthy women with 1st stage of labor, 1 patient in labor (30-week gestation)]</p>	<ul style="list-style-type: none"> • Fenoterol was administered to 13 patients during the first stage of labor. This led to complete inhibition of labor. To reduce cardiac side effects, a primarily cardiac β-blocker (5 mg Atenolol or 20 mg Metoprolol) was also given. • The maternal heart rate, which increased under the influence of the fenoterol, fell ($p < 0.01$) but did not return to normal. All patients complained of palpitations, nervousness, and tremor. Following the β-blockade patients lost these side effects and noted a subjective improvement. •The fetal heart rate remained largely unchanged, both during the fenoterol infusion as well as during the additional administration of the beta-blocker. <p>None of the newborn infants showed effects attributable to β-blockade.</p>
<p>Sandström B (1978)⁵⁰ Antihypertensive treatment with the adrenergic beta-receptor blocker metoprolol during pregnancy [Comparative clinical study]</p>	<ul style="list-style-type: none"> • Group A: Metoprolol 50 mg bid >>maxm up to 400 mg/day (n=101) plus hydralazine up to 50 mg qid (n=44 out of 101) for 4.1 weeks • Group B: Hydralazine 10 mg tid (n=97) for 5.5 weeks <p>Both groups received following concomitant medicine</p> <ul style="list-style-type: none"> - Chlorothiazide 250 mg bid, 1 week 	<ul style="list-style-type: none"> • In group A, one (1) fetus died in utero (due to major placental ablation in 30th week and mother had virus infection) and there was one postnatal death [due to trisomy 18 (a genetic disease of chromosomal abnormality) and cardiac malformation]. • In group B, five (5) in-utero deaths (due to pronounced intrauterine growth retardation) were reported. • Perinatal mortality was lower in the metoprolol group (2.0%) than

⁴⁹ Steyer M et al Combined use of beta-sympathomimetic drugs and beta-blockers during labour. Arch Gynecol. 1981;230(3):231-7.

⁵⁰ Sandström B Antihypertensive treatment with the adrenergic beta-receptor. Gynecol Invest. 1978;9(4):195-204.

Study	Treatment and Study Population (N)	Safety reported/comments
	<ul style="list-style-type: none"> - Bendroflumethiazide 2.5 mg od, 1 week [N=198 hypertensive gravidae] 	<p>in the hydralazine group (8.0%). The rate of fetal growth retardations also was lower when using metoprolol (11.7 and 16.3% respectively).</p> <ul style="list-style-type: none"> • Seven newborns in group A (metoprolol + hydralazine) and 9 in group B (hydralazine) showed signs of asphyxia. • Metoprolol crosses the placenta and enters the fetal circulation. Concentration of metoprolol in jugular venous blood was about the same as in the maternal venous blood. • No abnormal effect of the beta-blocker was noticed on the fetus.
<p>A 33-year-old multiparous woman at 35 weeks of gestation with palpitations, shortness of breath and fatigue and diagnosed with a supraventricular tachycardia (SVT)</p>	<ul style="list-style-type: none"> • Sotalol 160 mg twice daily which was changed to metoprolol 50 mg orally twice daily, increased to 3 times per day • Intravenous adenosine, digoxin, increasing doses of sotalol, electrolyte replacement, intravenous fluids • Intravenous magnesium sulphate 20 mmols • Flecainide 50 mg twice daily and a single dose of digoxin 500 µg were added 	<p>After increasing metoprolol dose to 50 mg three times per day, her heart rate intermittently decreased to 110/120 beats/min. On day 5 of her admission, at 35 weeks and 5 days of gestation, the tachycardia increased to 180/190 beats/min, and she experienced increased work of breathing, tachypnea and diaphoresis with a systolic blood pressure of 80/90 mmHg. On auscultation her chest was clear and it was considered that she was not in acute pulmonary edema. No adverse effect on pregnancy, labor, lactation and fertility is reported in this publication.</p>
<p>Stec S et al (2013)⁵¹ 26-year-old Caucasian woman during her first pregnancy (23rd week) with arrhythmogenic right ventricular dysplasia/ Cardiomyopathy (ARVD/C) diagnosed 3 years earlier.</p>	<ul style="list-style-type: none"> •Metoprolol •Sotalol •Benzodiazepines •Diazepam (3 × 5 mg) •Amiodarone iv •Midanium iv (1 mg) •Isoproterenol iv 	<ul style="list-style-type: none"> •During pregnancy, symptoms of PVCs (premature ventricular complexes) and recurrent VT (ventricular tachycardia) aggravated. •She was unsuccessfully treated with a high dose of metoprolol followed by sotalol. •The patient was diagnosed with post-traumatic stress disorder and treated with benzodiazepines. • Fetal examinations were normal prior and after radiofrequency ablation (RFCA). In the 36th week of pregnancy, a healthy girl was delivered by caesarian section. • During 12 months of follow up, the patient had no implanted cardioverter-defibrillator (ICD) interventions and monitoring revealed no premature ventricular complexes (PVC). • The patient was treated with a low dose of metoprolol for inadequate sinus tachycardia and antidepressant.
<p>Lalitha R and Opio CK (2013)⁵² 23-year-old gravid Ugandan female at 26 weeks pregnancy diagnosed with pre-eclampsia</p>	<ul style="list-style-type: none"> • Magnesium sulphate • Hydralazine iv • Metoprolol • Prazocin po, 1mg twice daily • Nifedipine po, 30mg twice daily 	<ul style="list-style-type: none"> • A diagnosis of pre-eclampsia was made. • Due to her labile blood pressures despite intravenous hydralazine and metoprolol, the pregnancy was terminated. • Histopathology revealed a benign pheochromocytoma. The mother had good post-operative outcome; however the premature baby died

