CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213330Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	September 29, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 213330
Product Name, Dosage Form, and Strength:	Labetalol Hydrochloride in Dextrose Injection, 200 mg/200 mL Labetalol Hydrochloride in Sodium Chloride Injection, 100 mg/100 mL, 200 mg/200 mL and 300 mg/300 mL
Applicant/Sponsor Name:	Hikma Pharmaceuticals International LTD (Hikma)
OSE RCM #:	2020-69-1
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 25, 2020 for Labetalol Hydrochloride in Dextrose and Labetalol Hydrochloride in Sodium Chloride. We reviewed the revised container labels and carton labeling for Labetalol Hydrochloride in Dextrose (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

7 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[a] Aidoo, M. Label and Labeling Review for Labetalol Hydrochloride in Dextrose (NDA 213330). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 23. RCM No.: 2020-69.

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/s/

MARIETTE A AIDOO
09/29/2020 03:01:34 PM

HINA S MEHTA
09/30/2020 11:00:37 AM

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

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

Memorandum

Date: September 3, 2020

To: Maryam Changi, PharmD, Regulatory Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology/Office of Regulatory Operations

Michael Monteleone, Associate Director for Labeling
Division of Cardiovascular and Nephrology (DCN)

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 LABETOLOL HYDCROCHLORIDE IN SODIUM CHLORIDE INJECTION and LABETOLOL HYCROCHLORIDE IN DEXTROSE INJECTION, for intravenous use

NDA/BLA: 213330

In response to DCN's consult request dated January 28, 2020, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for LABETOLOL HYDCROCHLORIDE IN SODIUM CHLORIDE INJECTION and LABETOLOL HYCROCHLORIDE IN DEXTROSE INJECTION, for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN (Maryam Changi) on August 31, 2020, and are provided below.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 1, 2020, 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
09/03/2020 04:17:28 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Division of Pediatric and Maternal Health Review

Date: June 25, 2020 **Date Consulted:** February 20, 2020

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Nephrology (DCN)

Drug: Labetalol HCL in Sodium Chloride Injection and Labetalol HCL in Dextrose Injection for intravenous use (Ready-to-Use Labetalol Hydrochloride Injection IV bags, preservative-free)

NDA: 213330

Applicant: Hikma Pharamceuticals

Subject: Pregnancy and Lactation Labeling

Indication: "indicated for control of blood pressure in severe hypertension"

Materials Reviewed:

- Applicant's proposed Pregnancy and Lactation labeling,
- Applicant's response to DPMH Information Request for documentation to support pregnancy and lactation labeling, conveyed in the 3/24/2020 74-Day Letter, 5/1/2020

NON-RESPONSIVE

[1] This review was part of the materials reviewed but was not a source relied upon for labeling recommendations provided in this review for NDA 213330.

NON-RESPONSIVE

Consult Question: "We would like to have DPMH input on the labeling. The RLD labeling is not in PLR/PLLR format."

INTRODUCTION AND BACKGROUND

On January 10. 2020, Hikma Pharmaceuticals submitted a new 505(b)(2) NDA for Ready-to-Use Labetalol Hydrochloride Injection IV bags (Labetalol HCL in Sodium Chloride Injection and Labetalol HCL in Dextrose Injection for intravenous use) for the control of blood pressure in severe hypertension patients. The Referenced Listed Drug (RLD) is Trandate (labetalol hydrochloride) injection (multidose vials, 100 mg/20 mL and 200 mg/40 mL), NDA 19425, approved December 31, 1985 (discontinued in 2006 for reasons other than safety or efficacy). The Reference Standard (RS) for comparative studies is Labetalol Hydrochloride Injection, 5 mg/mL, ANDA 075240. The Division of Cardiovascular and Nephrology (DCN) consulted the Division of Pediatric and Maternal Health (DPMH) on February 20, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Labetalol Drug Characteristics[3]

- An alpha-/beta-adrenergic blocking agent; labetalol combines both selective, competitive, $alpha_1$-adrenergic blocking and nonselective, competitive, beta-adrenergic blocking activity;
- Approximately 50% protein bound;
- Elimination half-life is about 5.5 hours following intravenous administration;
- Serous adverse reactions include hypotension, bradycardia, depression of myocardial contractility in patients with overt congestive heart failure, aggravation of angina, significant decline in cardiac output following coronary bypass, bronchospasm in patients with reactive airway disease, paradoxical hypertensive responses in patients with pheochromocytoma, hepatic injury, acute hypersensitivity reaction, can enhance the effect of antidiabetic agents.

RLD Labeling (discontinued)[4]

- Trandate Injection labeling is in the old labeling format (non PLR/PLLR format).
- There is no Boxed Warning for embryofetal toxicity.
- There are no Contraindications or Warnings for pregnancy or lactation.
- There are no human data; based on animal data, Pregnancy Category C. Adverse reactions described in neonates include: *Hypotension, bradycardia, hypoglycemia, and respiratory depression have been reported in infants of mothers who were treated with labetalol HCl for hypertension during pregnancy.*
- Current Nursing Mothers labeling language:

[2] *ibid*
[3] Refer to applicant's draft labeling, 1/10/2020
[4] Refer to Trandate Injection labeling, approved 11/22/2010

Nursing Mothers: *Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when Trandate Injection is administered to a nursing woman.*

- There are no existing pregnancy testing or contraception recommendations
- There are no known drug-drug interactions with hormonal contraceptives.
- There are no human or animal infertility data.

REVIEW

Pregnancy

Hypertension in Pregnancy

Hypertension in pregnancy is defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or both. Chronic hypertension and cardiovascular disease are among the leading causes of maternal and fetal/neonatal morbidity and mortality. Preeclampsia develops in approximately 13 to 40 percent of pregnant women with chronic hypertension and is associated with even higher rates of adverse outcomes. The prevalence of chronic hypertension in pregnant women in the U.S. is estimated to be 0.6 to 1.5 percent; however, these rates have increased overtime due to increased maternal age and increased obesity levels. Maternal risks of chronic hypertension include: acute kidney failure, pulmonary edema, superimposed preeclampsia, in-hospital mortality, stroke/cerebrovascular complications, cesarean delivery, placental abruption, postpartum hemorrhage, gestational diabetes, and hospitalization. Adverse fetal and/or neonatal outcomes include preterm birth, low birthweight, and increased neonatal NICU admission. Chronic hypertension in pregnancy has also been associated with an increased risk for congenital malformations, including cardiac malformations, esophageal atresia, and hypospadias.[5]

Severe hypertension in pregnancy is defined as systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥110 mmHg, or both. Acute onset severe hypertension (systolic, diastolic, or both) can occur during the prenatal, intrapartum, or postpartum periods. Urgent antihypertensive therapy is necessary in these women to avoid adverse maternal outcomes, including stroke. First-line therapy consists of intravenous labetalol and hydralazine. Oral nifedipine may be considered in situations when intravenous access is not available. Once the woman is stabilized, blood pressure should be closely monitored, and maintenance therapy should be instituted to maintain blood pressure control.[6]

Nonclinical Experience

The applicant is relying on nonclinical study data submitted with the RLD, Trandate (labetalol hydrochloride) injection (multidose vials, 100 mg/20 mL and 200 mg/40 mL), NDA 19425, approved December 31, 1985:[7]

[5] https://www.uptodate.com/contents/chronic-hypertension-in-pregnancy-management-and-outcome?search=hypertension%20in%20pregnancy&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2, accessed 5/18/2020

[6] ACOG Committee Opinion # 767 Interim Update: Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. *Obstetrics and Gynecology*, 2019; 133(2):e174-188

[7] Refer to Trandate Injection labeling, approved 11/22/2010

Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at IV doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus.

And

Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Review of Pharmacovigilance Database

The applicant has not conducted clinical studies with their new formulation and the product is not approved or marketed anywhere at this time.

