CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215252Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: October 18, 2021

To: Sabry Soukehal, RAC
Sr. Regulatory Health Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology (DRO-CHEN)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 215252**
DILTIAZEM HYDROCHLORIDE injection, for intravenous use only

In response to DRO-CHEN's consult request dated February 25, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for DILTIAZEM HYDROCHLORIDE injection, for intravenous use only.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRO-CHEN (Sabry Soukehal) on October 5, 2021 and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DRO-CHEN on October 13, 2021 and uploaded to the EDR by the sponsor on October 12, 2021 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at (301) 796-1233 or carrie.newcomer@fda.hhs.gov.

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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CARRIE A NEWCOMER
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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:	October 14, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 215252
Product Name and Strength:	Diltiazem Hydrochloride in 5% Dextrose Injection, 125 mg/125 mL (1 mg/mL) and 250 mg/250 mL (1 mg/mL)
Applicant/Sponsor Name:	Exela Pharma
OSE RCM #:	2021-61-1
DMEPA 2 Safety Evaluator:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 12, 2021 for Diltiazem Hydrochloride in 5% Dextrose Injection. We reviewed the revised container label and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

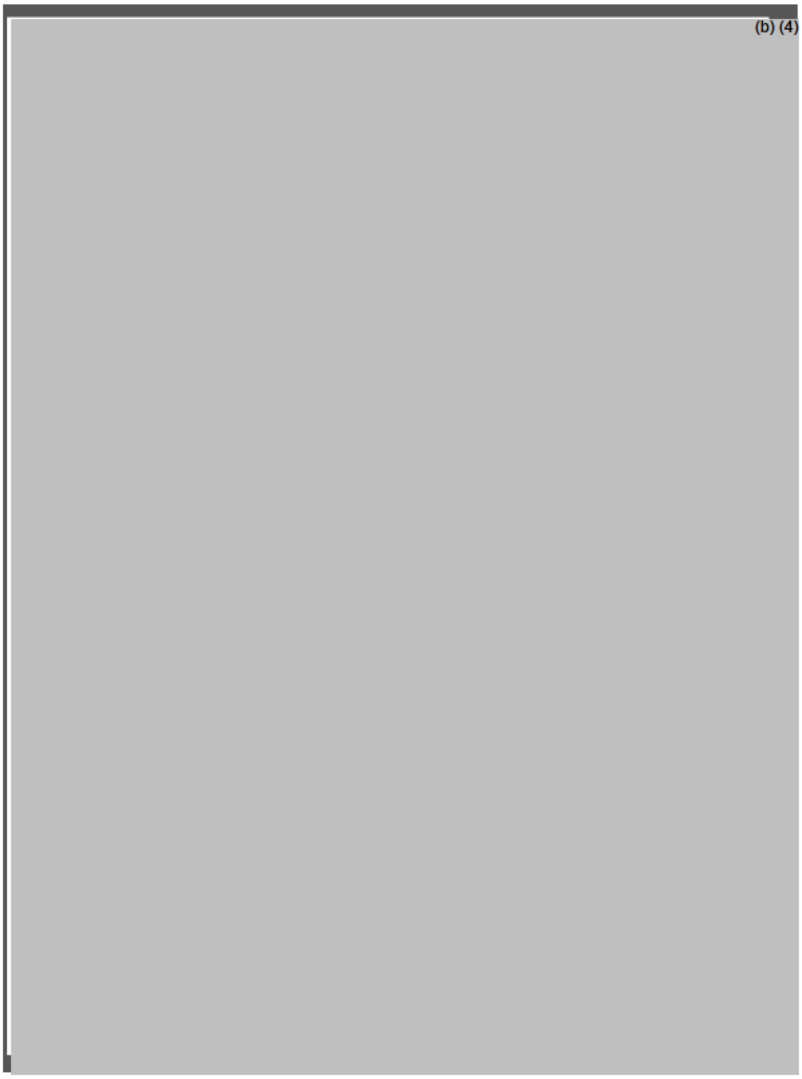
2 CONCLUSION

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

[a] Straka, M. Label and Labeling Review for Diltiazem Hydrochloride in Dextrose Injection (NDA 215252). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 JUN 28. RCM No.: 2021-61.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 12, 2021

Container labels



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/s/

HINA S MEHTA
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: September 21, 2021 **Date consulted:** May 24, 2021

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

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne Yao, MD, Director, DPMH

To: Division of Cardiology and Nephrology (DCN)

Drug: Diltiazem hydrochloride (HCL) injection for intravenous infusion

Drug Class Calcium channer blocker (CCB)

NDA: 215252

Applicant: Exela Pharma Sciences, LLC

Subject: Labeling review as per Pregnancy and Lactation Labeling Rule (PLLR)

Proposed Indication:

- Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter.
- Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.