⁵¹ Stec S et al "Rescue" ablation of electrical storm in arrhythmogenic right ventricular cardiomyopathy in pregnancy. BMC Cardiovasc Disord.2013;13:58.

⁵² Lalitha R and Opio CK A missed diagnosis or a masquerading disease: back to the basics. Pan African Medical Journal.2013;15:29.

Study	Treatment and Study Population (N)	Safety reported/comments
	<ul style="list-style-type: none"> • Propranolol po, 40mg twice daily 	<p>2 days later in the special care unit.</p> <ul style="list-style-type: none"> • All antihypertensive were withdrawn and BP remained normal throughout her recovery and one year following her discharge from hospital. <p>In this publication the pregnancy was terminated due to the labile blood pressure of pregnant women and there was no adverse effect of treatment drugs on the death or termination of pregnancy.</p>
Hasdemir C et al (2009) ⁵³ A 34-year-old pregnant woman with complaints of palpitations at 32 weeks gestation	<ul style="list-style-type: none"> • Metoprolol 5 mg iv • Diltiazem 25 mg • Adenosine 10 mg 	<ul style="list-style-type: none"> • The mother and the fetus tolerated the medications well. • Non-stress test for the assessment of the fetal well-being was normal. • Transthoracic echocardiography and thyroid function tests were normal. <p>The focus of this publication was effect of adenosine on pregnancy.</p>
Singh SI et al (2008) ⁵⁴ A 33 year-old nulliparous woman (26 weeks of gestation) with Marfan's syndrome and aortic root dilatation	<ul style="list-style-type: none"> • Metoprolol 100 mg bid plus metoclopramide 10 mg iv • Ranitidine 50 mg iv • Sodium citrate 30 mL po • Metoclopramide 10 mg iv 	<ul style="list-style-type: none"> • The patient remained stable and was admitted to the intensive care unit (ICU) for monitoring one day prior to delivery. On the morning of delivery, the patient received her usual dose of metoprolol, plus metoclopramide 10 mg iv, ranitidine 50 mg iv, and sodium citrate 30 mL po for aspiration prophylaxis, 30 min prior to surgery. • The patient remained hemodynamically stable, achieving a maximum systolic BP of 125 mmHg and a maximum HR of 65 beats per min. • The bispectral index (BIS) monitor values (40/57) confirmed that an adequate depth of anesthesia was maintained after surgery. • Both mother and baby recovered uneventfully.
Hutter DA et al (2006) ⁵⁵ A 41-year-old pregnant woman (32 weeks of gestation) with dyspnea for the past 2 months	<ul style="list-style-type: none"> • Metoprolol • Eplerenone • Furosemide 10 mg iv 	<ul style="list-style-type: none"> • At the completion of her pregnancy, she underwent Cesarean delivery without complication. She delivered a healthy newborn with an APGAR (Appearance, Pulse, Grimace, Activity, Respiration) score of 6/8.
Frigo P et al (1995) ⁵⁶ A 29 year old woman presented	<ul style="list-style-type: none"> • Metoprolol (100 mg daily) • Hexoprenaline iv (9µg/hour; 100µg/1000ml; reduced to 6 	<ul style="list-style-type: none"> • No adverse effects on the fetal heart rate nor on the umbilical cord blood flow reported.