Review of Literature - Applicant

The applicant conducted a search in PubMed for publications related to the use of labetalol in pregnancy between 1976 through 2019, using the following search terms: (labetalol) AND (pregnancy OR fetal OR neonatal OR teratogenesis OR embryotoxic). The applicant found 461 publications and deemed 30 articles clinically articles (refer to Appendix 1 for Applicant's Table 1 for a summary of the 30 relevant articles).

The applicant concluded that Labetalol is among the most widely used antihypertensive drug in pregnancy and has extensive clinical experience documented since 1976. Available data from published studies have not demonstrated an association of adverse developmental outcomes with maternal use of labetalol and untreated hypertension during pregnancy can lead to serious adverse outcomes for the mother and the fetus.

Reviewer Comment: The applicant's review of pregnancy data is adequate. Refer to the end of the Discussion/Conclusion section of this review for DPMH's opinion on the applicant's submission and recommedations.

Review of Literature - DPMH

DPMH conducted a search of available published articles in Embase, PubMed, and REPROTOX[8] regarding labetalol exposure or use during pregnancy using the following search terms: "labetalol AND embryofetal toxicity," "labetalol AND fetal malformations," "labetalol AND spontaneous abortion and miscarriage," and "labetalol AND neonatal effects" and did not locate any additional relevant publications.

REPROTOX summarizes that

> "…based on experimental animal studies and human reports, labetalol therapy does not appear to increase the risk of congenital anomalies, and in some reports, when labetalol was given to pregnant hypertensive women, it caused a decrease in maternal blood

[8] An information system developed by the Reproductive Toxicology Center; contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development

pressure without a decrease in indices related to blood flow in the fetal aorta, umbilical vein, or the intervillous space.[9]

Lactation

Nonclinical Experience

There are no animal lactation data described in the RLD labeling (Trandate, NDA 19425).

Review of Pharmacovigilance Database

The applicant has not conducted clinical studies with their new formulation and the product is not approved or marketed anywhere at this time.

Review of Literature - Applicant

The applicant conducted a search in PubMed for publications related to the use of labetalol during lactation between 1976 through 2019, using the following search terms: (labetalol) AND (lactation OR lactating OR prolactin OR milk OR breast milk OR milk excretion OR breast feeding OR breastfed). The applicant found 24 publications and deemed 4 articles as clinically relevant. The applicant also summarized the labetalol lactation data form LactMed (refer to Appendix 2 for Applicant's Table 2 for a summary of the 4 clinically relevant articles and the LactMed summary).

The applicant concluded that published data indicate that small amounts of labetalol are present in human milk with the estimated daily dose in breastfed infants to be between 0.004% and 0.07% of the maternal dose. The effect of labetalol on the breastfed infant and on milk production are not fully characterized.

Reviewer Comment: The applicant's review of lactation data is adequate. LactMed reported on one case of a 26 week gestation neonate experiencing bradycardia after receiving nasogastric breastmilk from its mother who was being treated with labetalol. Insufficient information was provided in the report to establish an assciation between ingestion of breastmilk and bradycardi,a as 26 week gestation neonates can have frequent episodes of bradycardia caused by prematurity alone or caused by procedures such as placement of a feeding tube. Refer to the end of the Discussion/Conclusion section of this review for DPMH's opinion on the applicant's submission and recommedations.

Review of Literature - DPMH

DPMH conducted a literature search in PubMed, Embase, REPROTOX, LactMed and Thomas Hale's *Medications in Mothers' Milk* regarding the use of labetalol during lactation. No other additonal relevant publications were located. Refer to the applicant's summary of LactMed labetalol information in Appendix 2 of this review.

[9]https://www micromedexsolutions.com/micromedex2/librarian/CS/1E08E6/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/457BD5/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=2175&contentSetId=35&title=LABETALOL&servicesTitle=LABETALOL&navResults=clinicalRefTox, accessed 5/19/2020

REPROTOX summarizes that "labetalol concentrations in milk were reported to be very low and significant exposure of nursing infants appeared to be an exceptional occurrence."[10]

Hale summarizes that, "In one study of 3 women receiving 600 - 1200 mg/day, the peak concentrations of labetalol in breastmilk were 129, 223, and 662 µg/L respectively. In only one infant were measurable plasma levels found (18 µg/L) following a maternal dose of 600 mg.[11] Therefore, only small amounts are secreted into human milk.[12]

The American Academy of Pediatrics (AAP) considers use of labetalol compatible with breastfeeding.[13]

Females and Males of Reproductive Potential

Nonclinical Experience

There are no animal fertility data described in the RLD labeling (Trandate, NDA 19425).

Review of Pharmacovigilance Database

The applicant has not conducted clinical studies with their new formulation and the product is not approved or marketed anywhere at this time.

Review of Literature – Applicant

The applicant conducted a search in PubMed for publications related to the use of labetalol in females and males of reproduction potential between 1976 through 2019, using the following search terms: (labetalol) AND (contraception OR contraceptive OR fertility OR infertility OR semen OR sperm OR spermatogenesis OR reproductive potential OR reproduction studies). The applicant located 113 publications deemed 2 articles as clinically relevant (refer to Appendix 3 for Applicant's Table 3 for a summary of the 2 clinically relevant articles).

The applicant summarized that published data report that labetalol may inhibit sperm motility and delay ejaculation in a dose dependent manner. No reports on females or male infertility were identified.

Reviewer Comment: The applicant's review of fertility data is adequate. Refer to the end of the Discussion/Conclusion section of this review for DPMH's opinion on the applicant's submission and recommedations.

Review of Literature – DPMH

DPMH conducted a literature search in PubMed, Embase, and REPROTOX regarding the use of labetalol and infertility. No relevant publications were located.

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[10]https://www micromedexsolutions.com/micromedex2/librarian/CS/1E08E6/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/457BD5/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=2175&contentSetId=35&title=LABETALOL&servicesTitle=LABETALOL&navResults=clinicalRefTox, accessed 5/19/2020

[11] Lunell NO, Kulas J, Rane A. Transfer of labetalol into amniotic fluid and breast milk in lactating women. *Eur J Clin Pharmacol*, 1985; 28(5):597-599.

[12] https://www.halesmeds.com/monographs/61204?q=labetalol, accessed 5/19/2020

[13] American Academy of Pediatrics, Committee on Drugs. The transfer of drugs and other chemicals into human milk. https://pediatrics.aappublications.org/content/pediatrics/108/3/776.full.pdf

REPROTOX summarizes that, "there have been case reports of men with ejaculatory failure on labetalol. Changes in libido or erectile function were not noted. In an experimental setting, a single dose of labetalol delayed ejaculation and detumescence in normal men."[14]

DISCUSSION AND CONCLUSIONS

Pregnancy

There is extensive clinical experience with the use of labetalol in pregnant women and the drug is recommended as first-line treatment for severe hypertension in pregnancy or the postpartum period. Published epidemiologic studies have not shown an association with labetalol use in pregnancy and major malformations; however, most of the studies report on maternal use of intravenous labetalol occurring after 20 weeks gestation. 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) and increases the fetal risk for intrauterine growth restriction and intrauterine death. There are inconsistent literature reports regarding labetalol use in pregnancy and adverse fetal/neonatal outcomes such as preterm birth, perinatal mortality, low birth weight, and intrauterine growth restriction. Fetal hypoglycemia and fetal bradycardia are common findings in pregnancy with hypertension and have been reported in pregnancies with labetalol treatment. Neonatal hypotension has been reported with prenatal labetalol exposure. Maternal labetalol use has not been shown to significantly affect umbilical blood flow, or fetal heart rate, blood pressure, or cerebral oxygenation.

Subsection 8.1 Pregnancy of Labetalol labeling should include summary information regarding the information from published literature and extensive clinical experience clinical experience, Clinical Considerations for disease-associated maternal and/or embryo/fetal risk and fetal/neonatal adverse reactions, and the background risk statement.

