CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214652Orig1s000

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:	August 16, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214652
Product Name and Strength:	Atropine Sulfate injection, 0.4 mg/mL, 1 mg/mL
Applicant/Sponsor Name:	Accord Healthcare Inc.
OSE RCM #:	2020-636-1
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Accord submitted revised container label and carton labeling received on September 3, 2020 for Atropine Sulfate Injection. We reviewed the revised container label and carton labeling for Atropine Sulfate Injection (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]

We note Accord stated "The blister labels are continuous printed blister labels i.e. blister is printed in a continuous manner in the direction of flow of the web through the machine. Hence, any one label coming out of the machine would have repeat text, appearing in a predetermined format continuously through the length of the blister." The Applicant ensures that there will not be any required label text missing in a specific blister and every blister will be having required text, however due to the nature of the printing process and the medical kraft paper foil to be used for blister label, there are chances of Print Registration Control (PRC) disturbances which will lead to concern of frequent machine stoppage and therefore the Applicant requests the agency to grant an exemption from realigning the blister labels so that only one complete label is present on each blister.

[a] Straka, M. Label and Labeling Review for Atropine Sulfate Injection (NDA 214652). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 17. RCM No.: 2020-636.

We issued an Information Request (IR) on September 10, 2020[b] asking:

"How will the blister foil labels be incorporated in the packaging of the 0.4 mg/mL and 1 mg/mL vials."

The Applicant replied on September 14, 2020[c] stating that:

"The drug product vial holding preprinted container labels will be packed in a blister having preprinted blister labels. These blisters will be further packed into preprinted carton of Atropine Sulfate Injection, USP 0.4 mg/mL, 1 mL and 1 mg/mL, 1 mL as per the pack style i.e. 10 vials per carton or 25 vials per carton (see Appendix A for images). In case of single vial carton, drug product vial holding preprinted container label will be packed directly into preprinted carton of Atropine Sulfate Injection, USP 0.4 mg/mL, 1 mL and 1 mg/mL, 1 mL." As each container vial will be labeled appropriately and then will be packed in a preprinted blister containing the same label information, we do not have any concerns with the Applicant's proposal.

2 CONCLUSION

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

[b] Nguyen, Q. FDA Communication for: "NDA 214652/Atropine Sulfate Injection, USP - Additional FDA Labeling Comments and DMEPA Information Request" Message to Sabita Nair. Silver Spring (MD): FDA, CDER, OND, DCN (US); 2020 SEP 10.

[c] Response to Additional FDA Labeling Comments and DMEPA Information Request for NDA 214652/ Atropine Sulfate Injection, USP. Durham (NC). 2020 SEP 14. Available from: \\CDSESUB1\evsprod\nda214652\0010\m1\us\response-0010.pdf

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/s/

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

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

Memorandum

Date: August 24, 2020

To: Quynh M. Nguyen, PharmD, RAC, 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 Atropine Sulfate Injection, for intravenous use

NDA/BLA: 214652

In response to DCN's consult request dated May 28, 2020, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for ATROPINE SULFATE INJECTION, for intravenous use.

Labeling: OPDP has reviewed the attached draft labeling received by electronic mail (link to SharePoint) from DCN (Quynh Nguyen) on August 18, 2020, and we have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 8, 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
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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
Tel 301-796-2200
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PLLR Labeling Memorandum

Date: August 17, 2020 **Date consulted:** July 13, 2020

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

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

To: Quynh M. Nguyen, Regulatory Project Manager (RPM)
Division of Cardiology and Nephrology (DCN)

Drug: Atropine Sulfate Injection, USP

NDA: 214652

Applicant: Accord Healthcare Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For temporary blockade of severe or life-threatening muscarinic effects

Materials Reviewed:

- NDA 214652 submission dated March 31, 2020.
- Applicant's response to information request (IR) dated July 8, 2020.
- DPMH Review of Atropine Sulfate Injection (NDA 209260) by Kristie Baisden, DO, dated September 14, 2017. DARRTS Reference ID: 4160393.[1]

[1]The cross-reference to the Atropine Sulfate Injection (NDA 209260) consult is included to avoid duplicating background information relevant to this class of products. DPMH's recommendations for the Atropine Sulfate Injection (NDA 214652) labeling discussed below are based solely on information from literature that is not specific to a particular atropine product.