⁵³ Hasdemir C et al Termination of idiopathic sustained monomorphic ventricular tachycardia by intravenous adenosine in a pregnant woman. *Europace*. 2009;11(11):1560-1.

⁵⁴ Singh SI et al General anesthesia using remifentanyl for Cesarean delivery in a parturient with Marfan's syndrome. *Can J Anaesth*. 2008;55(8):526-31.

⁵⁵ Hutter DA et al Application of continuous positive airway pressure in hypoxemic acute respiratory failure associated with diastolic dysfunction in pregnancy. *Congest Heart Fail*. 2006;12(3):174-5.

⁵⁶ Frigo P et al Management of supraventricular tachycardia during hexoprenaline therapy for preterm labour: benefit of cardioselective beta blockade? *Gynecol Obstet Invest*. 1995;39(3):212-4.

Study	Treatment and Study Population (N)	Safety reported/comments
with preterm labor at 32 weeks of gestation	µg/hour • Digoxin • Verapamil (10 mg/1000 ml) • Betamethasone (8 mg followed by 4 mg; 24 hour later) • Magnesium iv • Etilefrin 20 mg • Heparin	• Cardiological examinations were all normal (ECG, ECHO, exercise test, scan). It was concluded that the use of β-blocker was positive: the tachycardia subsided within reasonable time, and there were no adverse effects on both mother and fetus.

Applicant's submission, Response to IR, June 5, 2017

Table 2: Publications on Metoprolol and Lactation

Study	Treatment and Study Population (N)	Safety reported/comments
Ryu RJ et al (2016) ⁸ Pharmacokinetics of metoprolol during pregnancy and lactation. [Pharmacokinetic study]	<ul style="list-style-type: none"> Metoprolol (25 – 750 mg/day) [N=22 pregnant women] 	<ul style="list-style-type: none"> Metoprolol apparent oral clearance was significantly higher during both mid- and late pregnancy (P < 0.05). Metoprolol was present in umbilical cord blood collected at delivery. Relative infant exposure to metoprolol through breast milk was <1.0% of maternal weight-adjusted dose (n = 3).
Davanzo R et al (2014) ⁵⁷ Breastfeeding and migraine drugs [Systematic review]	<ul style="list-style-type: none"> Most common anti-migraine drugs (AMDs) Metoprolol (0.23 mg/kg/day) TID 	<ul style="list-style-type: none"> AMDs safe during breastfeeding are as follows: low dose acetylsalicylic acid (ASA), ibuprofen, sumatriptan, metoprolol, propranolol, verapamil, amitriptyline, escitalopram, paroxetine, sertraline, acetaminophen, caffeine, and metoclopramide. Majority of the revised AMDs were assessed to be compatible with breastfeeding. Metoprolol levels in milk are very low and it poses little risk to a breastfeeding infant.
Shannon ME et al (2000) ⁵⁸ Beta blockers and lactation: an update. [Review]	Metoprolol	<ul style="list-style-type: none"> All beta blockers have the potential to cross into breast milk. All agents used by lactating women, is the risk of harm to the infant. On average, the concentration of metoprolol in breast milk was 3.5 times higher than in plasma. The amount of drug consumed by the neonate was negligible (less than 9 mcg/kg per feeding). Despite the extensive degree of distribution seen with metoprolol, the American Academy of Pediatrics considers metoprolol to be compatible with breast feeding.
Kulas J et al (1984) ⁵⁹ Atenolol and metoprolol. A comparison of their excretion into human breast milk. [Clinical pharmacokinetic study]	<ul style="list-style-type: none"> Metoprolol (n=3) (dose range – 50 mg twice daily to 100 mg daily) for duration of 4 days to 60 days Atenolol (n=4) (dose of 100 mg daily) for duration of 4 days to 60 days <p>7 lactating women with hypertension</p>	<ul style="list-style-type: none"> From results it was reported that exposure of the infant to metoprolol can be minimized if nursing is not undertaken earlier than 3-4 hours after dose intake. No or only negligible plasma concentrations of metoprolol were found in the infant's plasma.