Lactation

The American Academy of Pediatrics (AAP) considers use of labetalol compatible with breastfeeding. Small studies and random breast milk sampling with maternal use of labetalol have shown very low levels of drug in breastmilk.

Subsection 8.2 Lactation of Labetalol labeling should include the summary lactation information that labetalol is present in human milk at low levels from published literature and tertiary sources and also contain the standard lactation benefit/risk statement. There is insufficient information from the published studies to provide actual levels of labetalol in human milk as the studies had methodological limitations and some lacked use of a validated assay.

[14]https://www micromedexsolutions.com/micromedex2/librarian/CS/1E08E6/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/457BD5/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=2175&contentSetId=35&title=LABETALOL&servicesTitle=LABETALOL&navResults=clinicalRefTox, accessed 5/19/2020

Due to available published lactation data with labetalol, extensive clinical use, and consensus agreement that maternal use of labetalol is compatible with breastfeeding, a lactation study for Labetalol is not recommended at this time.

Females and Males of Reproductive Potential

There are no pregnancy testing or contraception recommendations, and no adverse fertility effects to convey with labetalol use. However, class labeling exists for beta-blockers stating that drugs in this class may cause erectile dysfunction and inhibit sperm motility. This class language should appear in subsection 8.3 Females and Males of Reproductive Potential of labetalol labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, 8.3 and section17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on June 25, 2020. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy, Lactation, and Females and males of Reproductive Potential Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The extensive experience with use of labetalol in pregnant women, based on published interventional and observational studies, has not identified a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data).* Untreated hypertension during pregnancy can lead to serious adverse outcomes for the mother and the fetus *(see Clinical Considerations).* In animal reproduction studies, oral administration of labetalol to pregnant rats and rabbits during organogenesis at doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively, resulted in no fetal malformations; however, increased fetal resorptions were seen in both species at doses approximating the MRHD *(see Data).*

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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 Considerations

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.

Fetal/Neonatal Adverse Reactions
Labetalol crosses the placenta. Neonates born to mothers who are receiving labetalol during pregnancy, may be at risk for hypotension, bradycardia, hypoglycemia, and respiratory depression. Neonates should be monitored for symptoms of hypotension, bradycardia, hypoglycemia and respiratory depression and managed accordingly.

Data
Human Data
Data from published interventional and observational studies did not demonstrate an association between major congenital malformations and the use of labetalol in pregnancy, however, most studies reported the maternal use of intravenous labetalol occurring after 20 weeks gestation. The published literature has reported inconsistent findings of intrauterine growth retardation, preterm birth and perinatal mortality with maternal use of labetalol during pregnancy; however, these studies have methodological limitations hindering interpretation. These studies cannot definitively establish the absence of risk during pregnancy.

Animal Data
Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD.

A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus.

Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

8.2 Lactation
Risk Summary
Available published data report the presence of labetalol in human milk at low levels. There are no data on the effects on the breastfed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Labetalol and any potential adverse effects on the breastfed infant from Labetalol or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential
Infertility
Males
Based on the published literature, beta blockers, including labetalol, may cause erectile dysfunction and inhibit sperm motility.

APPENDIX 1

Table 1: Applicant's Review of Labetalol in Pregnancy Literature

Study or Reference	Treatment and Study Population (N)	Safety reported/comments
Yang X et al (2019) Distinct outcomes of labetalol exposed infants: case reports and systematic review. [Case Report evaluation and Systematic review]	A case of a premature infant with long-term maternal labetalol exposure died on day 5 after birth was reported. A comparison with two literature cases of labetalol-exposed premature infants having different prognoses was made to analyze their clinical features. Ten publications including two cases introduced previously, one observation, and seven cohorts were studied in terms of clinical symptoms and mechanism investigations	Reports of beta-adrenonergic blockade in newborns exposed to labetalol that are found in the literature are postulated by Yang et al to be withdrawal symptoms. "We call them early-onset withdrawal effects because theoretically, they would not maintain very long due to the short half-life. No matter based on our own observation or previous studies, early-onset effects are hypotension, hypoglycemia and bradycardia majorly, lasting no more than 3 d." It was concluded that neonatal labetalol withdrawal effects include early-onset and late-onset demonstrations, the latter can be life-threatening. Authors conclude that long-term labetalol exposed preterm infants, if complicated with asphyxia, acidosis, hypoalbuminemia and cardiac defects, should be provided with more intense care during the first week after birth and propose a mechanism that multiple factors induced imbalance of sympathetic homeostasis increases neonatal vulnerability to common stresses.

Gainder S et al (2019) To study the changes in fetal hemodynamics with intravenous labetalol or nifedipine in acute severe hypertension. [Randomized Clinical Trial] Objective: To compare the efficacy of intravenous labetalol or oral nifedipine in treatment of acute maternal hypertension and study the fetal hemodynamic changes using color Doppler ultrasound that follows treatment.	N = 30, with severe preeclampsia having acute hypertension (more than or equal to 160/ 105 mmHg). Randomized in 2 groups to receive intravenous labetalol or oral nifedipine until blood pressure was lowered to less than or equal to 140/90 mmHg. Doppler vascular indices namely pulsatility index, resistance index, S/D ratio of umbilical (UA) and middle cerebral artery (MCA) were measured baseline at the time of acute severe hypertension and repeated after control of blood pressure, to assess the changes in fetal hemodynamics if any with labetalol or nifedipine.	When comparing maternal and fetal heart rate before and after treatment no significant differences were observed in both labetalol (maternal heart rate: 88.53 ± 9.05 bpm vs. 86.53 ± 8.36 bpm, p = 0.055; fetal heart rate: 132.13 ± 6.94 bpm vs. 131.47 ± 7.07 bpm, p = 0.096; pre- vs. post treatment values, respectively) and nifedipine groups (maternal heart rate: 82.27 ± 8.27 bpm vs. 83.20 + 7.39 bpm, p = 0.05; fetal heart rate: 128 + 7.74 bpm vs. 126.80 + 6.48 bpm, p = 0.26; pre- vs. post treatment values, respectively). When comparing changes in the evaluated parameters between pregnant women who received labetalol or nifedipine, no significant difference was observed in umbilical artery indices (data shown in Table 4).

ACOG Committee Opinion No. 767: Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period (2019)	Pregnant women or women in the postpartum period with acute-onset, severe systolic hypertension; severe diastolic hypertension; or both require urgent antihypertensive therapy. Introducing standardized, evidence-based clinical guidelines for the management of patients with preeclampsia and eclampsia has been demonstrated to reduce the incidence of adverse maternal outcomes. Individuals and institutions should have mechanisms in place to initiate the prompt administration of medication when a patient presents with a hypertensive emergency.	Treatment with first- line agents should be expeditious and occur as soon as possible within 30–60 minutes of confirmed severe hypertension to reduce the risk of maternal stroke. Intravenous labetalol and hydralazine have long been considered first-line medications for the management of acute-onset, severe hypertension in pregnant women and women in the postpartum period. Parenteral labetalol may cause neonatal bradycardia and should be avoided in women with asthma, heart disease, or congestive heart failure. Nifedipine has been associated with an increase in maternal heart rate, and less risk of overshoot hypotension. No significant changes in umbilical blood flow have been observed with the use of either labetalol or hydralazine, and maternal and perinatal outcomes are similar for both drugs

National Institute for Health and Care Excellence (NICE). (2019). Hypertension in pregnancy: diagnosis and management (NICE Guideline No. 133)	This guideline includes new and updated recommendations on: assessing proteinuria managing chronic hypertension in pregnancy and gestational hypertension managing pre-eclampsia, including severe pre-eclampsia in critical care settings treatment during the postnatal period (including breastfeeding) advice and follow-up in community care It also includes recommendations on: Reducing the risk of hypertension in pregnancy fetal monitoring and care of women during labour and birth	Consider labetalol to treat gestational hypertension. Offer labetalol to treat hypertension in pregnant women with pre-eclampsia. Treat women with severe hypertension who are in critical care during pregnancy or after birth immediately with 1 of the following: • labetalol (oral or intravenous) • oral nifedipine • intravenous hydralazine. [2010, amended 2019] "Labetalol is specifically licensed for use in pregnancy and so is suggested as the first-line option, with nifedipine as the next alternative, and methyldopa as the third option (as it may lead to more side effects and be the least effective option of the 3)."