Materials Reviewed:

- DPMH consult request, dated May 24, 2021, DARRTS Reference ID 4800249.
- Applicant's submission, original new drug application, submitted December 30, 2020.

Consult Question: The Division of Cardiology and Nephrology (DCN) is in review of Diltiazem hydrochloride (calcium channel blocker) for temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter and rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. DCN requests DPMH-MHT assistance in the Pregnancy and Lactation subsections of the labeling as per PLLR.

INTRODUCTION AND BACKGROUND

On December 30, 2020, Exela Pharma Sciences, LLC submitted an original new drug application (NDA) for Diltiazem HCL injection. The proposed indications are:

- Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter.
- Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.

On May 24, 2021, DCN consulted DPMH to provide input to the Pregnancy and Lactation subsections of the labeling as per PLLR.

Regulatory History

The Diltiazem HCL, a calcium channel blocker, application was submitted for approval on December 30, 2020, under the 505(b)(2) pathway with drug relied upon Cardizem injectable, NDA 020027, approved on October 24, 1991, and held by Biovail Laboratory International SRL. Cardizem injectable was withdrawn (discontinued) on March 31, 2010. The applicant relied on FDA's findings for safety and effectiveness of Cardizem injectable for approval.

Drug Characteristics[1]

Drug Class	Calcium channel blocker
Molecular Weight	450.98 Daltons
Protein Binding	70-80%
Terminal Half-Life	2-5 Hours
Bioavailability	40%
Serious Adverse Reactions	Bradycardia or AV block, heart failure, acute hepatic injury, and severe skin reactions

[1] Based on proposed labeling by the applicant and verified by Clinical Pharmacology reviewer, H. Thanukrishnan.

REVIEW
PREGNANCY

Applicant's Review of Nonclinical Data[2]

The toxicity (carcinogenesis, mutagenesis, impairment of fertility or reproduction studies) of diltiazem has been characterized as per applicant in the December 30, 2020 submission, was based on the previous approved labeling of Cardizem injectable. There was no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day. Results from reproduction studies conducted in mice, rats and rabbits showed that administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. In the perinatal/postnatal studies, there was some reduction in early individual pup weight and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater. As per applicant, "Exela has reviewed relevant toxicology literature for diltiazem since its approval by searching PubMed and Medline databases and has found no additional toxicological profile to what previously had been reported."

Reviewer Comment:
DPMH in review of Reprotox[2] identified the following additional animal study information:

> *Diltiazem produced an increase in limb and tail malformations in rats and rabbits but no increase in malformations in mice[3]. Although some calcium blockers were associated with the induction of hyperphalangism in fetal rats, this effect was not found after diltiazem exposure.[4] Likewise, other calcium channel blockers increased the incidence of cardiovascular alterations in rat fetuses, but diltiazem did not.[5] The transfer of diltiazem and its active metabolites across the placenta has been demonstrated in rabbits.[6] In another rabbit study, chronic prenatal exposure to diltiazem impaired its own metabolism in offspring, a pharmacokinetic effect that also has been observed in adults receiving the drug.[7]*

In order to satisfy the PLLR content requirements for animal reproduction study descriptions, DPMH sought assistance from the DCN Nonclinical team for this 505(b)2 application to confirm the adverse developmental effects, the timing of maternal animal exposure, and type of studies conducted. Because Exela Pharma Sciences does not have access to these animal reproduction