⁵⁷ Davanzo R et al Breastfeeding and migraine drugs. Eur J Clin Pharmacol. 2014;70(11):1313-24.

⁵⁸ Shannon ME et al Beta blockers and lactation: an update. J Hum Lact. 2000;16(3):240-5.

⁵⁹ Kulas J et al (1984). Atenolol and metoprolol. A comparison of their excretion into human breast milk. Acta Obstet Gynecol Scand Suppl. 118:65-9.

Study	Treatment and Study Population (N)	Safety reported/comments
Liedholm H et al (1981) ⁶⁰ Accumulation of atenolol and metoprolol in human breast milk. [Clinical pharmacokinetic study]	<ul style="list-style-type: none"> • Metoprolol 50 mg bid to 100 mg once daily (n=5) for 4 days • Atenolol 50 mg once daily (n=2) <p>- - 7 lactating women treated with atenolol due to hypertension developing during pregnancy, and</p> <p>- - 3 healthy women who agreed to take metoprolol at cessation of lactation</p>	<ul style="list-style-type: none"> • Based on the maximum recorded concentrations in milk, i. e. 6.35 µmol/l for atenolol and 2.58 µmol/l for metoprolol, and assuming ingestion of 75 ml milk per meal, the dose at the time of the maximum maternal drug concentration would not exceed 0.13 mg (atenolol) and 0.05 mg (metoprolol) • It would seem likely that, unless renal (atenolol) or hepatic (metoprolol) function in the infant were pronouncedly impaired, breast feeding need not be interrupted due to maternal medication with ordinary doses of either of these drugs. • However, the infants should be observed for signs of beta blockade.

Applicant's submission, Response to IR, June 5, 2017

⁶⁰ Liedholm H et al Accumulation of atenolol and metoprolol in human breast milk. Eur J Clin Pharmacol.1981;20(3):229-31.

Table 3: Females and Males of Reproductive Potential

Study	Treatment and Study Population (N)	Safety reported/comments
Aldemir M et al (2016) ⁶¹ Randomized, double blind, prospective clinical study [N= 60 consecutive males undergoing coronary artery bypass graft (CABG)]	M group – Metoprolol succinate 50 mg orally for 2 weeks before surgery plus 12 weeks after surgery (n=30) N group – Nebivolol 5 mg orally 2 weeks before surgery plus 12 weeks after surgery (n=30)	<ul style="list-style-type: none"> • Erectile function in males undergoing coronary artery bypass graft (CABG) surgery decreases when metoprolol is used • After metoprolol administration for the same period as that of nebivolol administration, the total number of patients having erectile dysfunction (ED) increased from 22 to 27, and also, their distribution to subgroups changed • Each of the two patients with severe ED remained the same without any change. Of the seven patients with moderate ED • Three experienced no change, and four experienced deterioration to severe ED. Of the eleven patients with mild- moderate ED • Two remained in the same class, and nine experienced deterioration to moderate ED. One of the two patients with mild ED remained in the same class, and the other patient experienced deterioration to mild-moderate ED. Of the eight patients with normal erectile function, • Three remained unaltered, and five experienced deterioration to mild ED.
Yang L et al (2013) ⁶² Prospective, Randomized, Parallel, Active-controlled, Open-label study [N= 218 male participants with untreated hypertension]	<ul style="list-style-type: none"> • Felodipine (5 mg/day) plus metoprolol (47.5 mg/day) (F+M group; n = 105). • Felodipine (5 mg/day) plus irbesartan (150 mg/day) (F+I group; n = 113) Duration = 48 weeks 	<ul style="list-style-type: none"> • There was no significant difference in the prevalence of erectile dysfunction before and after treatment in either group (p > 0.05). • The total IIEF score in the F+M group did not differ significantly at week 48 of follow-up compared to baseline (p = 0.758). • Felodipine-irbesartan (F+I) may be more beneficial to the sexual desire of hypertensive male patients than felodipine- metoprolol (F+M). • Excluding the sexual desire score, other aspects of sexual function did not significantly differ between the two groups after drug administration. • This study suggests that selective β-blockers do not have a negative impact on the sexual function of patients with hypertension.
Cocco G (2009) ⁶³ Two Phase, Single Blind,	Metoprolol 100 mg OD for 60 days	<ul style="list-style-type: none"> • ED occurred in 12 men (32%) of group 1; in 3 men (13%) of group 2, and in 3 men (8%) of group 3.