Duan L et al (2018) Beta-blocker subtypes and risk of low birth weight in newborns. [Retrospective cohort study of pregnant women exposed to beta- blockers in the Kaiser Permanente Southern California Region between 2003 and 2014].	N = 379,238 singleton pregnancies Beta blockers (n = 4,847) Labetalol (n = 3,357) Atenolol (n = 638), propranolol (n = 489), and metoprolol (n = 324) The perinatal database reviewed includes maternal characteristics, infant gender, gestational age at birth, birth weight, APGAR scores, delivery methods, and pregnancy- associated complications. Patients were considered to be exposed to beta- blocker during pregnancy if they filled a prescription for a beta- blocker between their estimated conception date and the date of delivery	Mean birth weight and low birth weight (<2500 g) were 2926 ± 841 g and 24.4% for labetalol, 3058 ± 748 g and 18.0% for atenolol, 3163 ± 702 g and 13.3% for metoprolol, 3286 ± 651 g and 7.6% for propranolol, and 3353 ± 554 g and 5.2% for non- exposed controls. Exposure to atenolol and labetalol were associated with increased risks of infant born small for gestational age (SGA) (atenolol: adjusted OR 2.4, 95% CI: 1.7- 3.3; labetalol: adjusted OR 2.9, 95% CI: 2.6- 3.2). Exposure to metoprolol and propranolol were associated with higher mean birth weight and lower percentages of low birth weight compared to atenolol and labetalol. The rate of very low birth weight (<1500 g) was also highest in the group exposed to labetalol (7.4%). APGAR scores at 1 minute were lower in the beta- blocker exposed group compared to the non- exposed group. The percentages of infants with APGAR scores lower than seven at 1, 5, and 10 minutes of birth were higher in the beta- blocker exposed group compared to the non- exposed group. One limitation of (the) study is that beta- blocker exposure was based on pharmacy dispensing information. The authors also conclude that it is possible that the differences in underlying maternal cardiac conditions and confounding by indication played a role in the results observed.

Thewissen L et al (2017) Neonatal hemodynamic effects following fetal exposure to labetalol in hypertensive disorders of pregnancy. [Prospective observational case-control study]	N = 22 neonates of mothers treated with labetalol for Hypertensive Disorders in Pregnancy with a gestational age <32 weeks, admitted NICU of a tertiary referral center in the Netherlands. Exclusion criteria were neonates with known or strongly suspected congenital abnormalities. Clinical characteristics, vital parameters and cerebral oxygen delivery and extraction were collected during the first 24 h of life in labetalol- exposed preterm neonates and compared with two control groups. Infants participated in a longitudinal study in which cerebral oxygenation and extraction were monitored using near infrared spectroscopy (NIRS) for the first 72h of life.	Within the described dose range of maternal labetalol, no differences compared to controls concerning neonatal blood pressure, heart rate, blood pressure support nor differences concerning regional cerebral oxygen saturation and oxygen extraction were found. Labetalol dosage had no effect neither on cerebral oxygenation, heart rate nor on blood pressure of the preterm infant during the first 24 h after birth. To our best knowledge this is the first paper describing the exclusive effect of maternal labetalol on NIRS measured cerebral oxygenation. Study conclusions: Maternal disease severity seems to play a more important role in neonatal cerebral hemodynamics. Maternal labetalol treatment has no clinically important short-term side effects in the preterm neonate

Fitton CA et al (2017) In-utero exposure to antihypertensive medication and neonatal and child health outcomes: a systematic review.	The aim of this study was to systematically review published studies on adverse outcomes to the child associated with in-utero exposure to antihypertensive medications, including labetalol. Following review, 47 primary studies were eligible for inclusion. The Critical Appraisal Skills Programme checklist was used to assess study quality. Five studies were of excellent quality; the remainder were either mediocre or poor. Increased risk of low birth weight, low size for gestational age, preterm birth, and congenital defects following in-utero exposure to all antihypertensive agents were identified.	Reviewed 47 published studies reporting the effects of in-utero exposure to antihypertensive medication on the fetus and child. Thirty-two of these studies were of poor or mediocre quality, with small study populations, and incomplete adjustment for confounding, and lack of quality. Although there is a widely held view that antihypertensive patients, such as beta-blockers, may be associated with a variety of detrimental fetal outcomes, such as low birth weight or congenital malformations, these beliefs are not based on robust data from appropriately designed and powered studies to conclusively confirm any associations. Furthermore, few studies have investigated the possible long-term outcomes following in-utero exposure to anti- hypertensive agents. The four studies which have done so have had small study populations, lacked statistical power and reported conflicting results. Although no IQ or developmental differences were reported for methyldopa and labetalol in two studies, sleep disturbance following clonidine or methyldopa exposure, and increased incidence of attention deficit hyperactivity disorder with labetalol were reported in two of the four studies reporting long-term outcomes. Two studies reported an increased risk of attention deficit hyperactivity disorder following exposure to labetalol, and an increased risk of sleep disorders following exposure to methyldopa and clonidine A paucity of relevant published high-quality studies exists. A small number of studies suggest possible increased risk of adverse child health outcomes; however, most published studies have methodological weaknesses and/or lacked statistical power thus preventing any firm conclusions being drawn

Duan L et al (2017) β-Blocker Exposure in Pregnancy and Risk of Fetal Cardiac Anomalies.	N = 379,238 singleton pregnancies Beta blockers (n = 4,847) Labetalol (n = 3,357) Atenolol (n = 638) Propranolol (n = 489) Metoprolol (n = 324) The perinatal database reviewed includes maternal characteristics, infant gender, gestational age at birth, birth weight, APGAR scores, delivery methods, and pregnancy- associated complications. Patients were considered to be exposed to beta- blocker during pregnancy if they filled a prescription for a beta- blocker between their estimated conception date and the date of delivery	In this large population-based cohort study in California, authors found that β-blocker exposure was not associated with increased risks of fetal congenital cardiac anomalies after adjustment for maternal comorbidities. The previously reported association between β-blocker use and fetal cardiac anomalies in other studies may be attributed to confounding. One limitation of our study is that β-blocker exposure was based on pharmacy dispensing information,
Shekar S et al (2016) Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis.	Systematically searched for articles comparing oral nifedipine with intravenous labetalol for the treatment of severe hypertension during pregnancy in any language, over Medline, Cochrane Central Register of Clinical Trials and Google Scholar from inception till February 2014.	The pooled analysis of seven trials (four from developing countries) consisting of 363 woman–infant pairs showed that oral nifedipine was associated with less risk of persistent hypertension (RR 0.42, 95% CI 0.18–0.96) and reported maternal side effects (RR 0.57, 95% CI 0.35–0.94). However, on sensitivity analysis the outcome 'persistent hypertension' was no longer significant This review shows that nifedipine, when used for treatment of hypertensive crises of pregnancy, is as efficacious and safe as labetalol and may be advantageous in low resource settings.