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[2] Truven Health Analytics LLC. Micromedex/ReproTox
[3] Ariyuki F: Effects of diltiazem hydrochloride on embryonic development: species differences in susceptibility and stage specificity in mice, rats and rabbits. Okajimas Fol Anat Jpn 52:103-7, 1975. Cited in Shepard TH: Catalog of Teratogenic Agents, 7th Edition, Baltimore, Johns Hopkins University Press, 1992.
[4] Yoshida T, Tadegawa Y, Miyago M, Hasegawa Y: Hyperphalangism induced by Ca-blockers in rat fetuses. Teratology 40:668-9, 1989.
[5] Scott WJ Jr, Resnick E, Hummler H, Clozel JP, Burgin H: Cardiovascular alterations in rat fetuses exposed to calcium channel blockers. Reprod Toxicol 1997; 11: 207-14.
[6] Bregante MA, Aramayona JJ, Fraile LJ, Garcia MA, Solans C: Diltiazem blood pharmacokinetics in the pregnant and non-pregnant rabbit: maternal and foetal tissue levels. Xenobiotica 2000;30:831-41.
[7] Fraile LJ, Bregante MA, Garcia MA, Solans C: Altered diltiazem metabolism in the neonatal rabbit following intra-uterine chronic exposure to diltiazem. Xenobiotica 2001;31:177-85.

study data, the original data must be requested from the innovator, the Cardizem manufacturer, when the Cardizem labeling is under review for PLLR compliance. Therefore, for the Subsections 8.1 Pregnancy and 8.2 Lactation, DPMH labeling recommendations will reflect nonclinical data that is publicly available from the existing Cardizem labeling, with the understanding that Exela Pharma Sciences 505(b)2 product labeling will need to be updated accordingly once the Cardizem PLLR compliant labeling is approved.

Review of Clinical Data
Review of Literature

The applicant, Exela Pharma Sciences, did not provide a literature review on use of diltiazem during pregnancy, nor any pharmacovigilance (PV) review. During the drug development cycle, no pregnancies were identified. There is neither disease-based registry nor pregnancy registry for diltiazem for any indication; therefore, no interim of final reports exist.

DPMH conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for diltiazem use in pregnancy. Six relevant publications were identified. Table 1 below summarizes the studies and the outcomes reported.

Table 1: Publications on Diltiazem HCL and Pregnancy

Author and Year	Study Description	Time of Exposure	Drug	Outcome/Conclusion
Alablrazzaq F *et. al.*, 2012[8]	Population-based data from 5 health organizations in the United States, used to study the risks of perinatal complications and congenital defects among infants exposed in utero to calcium channel blockers (CCB)	Throughout pregnancy and third trimester	CCB	The authors concluded that CCBs have not been shown to increase teratogenic risk and that can be safely used during pregnancy and breastfeeding.
Bateman BT *et. al.*, 2015[9]	The Medicaid Analytic eXtract for the years 2000–2007 and included 2,529,636 completed pregnancies Controlled, population-based cohort study. 22908 (0.91%) pregnancies with exposure to CCB	The final month of pregnancy	CCB vs placebo	Neonatal seizures occurred in 53 (0.23%) neonates born to mothers exposed to CCB and in 4,609 (0.18%) neonates of unexposed women (unadjusted odds ratio [OR] 1.26, 95% confidence interval [CI] 0.96-1.65). After accounting for confounders, there was no increase in risk of neonatal seizures associated with CCB exposure (OR 0.95, 95% CI 0.70-1.30)
Bateman BT et. al., 2018[10]	A cohort study. Health registries in the 5 Nordic countries and the U.S. Medicaid database. Pregnant women, who have a diagnosis of hypertension, and have pregnancy outcomes of live birth.	3577 pregnant women with hypertension in the Nordic cohort and 14,900 in the U.S. cohort, 682 (19.1%) and 1668 (11.2%), respectively, were exposed to β-blockers in the first trimester; 107 (3%) and 700 (4.7%) were	First-trimester exposure to β-blockers was assessed	In a sensitivity analysis, overall malformations in infants exposed to beta-blockers versus CCB in the first trimester of pregnancy demonstrated similar risk for the Nordic cohort (RR, 1.01 [CI, 0.48 to 2.14]) and US cohort (RR, 1.22 [CI, 0.79 to 1.90]. For overall malformations, the adjusted relative risk (RR) for pregnancies exposed to β-blockers compared to pregnancies unexposed to any antihypertensive medication were 1.22 (95% CI, 0.88 to 1.71) for the Nordic cohort and

[8] Alabdulrazzaq F, Koren G, Facmt F., 746 Canadian Family Physician • Le Médecin de famille canadien | Fetal safety of calcium channel blockers [Internet]. [cited 2020 May 22]. Available from: www motherisk.org

[9] Bateman BT, Huybrechts KF, Maeda A, Desai R, Patorno E, Seely EW, et al., Calcium Channel Blocker Exposure in Late Pregnancy and the Risk of Neonatal Seizures HHS Public Access Author manuscript. Obs Gynecol. 2015;126(2):271–8.