Consult Question: DCN requests DPMH "please review the proposed package insert regarding the PLLR sections. The applicant has proposed novel language about atropine crossing the placenta (b) (4) ."

INTRODUCTION

On March 31, 2020, the applicant, Accord Healthcare Inc., submitted a new drug application (NDA 214652) for Atropine Sulfate Injection, USP via the 505(b)(2) regulatory pathway. On July 13, 2020, the Division of Cardiology and Nephrology (DCN) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- This 505(b)(2) application is relying on the FDA-approved drug Atropine Sulfate Injection (NDA 021146), Hospira Inc., which was approved on July 9, 2001 based on the published literature.
- The active ingredient atropine sulfate received initial U.S. market approval in 1960.
- Atropine is a muscarinic antagonist indicated for temporary blockade of severe or life-threatening muscarinic effects, e.g., as an antisialaogue, an antivagal agent, an antidote for organophosphorus or muscarinic mushroom poisoning, and to treat bradyasystolic cardiac arrest.
- On June 10, 2020, the Agency sent the applicant an information request (IR) to submit revised labeling and provide a review of available information regarding use of atropine in pregnant women, lactating women, and females and males of reproductive potential.
- On July 8, 2020, the applicant submitted the requested information.

Drug Characteristics[2]

- *Mechanism of action*: an antimuscarinic agent since it antagonizes the muscarinic-like actions of acetylcholine
- *Description*: a sterile, nonpyrogenic isotonic solution of atropine sulfate monohydrate in water for injection with sodium chloride sufficient to render the solution isotonic.
- *Dosage and administration:* for intravenous administration. Titrate according to heart rate, PR interval, blood pressure, and symptoms.
    - Adult dosage:
        - Antisialagogue or for antivagal effects: initial single dose of 0.5 mg to 1 mg.
        - Antidote for organophosphorus or muscarinic mushroom poisoning: initial dose of 2 mg to 3 mg, repeated every 20-30 minutes.
        - Bradysystolic cardiac arrest: 1 mg dose, repeated every 3-5 minutes if asystole persists.

[2] Atropine Sulfate Injection (NDA 021146) currently approved labeling, dated June 24, 2020.

    - Pediatric dosage: dosing in pediatric populations has not been well studied. Usual initial dose is 0.01 to 0.03 mg.
- *Dosage forms and strength:* 0.4mg/mL and 1 mg/mL injection in Glass Vial which differs from the RLD (0.05 mg/ and 0.1 mg/mL injection in Ansyr Plastic Syringes and 0.1 mg/mL injection in LifeShield Abboject Glass Syringes).
- *Warnings and Precautions*: tachycardia, acute glaucoma, pyloric obstruction, complete urinary retention, viscid plugs.
- *Adverse reactions*: dry mouth, blurred vision, photophobia, and tachycardia.
- *Elimination half-life*: 4.3 hours in adults, more than doubled in children < 2 years old.
- *Molecular weight:* approximately 289 Daltons.
- *Protein binding*: 44%.

Condition- Severe or life-threatening Muscarinic Events and Pregnancy

- *Organophosphate (OP) Poisoning:* The World Health Organization (WHO) estimates up to 3 million people worldwide are affected by pesticide poisoning yearly, with acute organophosphate pesticide poisoning (AOPP) being the most common type.[3] The case fatality rate in women is >15%. [4] AOPP is life-threatening for the pregnant woman and fetus due to the placental transfer of organophosphates. Early recognition and treatment of AOPP in pregnancy reduces the risk of maternal death and spontaneous abortion or stillbirth. The main drug therapy is atropine to counteract effects of accumulated acetylcholine.

- *Bradyasystolic Cardiac Arrest:* Cardiac arrest in pregnancy is rare, approximately 1:12,000 delivery admissions.[5] The estimated rate of survival to hospital discharge is 58.9%.[6] Resuscitation in pregnancy is similar to adult resuscitation, with the fetus as an additional consideration. Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS) guidelines are followed with manual uterine displacement and discontinuation of fetal monitoring. Perimortem cesarean delivery is done if no recovery after 4 minutes for fundal heights at or above the umbilicus to assist maternal resuscitation and improve survival for viable fetuses.[7] Atropine was removed from the 2010 AHA guidelines for ACLS cardiac arrest algorithm and is indicated only for bradycardia cases.[8]

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[3] Sun et al. Clinical management of organophosphate poisoning in pregnancy. American Journal of Emergency Medicine 33 (2015) 305.e1-305.e3

[4] Eddleston M, et al. Management of acute organophosphorus pesticide poisoning. Lancet. 2008. 371:597-607.