Magee LA et al (2016) The CHIPS Randomized Controlled Trial (Control of Hypertension in Pregnancy Study): Is Severe Hypertension Just an Elevated Blood Pressure? [Ad hoc analysis of prospective, randomized controlled trial data]	N =987 In this post-hoc analysis of CHIPS (Control of Hypertension in Pregnancy Study) data from 987 women with non-severe nonproteinuric preexisting or gestational hypertension, mixed effects logistic regression was used to compare the following outcomes according to occurrence of severe hypertension, adjusting for allocated group and the influence of baseline factors: CHIPS primary (perinatal loss or high-level neonatal care for >48 hours) and secondary outcomes (serious maternal complications), birth weight <10th percentile, preeclampsia, delivery at <34 or <37 weeks, platelets <100×109/L, elevated liver enzymes with symptoms, maternal length of stay ≥10 days, and maternal readmission before 6 weeks postpartum.	Women randomized to less tight control in the CHIPS trial (Control of Hypertension in Pregnancy Study) more often developed severe hypertension, which could not be predicted from clinical characteristics when hypertension developed. Severe hypertension was associated with higher rates of the primary perinatal outcome (pregnancy loss or high-level neonatal care for >48 hours), birth weight <10th percentile, preeclampsia, preterm delivery, platelets <100×109/L, elevated liver enzymes with symptoms, and maternal length of hospital stay for ≥10 days. Severe hypertension was associated with the secondary maternal outcomes (maternal death or serious maternal complications) only among women in less tight control. Severe hypertension remained a significant risk factor for adverse maternal and perinatal outcomes even after adjustment for preeclampsia.
Bateman BT et al (2016) Late Pregnancy β Blocker Exposure and Risks of Neonatal Hypoglycemia and Bradycardia.	The cohort included 2 292 116 completed pregnancies linked to liveborn infants, of which 10 585 (0.5%) pregnancies were exposed to β blockers at the time of delivery. Labetalol (n = 6748) Metoprolol (n = 1485) Atenolol (n = 1121)	The risk estimates for neonatal hypoglycemia in the PS-matched cohorts were similarly increased in association with exposure to each of the agents, including labetalol (OR, 1.78; 95% CI, 1.55– 2.04), metoprolol (OR, 1.64; 95% CI, 1.15–2.33), and atenolol (OR, 1.54; 95% CI, 0.99–2.40). Risk estimates for neonatal bradycardia across the specific β blockers in the PS-matched cohorts were less consistent, although the CIs for some estimates were wide: labetalol (OR, 1.34; 95% 1.08–1.67), metoprolol (OR, 0.59; 95% CI, 0.32–1.09), and atenolol (OR, 1.16; 95% CI, 0.60– 2.27). Findings suggest that neonates born to mothers exposed to β blockers in late pregnancy, including labetalol, are at elevated risk for neonatal hypoglycemia and bradycardia.

Xie RH et al (2014) Association between labetalol use for hypertension in pregnancy and adverse infant outcomes. [Retrospective population based study]	N = 1223 labetalol only (n = 300) methyldopa only (n= 923) Retrospective population-based cohort study using the linked maternal/infant databases in the Province of Saskatchewan. Women with a diagnosis of a hypertensive disorder of pregnancy who delivered a singleton in Saskatchewan from January 1, 1990 to December 31, 2005 and who were dispensed only labetalol or only methyldopa were included in the study.	For women with chronic hypertension, the rate of hospitalization for RDS, sepsis, and seizure during infancy was significantly higher for infants born to mothers who were dispensed labetalol only as compared with infants born to mothers who were dispensed methyldopa only (adjusted odds ratio (OR) 1.51, 95% confidence interval (CI) 1.02–2.22). Compared with methyldopa, the use of labetalol for chronic hypertension of pregnancy may be associated with increased rate of hospitalization during infancy
Thomas B et al (2014) A case of probable labetalol induced hyperkalaemia in pre-eclampsia. [Case description]	Hyperkalemia can cause altered cardiac electrical conduction resulting in death. Authors describe a case of a 23-year old pregnant patient who presented with severe epigastric pain and vomiting. She was severely pre-eclamptic and received initial treatment with intravenous labetalol and decision was taken to deliver.	The patient quickly became hyperkalaemic (serum potassium level 6.4 mmol/L) and labetalol was discontinued, and intravenous hydralazine commenced. Post-surgery, her potassium levels were normal but due to rapidly rising blood pressure labetalol was recommenced, resulting in elevated potassium levels. Labetalol was discontinued, hydralazine prescribed, and potassium levels normalized. The adverse reaction was classified as 'probably' due to labetalol using the Naranjo Adverse Drug Reaction scale. This is the first reported case of labetalol induced hyperkalaemia in pregnancy, with life threatening consequences and hence all health professionals should be alert to this potential effect.

Fischer JH et al (2014) Influence of Gestational Age and Body Weight on the Pharmacokinetics of Labetalol in Pregnancy [Prospective logetudinal study]	Data were collected from 57 women receiving the drug for hypertension from the 12th week of pregnancy through 12 weeks postpartum using a prospective, longitudinal design. A sparse sampling strategy guided collection of plasma samples. Samples were assayed for labetalol by high performance liquid chromatography. Estimation of population pharmacokinetic parameters and covariate effects was performed by nonlinear mixed effects modeling using NONMEM. Final population model was validated by bootstrap analysis and visual predictive check. Simulations were performed with the final model to evaluate the appropriate body weight to guide labetalol dosing.	Oral clearance of labetalol is increased in pregnancy. Pregnancy significantly influenced the disposition of labetalol. The CL/F increased with increasing gestational age from 1.4-fold greater than postpartum values at 12 weeks gestational age to 1.6-fold greater at 40 weeks, corresponding to a proportional decrease in dose-normalized AUC. The Vc/F and Vss/F were also larger during pregnancy. Intravenous labetalol is insensitive to pregnancy-related alterations in protein binding or hepatic enzyme activity compared to the oral route
Molvi SN et al (2012) Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa.	50 consecutive pregnant women without proteinuria and with physician-recorded systolic BP of 140–160 mmHg and/or diastolic BP of 90–105 mmHg on two occasions ≥6 h apart between 20 and 38 weeks of gestation were randomly allocated to receive either labetalol or methyldopa (50 patients each) plus standard care (treatment group) or only standard care (50 patients) (control group).	Compared to the control group, the treatment group had lower incidence of SGA babies (40% vs. 23%, P = 0.033), preterm birth (36% vs. 14%, P = 0.002), and admission to neonatal unit (30% vs. 15%, P = 0.036). After adjustment for maternal age, weight, baseline hemoglobin, resting heart rate, BP level, parity and previous history of PIH, fetal death, preterm delivery or SGA baby, anti- hypertensive therapy was associated with a lower incidence of adverse perinatal events (P = 0.016). Maternal and perinatal mortality rates were not significantly different between treatment and control groups. In conclusion, pharmacological treatment of mild to moderate PIH is associated with lower rate of some maternal and fetal-neonatal non-fatal adverse events compared to no routine use of antihypertensive therapy.

Heida KY et al (2012) Neonatal side effects of maternal labetalol treatment in severe preeclampsia.	All infants from mothers suffering severe PE (109 infants, 55 exposed to labetalol, whereas 54 were not, control) admitted to one tertiary care center were included. Infants exposed to labetalol in utero (labetalol infants) were compared with infants, who were not exposed to labetalol (controls). Neonatal records were reviewed for hypotension (RR < mean gestational age in weeks), bradycardia (heartrate < 100/ min) and hypoglycaemia (glucose < 2.7 mmol/L) in the first 48 postnatal hours.	Hypotension is more common after maternal labetalol exposure, regardless of the dosage and route of administration. The need for intubation and the presence of a PDA also play a role. Hypoglycemia is a very common finding in this population and is merely related to prematurity and independent of labetalol exposure as was the incidental occurrence of bradycardia. These findings on the neonatal side effects of maternal labetalol treatment in preeclampsia underline the importance of frequent blood glucose and blood pressure measurements in the first days of life, especially in intubated preterm infants with a PDA.
Bateman BT et al (2012) Prevalence, Trends, and Outcomes of Chronic Hypertension: a Nationwide Sample of Delivery Admissions.	A cohort of 2,292,116 completed pregnancies linked to liveborn infants of Medicaid-enrolled women from 2003 to 2007. Examined the risks of neonatal hypoglycemia and neonatal bradycardia associated with maternal exposure to β blockers at the time of delivery. Propensity score matching was used to control for potential confounders including maternal demographics, obstetric and medical conditions, and exposure to other medications.	There were 10,585 (0.5%) pregnancies exposed to β blockers at the time of delivery. The risk of neonatal hypoglycemia was 4.3% in the β blocker–exposed neonates versus 1.2% in the unexposed; the risk of neonatal bradycardia was 1.6% in the exposed versus 0.5% in the unexposed. After controlling for confounders, risk remained elevated for both neonatal hypoglycemia and bradycardia among exposed pregnancies versus unexposed (adjusted odds ratio, 1.68, 95% confidence interval, 1.50–1.89 and adjusted odds ratio, 1.29, 95% confidence interval, 1.07–1.55, respectively). Findings suggest that neonates born to mothers exposed to β blockers in late pregnancy, including labetalol, are at elevated risk for neonatal hypoglycemia and bradycardia.