[10] Bateman BT, Jørgensen UH,Einarsdóttir K, et. al. β-Blocker Use in Pregnancy and the Risk for Congenital Malformations: An International Cohort Study. Ann Intern Med. 2018 November 20; 169(10): 665–673

Author and Year	Study Description	Time of Exposure	Drug	Outcome/Conclusion
		exposed to CCB in the first trimester respectively		1.01 (CI, 0.80 to 1.27) for the US cohort.
Weber-Schoendorfer C *et. al.* 2008[11]	A multicenter (n=11), prospective observational study of the European Network of Teratology Information Services (ENTIS)	1st trimester of pregnancy	CCB exposed to vs unexposed (299 vs 806) 41 women took diltiazem	Major birth defects were not more common in the study group than in the control group. The authors concluded CCB during the first trimester of pregnancy do not represent a major teratogenic risk.
Khandelwal M. *et. al.*, 2002[12]	Retrospective data of pregnant women with chronic renal disease (chart review). 7 women		CCB (diltiazem) exposed to vs unexposed. The average duration of therapy with diltiazem was 20.5 ± 8.4 weeks.	The incidence of fetal growth restriction and need for labor induction were lower in the diltiazem-treated group. The authors concluded that diltiazem, decreases proteinuria and preserves renal structure and function and should be considered an alternative to angiotensin converting enzyme inhibitors in pregnancy in women with chronic renal disease.
Magee LA. *et. al.*, 1996[13]	A prospective, multicenter, cohort study 78 women	First-trimester exposure	First-trimester exposure to CCBs [most were nifedipine (44%), or verapamil (41%)]. Diltiazem 13%	There was no increase in major malformations (2/66 = 3.0% [CCBs] vs 0% [nonteratogenic controls], p = 0.27). The authors concluded that CCB do not represent a major teratogenic risk.

Reviewer Comment
All publications concluded that diltiazem and, in general, CCB do not cause any congenital malformations when administered during the 1st trimester of pregnancy or throughout

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[11] Weber-Schoendorfer C, Hannemann D, Meister R, Eléfant E, Cuppers-Maarschalkerweerd B, Arnon J, et al., The safety of calcium channel blockers during pregnancy: A prospective, multicenter, observational study. Reprod Toxicol. 2008 Sep;26(1):24–30.

[12] Khandelwal M, Kumanova M, Gaughan JP, Reece EA., Role of diltiazem in pregnant women with chronic renal disease. In: Journal of Maternal-Fetal and Neonatal Medicine. Parthenon Publishing Group Ltd; 2002. p. 408–12.

[13] MageeM L. Schick B, Donnenfeld AE *et. al.* The safety of calcium channel blockers in human pregnancy: A prospective, multicenter cohort study. Am. J Obstet Gynecol. 1996;174(3):823-8

pregnancy. No specific adverse reactions were identified. The available data failed to demonstrate a definitive association of adverse developmental outcomes and diltiazem use.

Micromedex/TERIS databases did not reveal any additional information. Briggs GG and Freeman RK in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, state that the limited human pregnancy data suggest that the risk is low, if it exists at all.

Reviewer Comment
The review of literature on diltiazem use in pregnant women has not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Summary
Rapid ventricular rate in atrial fibrillation or atrial flutter and paroxysmal supraventricular tachycardias (PSVT) occur mostly in older individuals and pose a significant risk, including death. Treatment of these conditions is urgent to save the life of the individual and treatment should not be withheld because of pregnancy. Review of the literature over 30 years of approved use has not demonstrated an association of adverse developmental outcomes with maternal use of diltiazem during pregnancy.

LACTATION
Nonclinical Data
From the Cardizem injectable labeling, reproduction studies had been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on mg/kg basis) than the daily recommended oral antianginal therapeutic dose had resulted in embryofetal lethality and skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weight and survival rates.