[5] Hess et al.Whats New in Ob Anesthesia:2016 Gerald Ostheimer Lecture. Anesth.& Analgesia 2017.124(3):863-71

[6] Mhyre JM et al. Cardiac arrest during hospitalization for delivery in the United States, 1998-2011. Anesthesiology. 2014; 120:810-818.

[7] Jeejeebhoy et al. Cardiac arrest in pregnancy: A scientific statement from the American Heart Association. Circulation. 2015. 132 (18): 1747-1773.

[8] Neumar et al. Part 8L: Adult advanced cardiovascular life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2011; 123:e236.

Current State of the Labeling[2]
Atropine Sulfate Injection (NDA 021146), the listed drug relied upon, currently approved labeling is in the Physician Labeling Rule (PLR) format but is not in PLLR format.

- *8.1 Pregnancy:* Animal reproduction studies have not been conducted with atropine. It is also not known whether atropine can cause fetal harm when given to a pregnant woman or can affect reproduction capacity.

- *8.3 Nursing Mothers:* Trace amounts of atropine was found in breast milk. The clinical impact of this is not known.

- *12.3 Pharmacokinetics*: Atropine readily crosses the placental barrier and enters the fetal circulation, but is not found in amniotic fluid.

DATA REVIEW
PREGNANCY
Nonclinical Experience[2]
Animal reproduction studies have not been conducted with atropine.

Clinical Experience
Applicant's Review of the Published Literature
The applicant performed a search in PubMed using terms "atropine and pregnancy" with the species filter of "human" and the article type filter of "clinical trials, randomized controlled trials, meta-analysis, review and systematic reviews" which identified a total of 55 articles. An additional search was performed in ScienceDirect using terms "atropine and pregnancy" with the filter "title, abstract, and author specific keyword search" which identified a total of 38 articles.

From these articles, the applicant provided a summary of the information that was found to be relevant to atropine use during pregnancy. This Reviewer notes the applicant submitted review articles and several studies that were already previously reviewed by DPMH in 2017 (see Appendix A Table 1 for details).[9] The applicant also submitted additional pharmacokinetic studies describing the placenta transfer of atropine.[10, 11,12,13]

[9] DPMH Review of Atropine Sulfate Injection (NDA 209260) by Kristie Baisden, DO, dated September 14, 2017. DARRTS Reference ID: 4160393.
[10] Kanto J, et al. Pharmacokinetic implications for the clinical use of atropine, scopolamine and glycopyrrolate. Acta Anaesthesiol Scand 1988:32:69-78.
[11] Shutt LE et al. Atropine and hyoscine. Anaesthesia 1979; 34:476-490.
[12] Klvalo I, et al. Placental transmission of atropine at full term pregnancy. Br J Anaesth 1977; 49:1017-1021.
[13] Rowell PP, et al. The influence of cholinergic blockade on the uptake of alfa-aminoisobutyric acid by isolated human placental villi. Toxicol Appl Pharmacol 1978; 45:79-93.

DPMH's Review of the Published Literature
Clinical experience on atropine use in pregnancy was previously reviewed by DPMH in 2017.[9] DPMH concluded the following:

> There are no adequate and well-controlled studies evaluating atropine use in human pregnancy. Limited data based on observational studies and case reports do not show evidence for an association with atropine use and congenital malformations, but are insufficient to exclude risk. Animal reproduction studies have not been performed to current standards therefore will not be included in the labeling as per discussion with the Pharmacology/Toxicology Review Team. Atropine crosses the placenta and may affect fetal heart rate and breathing though no adverse outcomes are reported.

This Reviewer performed a focused literature search in PubMed, Embase, Micromedex[14], TERIS[15], Reprotox[16], and Briggs[17] to find any relevant articles published since the most recent DPMH PLLR Review of atropine in 2017. Search terms included: "atropine" AND "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," OR "miscarriage." No additional relevant articles were identified.