Baggio MR et al (2011) Changes in fetal and maternal Doppler parameters observed during acute severe hypertension treatment with hydralazine or labetalol: a randomized controlled trial.	16 pregnant women with gestational age between 20 and 32 weeks with acute severe hypertension were randomly allocated to receive either hydralazine or labetalol Hydralazine: 5–10-mg doses intravenously every 15– 20 min until blood pressure lower than 150/100 mm Hg Labetalol: 20-mg intravenous bolus dose followed by 40 mg if not effective within 10 min; then, 80 mg every 10 min until blood pressure lower than 150/100 mmHg or maximum total dose of 220 mg.	The use of hydralazine and labetalol were not related to any significant changes in fetal Doppler, which is reassuring about the safety of these drugs when treating acute severe hypertension in pregnancy.

Chan WS et al (2010) Neurocognitive development of children following in-utero exposure to labetalol for maternal hypertension: a cohort study using a prospectively collected database.	Mother-child pairs were divided into groups based on in-utero exposure to labetalol (n = 32), non-teratogenic substances (n = 42), and methyldopa (n = 25). The main outcome measures were children's Full-Scale IQ, Performance IQ and Verbal IQ assessed with the Wechsler Preschool and Primary Scale of Intelligence	There were no statistically significant differences in scores on Full-Scale IQ, Performance IQ, or Verbal IQ between children exposed in utero to labetalol and to non-teratogenic substances (Full-Scale IQ: 109.60 ± 8.20 vs. 111.90 ± 11.39, p = 0.647; Performance IQ: 104.80 ± 8.69 vs. 110.19 ± 12.91, p = 0.186; Verbal IQ: 112.27 ± 11.05 vs. 11.21 ± 11.98, p = 0.922, respectively). Children in the methyldopa group achieved lower scores on measures of Full-Scale IQ and Performance IQ when compared to children exposed to non-teratogenic substances (Full-Scale IQ: 105.24 ± 12.46 vs. 111.90 ± 11.39, p = 0.043; Performance IQ: 98.80 ± 16.16 vs. 110.19 ± 12.91, p = 0.002, respectively). Conclusion: In-utero exposure to labetalol does not appear to adversely affect the neurocognitive development of young children. These reassuring results may aid disease management for pregnant women with hypertension.
Magee LA et al (2003) Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis.	Meta-analysis of randomized controlled trials of short acting antihypertensives for severe hypertension in pregnancy Goal: to compare the effects of short acting antihypertensive agents (in comparison to parenteral hydralazine) on perinatal, maternal, and neonatal outcomes, particularly maternal hypotension. Independent data abstraction by two reviewers. In a secondary analysis, risk difference was also calculated.	Labetalol has been used extensively in pregnancy and has a favorable side effect profile. However, specific concern has been raised about the risk of neonatal bradycardia with parenteral labetalol In summary, hydralazine was associated with more maternal side effects than labetalol or ketanserin, and more headache, palpitations, and maternal tachycardia than other antihypertensives

Rosenthal T and Oparil S (2002) The effect of antihypertensive drugs on the fetus.	A critical review of the literature on the effects of antihypertensive drugs on the fetus in pregnant women is presented. The survey covers the alpha-adrenergic receptor agonists, beta-blockers including topical eye medications, alpha-beta blockers, calcium antagonists, diuretics, and angiotensin-converting enzyme (ACE) inhibitors.	Clinical experience with labetalol is extensive and it is among the most widely used antihypertensive drugs in pregnancy. Blood pressure and proteinuria fell significantly in a placebo-controlled trial of labetalol in a cohort of 144 women with pregnancy-induced mild and moderate hypertension. However, gestation was not significantly prolonged and measures of clinical outcome were not significantly altered in these women. Diagnosing any drug-related disorder can be difficult. The relationship between a drug and an effect can be definitively established only by withdrawal of the suspected offending agent and re-challenge is clearly out of the question in most cases. Studies that attempt to establish a cause and effect relationship based on clinical data are done on cohorts of varying sizes and are usually very small. The effects of treating severe hypertension in pregnancy have been investigated in only a few placebo-controlled trials.
Petersen OB et al (1994) The effects of dihydralazine, labetalol and magnesium sulphate on the isolated, perfused human placental cotyledon.	To assess the effects of dihydralazine, labetalol and magnesium sulphate on the vascular tone in the isolated, perfused human placental cotyledon.	Neither labetalol nor hydralazine vasodilates the perfused human cotyledon.

Pickles CJ et al (1992) A randomized placebo-controlled trial of labetalol in the treatment of mild to moderate pregnancy induced hypertension.	N=144 pregnant women who developed pregnancy induced hypertension. Treatment with oral labetalol up to 600 mg daily or placebo Primary outcome: Number of days spent as an antenatal inpatient; the development of proteinuria; the perceived need for induction of labour or elective caesarean section; and gestation age at delivery.	Labetalol significantly lowered the blood pressure and reduced the incidence of proteinuria. However, neither the number of days spent as an antenatal inpatient, nor the perceived need for induction of delivery or elective caesarean section, nor the gestation age at delivery differed significantly between the two treatment groups. Post-randomization consideration of early (≤32 weeks) and late (>32 weeks) onset groups showed the placebo treated early-onset group (n = 15) to have more patients with severe hypertension (>150/110 mmHg) and a greater requirement for additional antihypertensive therapy prior to labor than the group treated with labetalol (n = 16).
Munshi UK et al (1992) Effects of maternal labetalol on the newborn infant.	Forty-eight neonates, born to mothers suffering from pregnancy induced hypertension and receiving labetalol for control of blood pressure, were studied for the possible adverse effects of the drug. These were compared with eighty-one neonates matched for gestation and weight and born to mothers with pregnancy induced hypertension treated with drugs other than labetalol.	Incidence of birth asphyxia and intrauterine growth retardation (IUGR) in the study population was 10.4 and 22.9%, respectively and in the control group 5 and 19.7%, the difference between two groups was not statistically significant ($p > 0.05$). However, the incidence of hypoglycemia was significantly higher ($p < 0.01$) in the study group (47.9%) as compared to the control group (17.2%). It is concluded that maternal labetalol therapy is associated with increased risk of neonatal hypoglycemia.