Review of Literature
The applicant did not provide any publications on lactation and use of diltiazem.

DPMH conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases, Briggs GG and Freeman RK in Drugs in Pregnancy and Lactation and Thomas Hale Medications and Mothers' Milk for diltiazem and use in lactation.
No adverse reactions have been reported to the breastfed infants. Hale reports a single patient receiving 240 mg/day on day 14 postpartum, levels in milk were parallel to those of serum (milk/plasma ratio is approximately 1).[14] The American Academy of Pediatrics classifies diltiazem as compatible with breastfeeding.[15]

Reviewer Comment
The limited clinical data was discussed with the DCN review team. It was determined that because this Diltiazem HCL injection would be administered to treat an urgent/life-threatening

[14] Okada M, Inoue H, Nakamura Y, Kishimoto M, Suzuki T. Excretion of diltiazem in human milk. N Engl J Med 1985; 312(15):992-993HIGHLIGHT
[15] Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108: 776-89.

condition by intravenous infusion for up to 24 hours, and the drug would clear systemic circulation within approximately 1 day (half-life 5 hours x 5) after final dosing, the considerations for breastfeeding would be left to the judgement of the treating physician.

Summary
Based on a single published case, diltiazem is present in human milk. No adverse reactions have been reported to the breastfed infant. Neither Briggs nor Hale recommend against breastfeeding during treatment with diltiazem. The American Academy of Pediatrics classifies diltiazem as compatible with breastfeeding. Therefore, for the clinical situation and short duration of use as this diltiazem HCl infusion requires, DPMH proposes the risk/benefit statement for the Lactation labeling subsection.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Data
As per Cardizem injectable labeling, no evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Review of Literature
The applicant did not provide any information/publications on the effects of diltiazem on human fertility. No PV data has been reported.
DPMH did not identify any publications with adverse effects of diltiazem on human fertility.
TERIS state

> Diltiazem increased the motility of human sperm in vitro.[16] Based on a small number of cases with unsuccessful in vitro fertilization, the use of verapamil and other calcium antagonists for hypertension control in men was associated with reversible male infertility.[17] Calcium plays important roles in sperm activation during fertilization. The inhibitory effects of calcium antagonists on sperm can occur at concentrations 2 to 4 orders of magnitude below the concentrations found in patients on long-term therapy.[17] Some investigators challenged the conclusion that calcium antagonists can impair male fertility in the absence of other factors.[18]

Summary
There is no evidence that diltiazem has any serious effect on sperm or oocyte or human fertility. There was no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats. In addition, review of the literature have not demonstrated an association of adverse developmental outcomes with maternal use of diltiazem during pregnancy. Therefore, the subsection 8.3 Females and Males of Reproductive Potential will be omitted from the labeling because there are no recommendations about pregnancy testing or contraception and no effects on fertility.

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[16] Hong CY et al: Calcium antagonists stimulate sperm motility in ejaculated human semen. Br J Clin Pharmacol 19:45-9, 1985.
[17] Benoff S, Cooper GW, Hurley I et al: The effect of calcium ion channel blockers on sperm fertilization potential. Fertil Steril 62:606-17, 1994.
[18] Katsoff D, Check JH: A challenge to the concept that the use of calcium channel blockers causes reversible male infertility. Hum Reprod 1997;12:1480-2.

CONCLUSIONS

Diltiazem HCL labeling has been edited to comply with the PLLR. DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below) and discussed labeling recommendations with the Division on August 30, 2021 and September 14, 2021. DPMH recommendations reflect Nonclinical input.

DPMH refers to the final NDA action for final labeling

RECOMMENDATIONS

DPMH has the following recommendations for Diltiazem HCL labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

(b) (4)

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/s/

TAMARA N JOHNSON
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Also signing for Christos Mastroyannis.