⁶¹ Aldemir M et al Nebivolol compared with metoprolol for erectile function in males undergoing coronary artery bypass graft. *Anatol J Cardiol.* 2016;16(2):131-6.

⁶² Yang L et al The Effect of Combined Antihypertensive Treatment (Felodipine with Either Irbesartan or Metoprolol) on Erectile Function: A Randomized Controlled Trial. *Cardiology.* 2013;125:235–241.

⁶³ Cocco G (2009). Erectile dysfunction after therapy with metoprolol: the Hawthorne effect. *Cardiology.* 112(3):174-7.

Study	Treatment and Study Population (N)	Safety reported/comments
Parallel Design, Randomized [N= 114 men (age 57±4.7 years) without erectile dysfunction (ED) but with newly diagnosed arterial hypertension]	In group 1 - (38 men), the patients were informed that the drug was metoprolol and patients were orally informed that metoprolol 'might induce ED, In group 2 - (38 men), patients were informed that the drug was metoprolol, but the possible occurrence of ED had been canceled; In group 3 - (38 men), metoprolol was given anonymously, under a code number and mentioned all possible side effects with the exception of ED.	<ul style="list-style-type: none"> • The intergroup statistical difference is statistically significant: p<0.01 between group 1 and group 2 and group 3, and p<0.01 between group 2 and group 3. • Fatigue and dizziness occurred in 26% of the men treated with metoprolol, with the same frequency and severity in all groups. • Untoward reactions were mild and did not require discontinuation of treatment.
Brixius K et al (2007) ⁶⁴ Double-blind, 1 : 1 Randomized, Parallel-Group, Cross-Over pilot study [N= 50 Male patients (age range 40–55 years) with newly diagnosed or existing stage 1 essential hypertension]	<ul style="list-style-type: none"> • Treatment Group A: Nebivolol, 5 mg once daily for first 12 weeks, then a once-daily placebo for 2 weeks before being crossed-over to once- daily metoprolol succinate 95 mg for a further 12 weeks. • Treatment Group B: Metoprolol succinate 95 mg once daily for 12 weeks, followed by a 2- week once-daily placebo period and then once- daily nebivolol 5 mg treatment for the final 12 weeks 	<ul style="list-style-type: none"> • here was a clear decrease of 1.17 points [International index of erectile function (IIEF)] in patients who received metoprolol during Treatment period 1 and a similarly clear decrease of 0.68 points in patients who received metoprolol after cross-over. • During the wash-out period, erectile function only partially recovered in the metoprolol group. • The mean erectile function subscore decreased significantly under metoprolol by -0.92 points. • The results of safety analysis confirmed a good safety profile for both study drugs. • Metoprolol significantly decreased the majority of sexual efficacy variables assessed when used to treat middle-aged hypertensive men.
Doumas M et al (2006) ⁶⁵ Open, Prospective Study [N= 44 young and middle-aged men (31–65 years) with essential hypertension]	<p>Medical history of subjects -</p> <ul style="list-style-type: none"> • Atenolol (50 – 100 mg per day), n=40 • Metoprolol (100 mg per day) n=2 • Bisoprolol (10 mg per day) n=2 <p>Duration: More than 6 months</p> <p>Study treatment -</p> <ul style="list-style-type: none"> • Nebivolol (5 – 10 mg per day) for 3 months 	<ul style="list-style-type: none"> • Erectile dysfunction (ED) of any degree was found in 29 out of 44 patients (65.9%) taking β-blockers. - Severe ED [8 of 44 patients (18.2%)], - Moderate ED [13 of 44 patients (29.5%)], - Mild ED [8 of 44 patients (18.2%)]. • β-blockers seem to exert a negative effect on male erectile function.