Cruickshank DJ et al (1992) Does labetalol influence the development of proteinuria in pregnancy hypertension? A randomized controlled study.	A randomized controlled study design was used to investigate whether labetalol treatment for high blood pressure influenced the subsequent development of proteinuria. N = 114 women with singleton pregnancies and hypertension in the absence of proteinuria were randomized to receive either labetalol or no antihypertensive therapy. At recruitment maternal age, blood pressure and gestation were similar in both the labetalol and control groups.	There was no difference in the frequency, quantity or timing of subsequent proteinuria between treatment and control groups. Overall 34% of primigravidae and 10% of parous women developed proteinuria. Labetalol did, however, control the blood pressure in 45 of the 51 treated women (88%) within 24 h. This effect was often short-lived requiring dose escalation after 3 to 5 days in the majority of cases. Labetalol was well tolerated, and no significant maternal toxicity was noted.
Rodgers RC et al (1990) Labetalol pharmacokinetics in pregnancy-induced hypertension.	Eight women with pregnancy-induced hypertension in the third trimester of pregnancy Labetalol 100 mg every 8 hours was administered orally at 6 AM, 2 PM, and 10 PM	Labetalol exhibited rapid absorption; peak serum concentrations of 881 ± 219 ng/ml occurred at 20 minutes after labetalol ingestion. The terminal elimination half-life (mean, 1.7 ± 0.27 hours) was found to be shorter than that reported for normotensive volunteers or nonpregnant hypertensive patients (mean, 6 to 8 hours). A mean apparent oral elimination clearance of 21.8 ml/min/kg compared favorably with that seen in other pregnant and nonpregnant populations. Food delayed the time to peak serum concentration to approximately 60 minutes. Labetalol was detected in fetal cord samples and amniotic fluid samples at concentrations approximately 50% and 16% that of simultaneous maternal vein samples, respectively.

Macpherson M et al (1986) The effect of maternal labetalol on the newborn infant.	The possibility that placentally-transferred labetalol might cause sympathetic blockade in the newborn infant was examined by measuring systolic blood pressure, heart and respiratory rates, palmar sweating, blood glucose and the metabolic and vasomotor responses to cold stress. Measurements were made serially over the first 72 h of life in 22 term infants, 11 born to mothers treated with labetalol and 11 carefully matched controls.	Infants of mothers treated with labetalol showed a mild transient hypotension which had disappeared within 24 h [mean systolic blood pressure at 2 h, 58.8 (SEM 2.4) mmHg compared with 63-3(SEM 3.0) mmHg for controls, $P<0.05$]. There were no other significant differences between the two groups. It is concluded that labetalol does not cause clinically important sympathetic blockade in the mature newborn infant. The authors conclude that labetalol is a relatively safe drug and that no special observations or precautions are necessary in term infants whose mothers have received it before delivery. Hyper- tensive disease of pregnancy, however, is associated with poor fetal growth and a high incidence of prematurity. Further study is necessary to see whether stressed preterm infants show more significant signs of sympathetic blockade than are seen in their healthy mature counterparts.
Riley AJ (1981) Clinical pharmacology of labetalol in pregnancy.	A review of the clinical pharmacology of labetalol for use in moderate to severe hypertension in pregnancy	The results of published materials on labetalol up until this point in time indicate effective control of blood pressure with minimal side effects.
Lunell NO et al (1981) Circulatory and metabolic effects of a combined alpha- and beta-adrenoceptor blocker (labetalol) in hypertension of pregnancy.	Seven women with hypertension of pregnancy were given the combine labetalol (50 mg i.v.) in their last trimester. Acute effects were studied for 3 hours after administration.	Plasma noradrenaline increased significantly from1.54+0.16 to a peak value of 2.37+0.41nmol/l suggesting sympathetic activation following labetalol. Plasma adrenaline levels were essentially unchanged. Plasma glucose, insulin and C-peptide showed only minor changes. No major effects on lipid metabolism were seen except a significant fall of non-esterified fatty acids at 60min. Plasma cyclic AMP increased significantly throughout the observation period, perhaps indicating f-adrenoceptor agonist activity of labetalol.
Hopkins R et al (1976) The metabolism of labetalol in animals and man.	The metabolism of labetalol was studied in rat, rabbit, dog and man regarding tissue distribution,	Radioautographic examination of the normal and the pregnant rat given [14C] labetalol orally (50-200mg/kg) or intravenously (25mg/kg) showed that the radioactivity was quickly taken up into the tissues and rapidly cleared from the body via both the kidney and bile.

APPENDIX 2

Table 2: Applicant's Review of Labetalol in Lactation Literature

Study or Reference	Treatment and Study Population (N)	Safety reported/comments
Drugs and Lactation Database (2018) LactMed Labetalol.	The breastfeeding data presented in the Drugs and Lactation database Labetalol Summary include the four studies described below in this table, (McGuinness 2013, Lunell 1985, Barbieri 1981, Michael 1979) as well as the data from two additional studies that were not available for review; therefore, this page was relied upon for the data from these two studies.	Summary of Use during Lactation Because of the low levels of labetalol in breastmilk, amounts ingested by the infant are small and would not be expected to cause any adverse effects in full-term breastfed infants. No special precautions are required in most infants. However, other agents may be preferred while nursing a preterm infant. Drug Levels The excretion of beta-adrenergic blocking drugs into breastmilk is largely determined by their protein binding. Those with low binding are more extensively excreted into breastmilk. Accumulation of the drugs in the infant is related to the fraction excreted in urine. With 50% protein binding, 5% renal excretion and a moderate half-life, labetalol presents moderately low risk for accumulation in infants. Maternal Levels. Random milk levels from 15 women on the third day postpartum averaged 27.5 mcg/L after maternal doses ranging from 330 to 400 mg daily. One of the women who took labetalol 400 mg daily for 5 weeks had no detectable drug in breastmilk (assay limit not specified). In another 9 women taking 600 to 800 mg daily, the average random milk level was 41 mcg/L. In one patient taking 1200 mg daily, a random milk level of 600 mcg/L was found. Infant Levels. The average dose received by breastfed infants is estimated to be between 0.004% and 0.07% of the maternal dose.

McGuinness N and Cording V (2013) Raynaud's phenomenon of the nipple associated with labetalol use.	This is a case of a 37-year-old woman, Gravida 2, Para 1, who was first seen in the antenatal clinic at 34 weeks' gestation. A diagnosis of Raynaud's phenomenon of the nipple was made after she began taking labetalol for pregnancy-induced hypertension. The phenomenon had occurred in both of her previous pregnancies on commencing labetalol and resolved postnatally on cessation of the drug.	Ultimately, the aim of treatment is control of blood pressure, which requires educating patients about risks and benefits of medication. In the United Kingdom, first line treatment of hypertension in pregnancy is with labetalol and the majority of patients are well controlled and free from side effects, but this case study reports on a potential and previously undocumented side effect of this commonly prescribed medication.
Lunell NO et al (1985) Transfer of labetalol into amniotic fluid and breast milk in lactating women.	Eleven women with hypertension in pregnancy received either 600 mg (n =10) or 1200 mg (n=1) labetalol per day.	The milk and maternal plasma levels of labetalol were not consistently related to each other within or between the patients. In two of them there was a lag between the plasma and the milk concentration profiles, with a higher level in milk than plasma late in the dose interval.
Barbieri C et al (1981) Endocrine and metabolic effects of labetalol in man.	The effects of intravenous infusion of the alpha- and beta-adrenoceptor blocking drug labetalol (100 mg over 10 min) on heart rate, blood pressure, and several endocrine and metabolic variables have been evaluated in 12 hypertensive patients (6 men and 6 women)	Intravenous labetalol can increase serum prolactin in men and non-nursing women, although the increase is greater in women. Oral labetalol does not increase serum prolactin

Michael CA (1979) Use of Labetalol in The Treatment of Severe Hypertension During Pregnancy	N = 25, (three with twin pregnancy) were treated and delivered. Six of these patients were known to be hypertensive before week 20 of pregnancy, the remainder developed hypertension for the first time after week 20. The longest duration of treatment was 12 weeks and the shortest 6 days. All patients were admitted to hospital for the commencement of therapy. The initial dose of labetalol was 100 mg orally three times daily and this was increased at half-weekly intervals until control of BP was achieved	The concentration of labetalol in breast milk is shown (Table 3), related to dose of the drug and mean maternal plasma levels. No adverse effects in the feeding infants were noted. One patient who received labetalol 400mg daily for 5 weeks did not have any of the drug present in the breast milk. Another a diabetic on 1200 mg daily, reached a peak level of 600 ng/ml in the breastmilk but she did not breastfeed. Labetalol did not interfere with labor nor complicate caesarean section. There was no spontaneous onset of labor, indicating that myometrial irritability was not a problem With the exception of the one patient receiving 1200 mg daily the levels of labetalol reached were well below the therapeutic levels obtained in each mother when related to the total daily dose of labetalol. One of the infants was hypotensive at birth but none had bradycardia. Oculotoxicity due to the labetalol was not observed in the infants delivered. It is concluded that the efficient hypotensive action of labetalol, together with apparent freedom from maternal and fetal side-effects, and consequent improved perinatal mortality, suggest that it is a suitable drug for use in pregnancy complicated by hypertension.