Reviewer's Comment
DCN requested DPMH evaluate the applicant's proposal to include pharmacokinetic studies related to the placental transfer of atropine in subsection 8.1 of labeling. DPMH notes subsection 12.3 of currently approved labeling for the listed drug includes a statement that atropine readily crosses the placenta. The 2017 DPMH review on atropine use during pregnancy noted the following regarding placental transfer of atropine:

> *Published literature indicates atropine crosses the placenta leading to fetal exposure. The effects observed on fetal heart rate appear to be a transient mild tachycardia. The reported decreased fetal breathing is also transient and has not been shown to induce fetal hypoxia. These short term fetal side effects associated with maternal administration of atropine have not been shown to impact the fetus adversely.*

Considering Atropine Sulfate Injection is indicated for acute short-term use for life-threatening conditions, DPMH recommends subsection 8.1 emphasize the potential benefit of treatment for the pregnant woman and fetus. Therefore, DPMH recommends including a Clinical Consideration that life-sustaining therapy for the pregnant woman should not be withheld due to potential concerns regarding the effects of atropine on the fetus. A statement noting that atropine crosses the placenta can also be included in 8.1.

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[14]Truven Health Analytics information, http://www micromedexsolutions.com Accessed 8/10/20
[15]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 810/20.
[16]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 8/10/20.
[17] Briggs GG, et al. Drugs in Pregnancy and Lactation: A Reference Guide , 9th Ed. 2011.

LACTATION

Nonclinical Experience

Animal lactation studies have not been performed with atropine.

Clinical Experience

Applicant's Review of the Published Literature

The applicant performed a search in PubMed using terms "atropine and lactation" AND "atropine and breastfeeding" which identified a total of 12 articles. An additional search was performed in ScienceDirect using terms "atropine and lactation in humans" with the filter "title, abstract, and author specific keyword search" of "atropine" which identified a total of 16 articles.

From these articles, the applicant provided a summary of the information that was found to be relevant to atropine use during lactation. This Reviewer notes no new relevant clinical information was identified in the applicant's submission since the previous DPMH review of published literature for atropine use during lactation in 2017.[9]

DPMH's Review of the Published Literature

Clinical experience on atropine use during lactation was previously reviewed by DPMH in 2017.[9] DPMH concluded the following:

> Trace amounts (<0.1 mg/100mL) of atropine have been reported in lactating women after oral intake. Atropine levels in human milk after intravenous administration have not been studied. The amount of atropine absorbed by the breastfed infant and the potential effects of such are not known. Since the elimination half-life of atropine is doubled in children less than 2 years of age, DPMH recommends lactating women consider pumping and discarding breastmilk for 24 hours [based on approximately 5-6 half-lives] following the last dose of Atropine Sulfate Injection to minimize potential infant exposure. There is no available data regarding the effect of atropine on milk production.

This Reviewer performed a focused search in Briggs[17], *Medications and Mother's Milk*[18], LactMed[19], Micromedex[14], Reprotox[16], PubMed, and Embase to find any relevant articles published since the most recent DPMH PLLR Review of atropine in 2017. Search terms included: "atropine" AND "lactation" OR "breastfeeding." No relevant articles were identified.

Reviewer's Comment

DCN requested DPMH evaluate the applicant's proposal to include a statement in subsection 8.2 of labeling that atropine use may suppress lactation. As noted in the 2017

[18] Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.

[19] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 8/10/20

DPMH review of published literature on atropine use during lactation, according to the LactMed database "no information is available on the use of atropine during breastfeeding. Long-term use of atropine might reduce milk production or milk letdown, but a single systemic dose is not likely to interfere with breastfeeding.[19] Anticholinergic drugs can reduce serum prolactin in nonnursing women.[20] The prolactin level in a mother with established lactation may not affect her ability to breastfeed."

Considering Atropine Sulfate Injection is indicated for short-term acute use rather than long-term use, DPMH recommends including a statement in subsection 8.2 of labeling that there are no available data on the effects of atropine on milk production.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience[2]

Animal fertility studies have not been performed with atropine.