⁶⁴ Brixius K et al Nitric oxide, erectile dysfunction and beta-blocker treatment (MR NOED study): benefit of nebivolol versus metoprolol in hypertensive men.2007

⁶⁵ Doumas M et al Beneficial effects of switching from beta-blockers to nebivolol on the erectile function of hypertensive patients. Asian J Androl. 2006;8(2):177-82.

Study	Treatment and Study Population (N)	Safety reported/comments
Piha J and Kaaja R (2003) ⁶⁶ Open, Cross Over [N=12 non-smoking hypertensive men with erectile dysfunction, otherwise healthy, participated in the study]	<ul style="list-style-type: none"> • Metoprolol (100 mg o.d.) for 3 weeks (thereafter the dose of metoprolol was increased to 100 mg × 2 if needed) • Oxonidine 0.2+0.2 mg daily (after 3 weeks the dose was increased to 0.4+0.2 mg if BP was >160/100mmHg) 	<ul style="list-style-type: none"> • 9/11 patients reported impaired erectile function after metoprolol treatment and this difference was statistically highly significant when compared with moxonidine treatment (P<0.0002, x2 test). • Resting and stimulated deep penile diameters were higher after moxonidine therapy compared to the diameters after metoprolol therapy (P<0.004 and P<0.001, respectively). • Resting and stimulated deep penile artery velocities were also higher after moxonidine therapy compared to metoprolol (0.008 and P<0.038, respectively). • Beta-blockers have been reported to be responsible for erectile dysfunction in many, but not all studies.
Franzen D et al (2001) ⁶⁷ Prospective, Randomized, Double Blind [N=192 consecutive male patients undergoing elective coronary angioplasty (PTCA)]	<ul style="list-style-type: none"> • Metoprolol 95mg sustained release OD • Placebo <p>(Beginning at least 1 day before PTCA)</p>	<ul style="list-style-type: none"> • Erectile Dysfunction (ED) scores were similar in the metoprolol and in the placebo group at study entry and did not change significantly while taking the study medication. • 60% of the study participants had no problems achieving a sufficient erection of their penis and reaching orgasm. • Most patients felt unaffected in their sex life by either metoprolol or placebo treatment • Overall, in this selected cohort success and frequency of the sexual intercourse seemed unaffected by metoprolol treatment.
Rosen RC et al (1988) ⁶⁸ Placebo Controlled, Double Blind, Latin square design [N=30 healthy male volunteers]	<ul style="list-style-type: none"> • Metoprolol (100 mg bid) • Atenolol (100 mg od) • Pindolol (10 mg bid) • Propranolol (80 mg bid) <p>Duration = 7 days</p>	<ul style="list-style-type: none"> • A significant drug effect was found on average time of maximum erection (p = 0.01) • Significant drug effects on both total (p=0.001) and free testosterone (p=0.0001) were found during treatment with all four beta-blockers • Although it appeared that the nonselective drugs (pindolol, propranolol) were associated with the greatest reduction in testosterone. • It was suggested that some men may be especially vulnerable to the sexually disruptive effects of beta-blockers.

⁶⁶ Piha J and Kaaja R Effects of moxonidine and metoprolol in penile circulation in hypertensive men with erectile dysfunction: results of a pilot study. Int J Impot Res. 2003;15(4):287-9.

⁶⁷ Franzen D et al Effects of beta-blockers on sexual performance in men with coronary heart disease. A prospective, randomized and double blinded study. Int J Impot Res. 2001;13(6):348-51.

⁶⁸ Rosen RC et al Beta-blocker effects on sexual function in normal males. Arch Sex Behav. 1988;17(3):241-55.