APPENDIX 3

Table 3: Applicant's Review of Labetalol and Females and Males of Reproductive Potential Literature

Study or Reference	Treatment and Study Population (N)	Safety reported/comments
Hong CY and Chiang BN (1984) Local anesthetic effect of antiarrhythmic drugs and human sperm immobilization: mechanism and application of the interrelationship. In-vitro study	Sperm immobilizing activity of quinidine, procainamide, mexiletine, as well as labetalol and one calcium channel blocking drug, diltiazem was measured with a trans-membrane migration method. Study evaluated human sperm motility by measuring the proportion of sperm that moved across a Nuclepore membrane (Nuclepore Ltd. USA) during 2-hour incubation at 37°C.	The concentrations that decreased sperm motility to 50% of control (EC50) were 0.5, 1.2, 1.4, 2.2, 2.8 and 20 mm for quinidine diltiazem in 5% ethanol, diltiazem in phosphate buffered saline, labetalol, mexiletine and procainamide respectively The authors concluded that all the drugs immobilized human sperm. Local anaesthetic effect is the underlying mechanism for these drugs to inhibit sperm motility.
Riley AJ et al (1982) A method for monitoring drug effects on male sexual response: the effect of a single dose of labetalol. [Double blind, placebo-controlled conditions]	N=6 males Treatment included 1 (100mg) labetalol tablet and 2 placebos Or 3 (100mg labetalol tablets) Genital response to stimulation provided by vibration is described in males	In the present study, labetalol produced a dose-related delay in ejaculation. However, in no subject was ejaculation abolished, even by the high dose (300mg) of labetalol was used. Ability to obtain or maintain an erection was not affected.

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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)

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Date of This Review:	June 23, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 213330
Product Name, Dosage Form, and Strength:	Labetalol Hydrochloride in Dextrose, Injection, 200 mg/200 mL Labetalol Hydrochloride in Sodium Chloride, 100 mg/100 mL, 200 mg/200 mL and 300 mg/300 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hikma Pharmaceuticals International LTD (Hikma)
FDA Received Date:	January 10, 2020, and May 1, 2020
OSE RCM #:	2020-69
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As a part of the approval process for 505(b)(2) NDA submission, this review evaluates the proposed Prescribing Information (PI), container labels and carton labeling for Labetalol Hydrochloride in Dextrose and Labetalol Hydrochloride in Sodium Chloride.

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 Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
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 or ISMP Newsletters 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

DMEPA performed a risk assessment of the full prescribing information (PI) and container labels to identify deficiencies that may lead to medication errors and areas for improvement.

4 CONCLUSION & RECOMMENDATIONS

Our review concludes the proposed PI, container label and carton labeling for Labetalol in Dextrose and Labetalol in Sodium Chloride may be improved to promote safe product use.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. Dosage and Administration Section

   a. Consider reorganizing subsections of Section 2 to modernize the organization, such as revise [redacted] to "2.1 Recommended Dosage".

   b. Consider using sentence case for statements [redacted] to improve readability [redacted].

   c. [redacted]

   d. [redacted]

   e. [redacted]

2. Dosage Forms and Strength Section

   a. Consider revising Section 3 to be presented in a sentence or bullet format instead of a table format.

   b. Revise Section 3 to include description of the product, such as "preservative-free, clear, colorless to light yellow sterile solution".

   c. Remove the statements [redacted] from section 3 as it does not belong in this section.

3. How Supplied/ Storage and Handling Section

   a. In Section 16.2, revise the statement [redacted] to read: "Do not remove from overwrap until ready to use."

4. Patient Counseling

   a. In Section 17, revise the statement [redacted] to read: "Advise patients to remain supine and to proceed gradually in becoming ambulatory during and immediately following infusion (for up to 3 hours) of Labetalol HCl injection."

4.2 RECOMMENDATIONS FOR HIKMA PHARMACEUTICALS INTERNATIONAL LTD

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

A. General Comments (**CONTAINER LABEL AND CARTON LABELING**)

1. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use for the expiration date. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.[5]
2. Consider removing the statement (b) (4) after "Ready to Use". (b) (4)
3. Revise the statement (b) (4) to read "Recommended Dosage: see Prescribing Information."

B. Container Label

1. Ensure the lot number and expiration date are presented on the container labels in accordance with 21 CFR 201.10(i)(1) and 21 CFR 201.17, and ensure that they are clearly differentiated from one another. Ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.

[5] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Labetalol Hydrochloride in Dextrose and Labetalol Hydrochloride in Sodium Chloride received on May 1, 2020 from Hikma Pharmaceuticals International LTD, and the listed drug (LD).

Table 2. Relevant Product Information for Labetalol Hydrochloride in Dextrose and Labetalol Hydrochloride in Sodium Chloride, and the Listed Drug

Product Name	Labetalol Hydrochloride in Dextrose, and Labetalol Hydrochloride in Sodium Chloride	TRANDATE (Labetalol Hydrochloride) injection [NDA 019425]
Initial Approval Date	N/A	December 31, 1985
Active Ingredient	Labetalol HCl	Labetalol HCl
Indication	Control of blood pressure in severe hypertension.	Control of blood pressure in severe hypertension.
Route of Administration	Slow continuous intravenous infusion	Repeated intravenous injection, or slow continuous infusion.
Dosage Form	Injection	Injection
Strength	Labetalol Hydrochloride in Dextrose: 200 mg/200 mL (1 mg/mL) Labetalol Hydrochloride in Sodium Chloride: 100 mg/100 mL, 200 mg/200 mL and 300 mg/300 mL (1 mg/mL)	100 mg/20 mL, and 200 mg/40 mL (5 mg/mL)
Dose and Frequency	Continuous intravenous Infusion rate: 2 mL/minute (2 mg/min) until the desired response is obtained. Effective intravenous dose: 50 to 200 mg Efficacy unestablished: >300mg	Infuse 20 mg intravenously over 2 minutes initially, then 40-80 mg intravenously every 10 minutes. Total dose ≤ 300 mg.
How Supplied	Labetalol HCl in Dextrose: 200 mg/200 mL. A box of 10 bags. Labetalol HCl in Sodium Chloride: 100 mg/100 mL, 200 mg/200 mL, and	A box containing 1 vial.

	300 mg/300 mL. A box of 10 bags.	
Storage	Store at 20° to (b) (4) (68° to 77°F) [See USP Controlled Room Temperature]. DO NOT FREEZE. PROTECT FROM LIGHT. DO NOT REMOVE FROM OVERWRAP UNTIL READY TO USE.	Store between 2° and 30°C (36° and S6°F). Do not freeze. Protect from light.
Container Closure	Single-dose, single-port bag with an aluminum overwrap	Glass vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 30, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, labetalol. Our search identified no previous reviews for labetalol injection.

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,[a] along with postmarket medication error data, we reviewed the following Labetalol Hydrochloride in Dextrose labels and labeling submitted by Hikma Pharmaceuticals International LTD.

- Container labels received on January 10, 2020
- Carton labeling received on January 10, 2020
- Prescribing Information (Image not shown) received on May 1, 2020, available from \\cdsesub1\evsprod\nda213330\0005\m1\us\final-labeling-text-clean.pdf

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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