LYNNE P YAO
09/22/2021 09:41:39 AM

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:	June 28, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 215252
Product Name, Dosage Form, and Strength:	Diltiazem Hydrochloride in Dextrose Injection, 125 mg/ 125 mL and 250 mg/ 250 mL (1 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
FDA Received Date:	December 30, 2020 and March 17, 2021
OSE RCM #:	2021-61
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Exela Pharma Sciences, LLC submitted a 505(b)(2) for NDA 215252 Diltiazem Hydrochloride in Dextrose Injection on December 30, 2020. The reference Listed Drug (LD) is Cardizem Injectable (diltiazem hydrochloride injection, 5 mg/mL), NDA 020027. Diltiazem is a calcium-channel blocker proposed for the temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter and the rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. Exela Pharma Sciences, LLC is proposing 1 mg/mL with 125 mL and 250 mL fill volumes single dose bag presentations.

As part of the approval process we reviewed the proposed Prescribing Information (PI), container labels, overwrap labels, and carton labeling for areas of vulnerability that may lead to medication errors.

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

Exela Pharma Sciences, LLC submitted a 505(b)(2) for NDA 215252 Diltiazem Hydrochloride Injection. The reference Listed Drug (LD) is Cardizem Injectable (diltiazem hydrochloride injection, 5 mg/mL), NDA 020027. We note that the LD has been withdrawn FR Effective June 8, 2011 however, not for safety or efficacy concerns.

We note that while the proposed Diltiazem Hydrochloride in Dextrose Injection has the same indication, route of administration, dosage form, dose, frequency and storage as the LD, it differs in strength (1 mg/mL vs. 5 mg/mL) and presentation (b) (4) bag vs. glass vials).

We performed a risk assessment of the prescribing information (PI), carton labeling, container and overwrap labels to identify deficiencies that may lead to medication error and areas for improvement. We note the labeling did not specify the vehicle of the product. We confirmed

with the Office of Pharmaceutical Quality (OPQ) that the vehicle is 5% Dextrose. For the Division, we recommend inclusion of the vehicle in the product title and replacing abbreviations with intended meaning to prevent confusion. For the Applicant, we recommend revisions to the dosage statement, storage statement, and inclusion of the concentration of the vehicle for the drug product. We provide recommendations for the Division in 4.1 and for Exela Pharma Sciences, LLC in Section 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, container labels, overwrap labels and carton labeling can be improved from a medication error perspective. We provide recommendations for the PI for the division in 4.1 and the carton and container labeling for Exela Pharma Sciences, LLC in Section 4.2 below. We recommend they be implemented prior to the approval of NDA 215252.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

1. General Comments

    a. We recommend changing the official name from (b) (4) to "Diltiazem Hydrochloride in Dextrose Injection" throughout the PI in accordance with the January 2018 Product Title and Year of Approval Guidance.

    b. We note the use of the abbreviation of 'h' for hour throughout the PI. We recommend changing 'h' to 'hour' for clarity.

4.2 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES, LLC

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

A. General Comments (Container Labels, Overwrap Labels & Carton Labeling)

1. Per the draft guidance *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products – Content and Format* (line 1078-81), the concentration of the vehicle named in the official title is stated as part of the official title on the container label and carton labeling. Revise from "(b) (4)" to "Diltiazem Hydrochloride in 5% Dextrose Injection".

2. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4) on the container label and carton labeling to read "Recommended Dosage: See prescribing information."

3. Revise and bold the statement "**Store refrigerated at 2°C to 8°C (36°F to 46°F)**.". We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

4. We note that the strength statement on the overwrap for the 125 mL and 250 mL fill volume bags share the same color scheme (b) (4)

(b) (4). We recommend varying the color for each overwrap to differentiate the two volumes so that practitioners can choose the correct volume size.

B. Carton Labeling

1. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[a] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

[a] The draft guidance is available from: https://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Diltiazem received on March 17, 2021 from Exela Pharma Sciences, LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Diltiazem and the Listed Drug