Study	Treatment and Study Population (N)	Safety reported/comments
Hong CY and Turner P (1982) ⁶⁹ Fresh human semen samples were collected from either healthy volunteers or patients. Six semen samples were used for each drug.	<ul style="list-style-type: none"> • Metoprolol • Propranolol • Oxprenolol • Acebutolol • Sotalol 	<ul style="list-style-type: none"> • β-adrenoceptor blockers (propranolol, oxprenolol, metoprolol, acebutolol and sotalol) inhibit sperm motility by stabilizing the cellular membrane. • Sperm motility might be expected from more lipid soluble drugs, which in turn could be distributed to a greater extent in the tissues, including male reproductive organs.

Applicant's submission, Response to IR, June 5, 2017

⁶⁹ Hong CY and Turner P Influence of lipid solubility on the sperm immobilizing effect of beta-adrenoceptor blocking drugs. Br J Clin Pharmacol. 1982;14(2):269-72.

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/s/

CHRISTOS MASTROYANNIS
12/22/2017

LYNNE P YAO
12/25/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 30, 2017

To: Maryam Changi, PharmD
Division of Cardiovascular and Renal Products (DCRP)

Michael Monteleone, Associate Director for Labeling, (DCRP)

From: Zarna Patel, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for metoprolol succinate ER capsules

NDA/BLA: 210428

In response to DCRP's consult request dated April 5, 2017, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for metoprolol succinate capsules, extended-release , for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DCRP on November 20, 2017, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 10, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
11/30/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 13, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products
Application Type and Number:	NDA 210428
Product Name and Strength:	Metoprolol succinate extended-release capsules, 25 mg, 50 mg, 100 mg, and 200 mg
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sun Pharmaceutical Industries, Inc.
Submission Date:	July 13, 2017
OSE RCM #:	2017-693
DMEPA Safety Evaluator:	Ashleigh Lowery, PharmD, BCCCP
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the proposed Metoprolol succinate container labels and prescribing information submitted on July 13, 2017 for risk of medication error.

This 505(b)(2) application seeks approval for a metoprolol succinate extended-release capsule. The listed drug is Toprol-XL (NDA 019962) tablets.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the materials finds the container label and PI may be improved to promote safe use of the proposed product.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed Metoprolol succinate container labels and PI that can be improved to increase clarity and to promote the safe use of this product. We provide recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. See Appendix H for our recommendations in track changes.

4.2 RECOMMENDATIONS FOR SUN PHARMACEUTICAL INDUSTRIES

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Prescribing Information and Container labels)

1. We refer you to the “Proprietary name request – unacceptable” letter dated October 10, 2017 concluding that the proposed proprietary name, (b) (4) is unacceptable. Remove the words “ (b) (4) from all labels and labeling.

B. Container Labels

1. (b) (4)
2. Remove the statement (b) (4) This is not required information and adds clutter to the label.
3. For the 25 mg and 50 mg container labels, consider (b) (4)

^a Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

^b Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for [REDACTED] (b) (4) that Sun Pharmaceutical Industries, Inc. submitted on March 30, 2017 and July 13, 2017, and the listed drug (LD).

Table 2. Relevant Product Information for [REDACTED] (b) (4) and the Listed Drug		
Product Name	[REDACTED] (b) (4)	Toprol-XL
Initial Approval Date	N/A	January 10, 1992
Active Ingredient	Metoprolol succinate	Metoprolol succinate
Indication	Angina, hypertension, heart failure	Angina, hypertension, heart failure
Route of Administration	Oral	Oral
Dosage Form	Extended-release capsules	Tablets
Strength	25 mg, 50 mg, 100 mg, and 200 mg	25 mg, 50 mg, 100 mg, and 200 mg
Dose and Frequency	25 mg to 400 mg once daily	12.5 mg to 400 mg once daily
How Supplied	30 count bottles	100 count bottles, Unit dose packages of 100
Storage	Store at 20°C to 25°C (68°F to 77°F).	Store at 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Metoprolol succinate labels and labeling submitted by Sun Pharmaceuticals on July 13, 2017.

- Container labels
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

(b) (4)



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^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

ASHLEIGH V LOWERY
10/13/2017

CHI-MING TU
10/16/2017