Product Name	**Diltiazem**	**Cardizem[b]**
Initial Approval Date	N/A	October 24, 1991
Active Ingredient	Diltiazem Hydrochloride in Dextrose	diltiazem hydrochloride
Indication	• Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. • Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.	• Temporary control of rapid ventricular rate in Atrial fibrillation or atrial flutter. • Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	125 mg/ 125 mL and 250 mg/ 250 mL (1 mg/mL)	25 mg/5 mL and 50 mg/10 mL (5 mg/mL)
Dose and Frequency	Continuous Intravenous Infusion: • Immediately following bolus administration of 20 mg (0.25 mg/kg) or 25 mg (0.35 mg/kg) diltiazem hydrochloride injection and reduction of heart rate, begin an intravenous infusion. • Initial infusion rate of diltiazem hydrochloride is (b) (4) mg/h, rate may be increased in 5 mg/h increments up to 15 mg/h as needed if further reduction in heart rate is required. The infusion may be maintained for up to 24 hours.	Direct Intravenous Single Injections (Bolus): • 0.25 mg/kg actual body weight is a bolus administered over 2 minutes (20 mg is a reasonable dose for the average patient). If response is inadequate, a second bolus dose should be 0.35 mg/kg actual body weight administered over 2 minutes (25 mg is reasonable dose for the average patient). Subsequent intravenous bolus doses should be individualized for each patient. Patients with

[b] Prescribing Information for Cardizem received on December 30, 2020, available from: \\CDSESUB1\evsprod\nda215252\0001\m1\us\114-labeling\listed-drug-label\annot-comparison\annot-comparison-pi.docx

		low body weights should be dosed on a mg/kg basis. Some patients may respond to an initial dose of 0.15 mg/kg, although duration of action may be shorter. Continuous Intravenous Infusion • For continued reduction of the heart rate (up to 24 hours) in patients with atrail fibrillation or atrial flutter, an intravenous infusion of Cardizem may be administered immediately following bolus administration of 20 mg (0.25 mg/kg) or 25 mg (0.35 mg/kg). • The recommended initial infusion rate is 10 mg/h. • Some patients may maintain response rate of 5mg/h. The infusion rate may be increased in 5 mg/h increments up to 15 mg/h as needed, if further reduction in heart rate is required. The infusion may be maintained for up to 24 hours.
How Supplied	Diltiazem Hydrochloride Injection is supplied as a sterile, unpreserved, colorless solution in a single-dose (b) (4) bag containing 1 mg/mL of diltiazem: • 125 mg of diltiazem in 125 mL of solution (51754-3000-1) • 250 mg of diltiazem in 250 mL of solution (51754-3500-1)	Cardizem Injectable (diltiazem hydrochlonde injection) is supplied: • In boxes of six 5-mL vials with each vial containing 25 mg of diltiazem hydrochloride (5 mg/mL) (NDC 0088-1790-32) • In boxes of six 10-mL vials with each vial containing 50 mg diltiazem hydrochloride (5 mg/mL) (NDC 0088-1790-33). Cardizem Lyo-Ject Syringe 25-mg syringe is available in a dual chamber, disposable syringe. Chamber 1 contains lyophilized powder comprised of diltiazem hydrochloride 25 mg and mannitol USP 37.5 mg. Chamber 2 contains

		sterile diluent composed of 5 mL water for injection with 0.5% benzyl alcohol NF, and 0.6% sodium chloride USP. Cardizem Monovial (diltiazem hydrochloride for injection), after reconstitution in an infusion bag, produces a clear, colorless, sterile nonpyrogenic solution. Cardizem Monovial for continuous intravenous infusion is available in a glass vial with transfer needle set. The vial contains lyophilized powder comprised of diltiazem hydrochloride 100 mg and mannitol USP 75 mg.
Storage	Store under refrigeration at 2°C to 8°C (36°F to 46°F). The single-dose bags in their original pouches are stable for up to one month at room temperature without significant loss of potency.	Store product under refrigeration 2-8°C (36-46°F) Do not freeze. May be stored at room temperature for up to 1 month. Destroy after 1 month at room temperature. Single-use containers discard unused portion.
Container Closure	Single-dose (b) (4) bag sealed with a (b) (4) port and (b) (4)	Glass vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 21, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, diltiazem, NDA 215252 and Exela. Our search did not identify any previous reviews applicable to this current review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

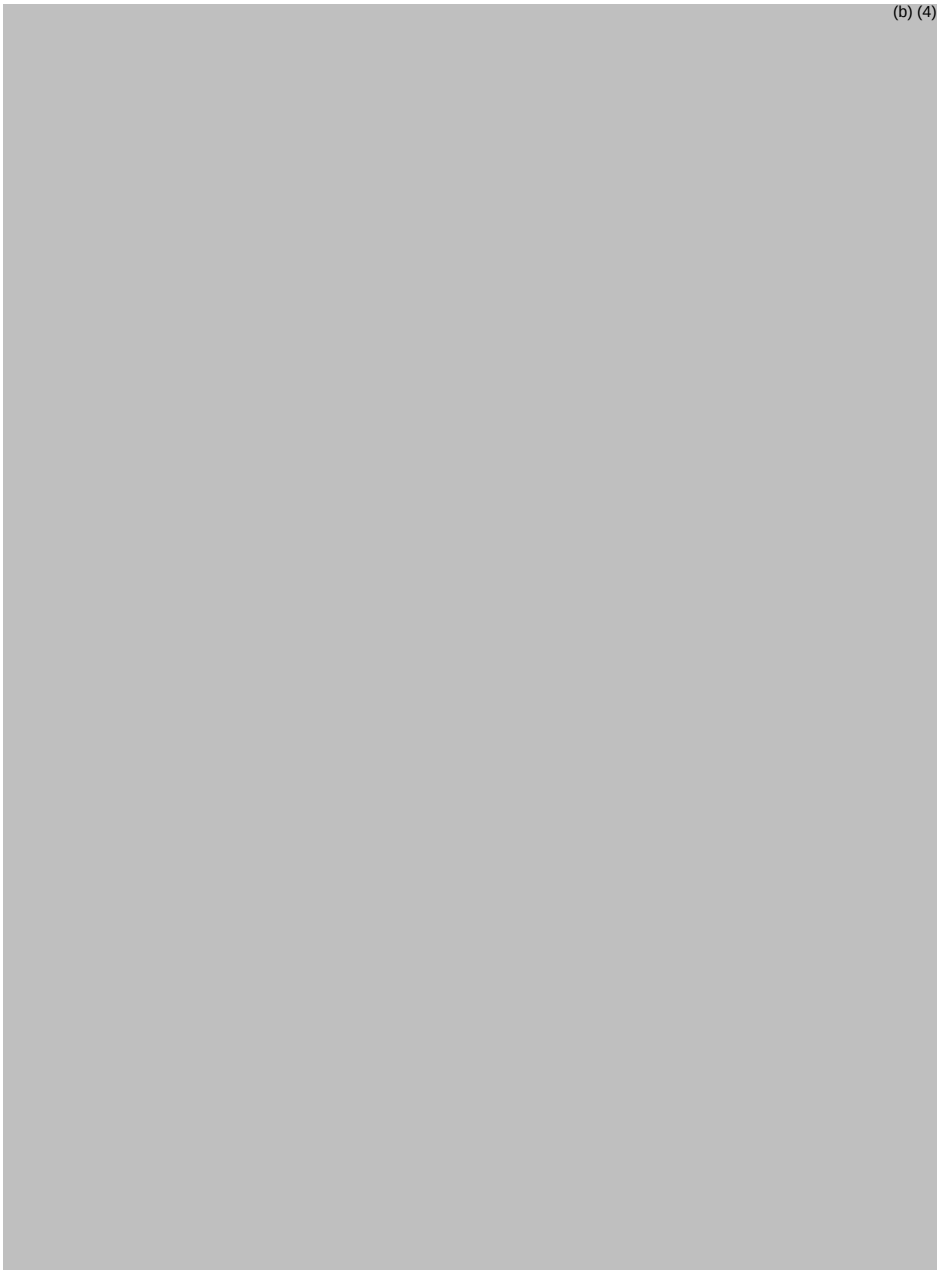
Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following labels and labeling submitted by Exela Pharma Sciences, LLC.

- Container label received on December 30, 2021
- Carton labeling received on December 30, 2021
- Prescribing Information (Image not shown) received on March 17, 2021, available from:
    - Clean: \\CDSESUB1\evsprod\nda215252\0005\m1\us\114-labeling\draft-labeling\draft-label-text\packageinsert\draft-labeling-text-package-insert-clean-pdf-0005.pdf
    - Tracked: \\CDSESUB1\evsprod\nda215252\0005\m1\us\114-labeling\draft-labeling\draft-label-text\packageinsert\draft-labeling-text-package-insert-track-changes-pdf-0005.pdf

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

G.2 Label and Labeling Images

Container Labels:



5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MAXIMILIAN STRAKA
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06/29/2021 02:05:18 PM