Clinical Experience

Applicant's Review of the Published Literature

The applicant performed a search in PubMed using terms "atropine and fertility" with the applied filter of "humans" which identified a total of 20 articles. An additional search was performed in ScienceDirect using terms "atropine and fertility" with the filter "title, abstract, and author specific keyword search" of "atropine" which identified a total of 27 articles. From these articles, the applicant provided a summary of the information that was found to be relevant to atropine use and effects on fertility. DPMH notes no clinical information was submitted, only nonclinical information and defers this review to the DCN Pharmacology/Toxicology Review Team.

The applicant subsequently performed a search in PubMed using terms "atropine and females and males of reproductive potential" with the applied filter of "humans" which identified a total of 4 articles. An additional search was performed in ScienceDirect using terms "atropine and females and males of reproductive potential" with the filter "title, abstract and author specific keyword search" of "atropine" which identified a total of 16 articles. From these articles, the applicant provided a summary of the information that was found to be relevant to atropine use and effects on males and females of reproductive potential. This Reviewer notes only 1 clinical article was submitted as follows:

- Women (n=43,740) from the EFEMERIS cohort, a French database were evaluated for the potential effect of *in utero* exposure to drugs with atropinic properties on infant psychological development using atropinic burden (AB) scales. Overall, 34% (n=14,925) of women received at least one atropinic drug during pregnancy. At 24 months, more infants of mothers with AB $\geq$ 1 had difficulties to "name a picture" (OR 1.18, 95% CI 1.03-1.36) and to 'understand instructions' (OR 1.61, 95% CI 1.13-2.30) compared with infants of unexposed women. The results indicated a significant association between *in utero* exposure

[20] Masala A, et al. Muscarinic receptor blockade by pirenzepine: effect on prolactin secretion in man. J Endocrinol Invest. 1982;5:5:53-5.

to drugs with atropinic properties and fewer infant cognitive acquisitions at 24 months.[21]

Reviewer's Comment
The above database study evaluated drugs with atropinic properties rather than specifically evaluating the effects of atropine exposure during pregnancy. The most commonly prescribed substances with atropinic properties in this study were domperidone (47% of exposed women), metopimazine (25%), cetirizine (11%), oxomemazine (7%), and ranitidine (4%).

Overall, no new relevant clinical information was identified in the applicant's submission since the previous DPMH review of published literature for atropine use and effects on fertility in 2017.[9]

DPMH's Review of the Published Literature
Clinical experience on atropine use and potential effects on fertility was previously reviewed by DPMH in 2017.[9] DPMH concluded the following:

> There are no human data available regarding the effect of atropine on fertility. Animal reproduction studies from the published literature do not meet current standards, thus the quality and reliability of these studies cannot be evaluated. Therefore, the data from these nonclinical studies will not be included in labeling as per discussion with the Pharmacology/Toxicology Review Team. DPMH recommends section (b) (4)

This Reviewer performed a focused search in PubMed, Embase, and Reprotox[16] to find any relevant articles published since the most recent DPMH PLLR review of atropine in 2017. Search terms included: "atropine" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No relevant articles were identified.

DISCUSSION/CONCLUSIONS
Pregnancy
No adequate and well-controlled studies are available regarding the use of atropine in pregnant women. Available data from published observational studies have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, these studies are insufficient to exclude risk. Animal reproduction studies have not been performed to current standards. Therefore, DPMH recommends subsection 8.1 of labeling include a Risk Summary statement and Human Data section to describe the available published data as well as methodological limitations of the studies.

Available data from published pharmacokinetic studies indicate that atropine crosses the placenta and may affect fetal heart rate and breathing although no adverse outcomes are reported. Considering Atropine Sulfate Injection is indicated for acute life-threatening conditions, DPMH recommends including a Clinical Consideration to emphasize that

[21] Beau AB, et al. Atropinic burden of drugs during pregnancy and psychological development of children: a cohort study in the EFEMERIS database. Br J Clin Pharmacol 2016; 82:478-486.

treatment should not be withheld due to pregnancy. Further, DPMH recommends omitting the background risk statements for major birth defects and miscarriage in the general population and indicated populations which are not relevant to this product considering the acute life-threatening emergency indications for which treatment should not be withheld due to pregnancy.

Lactation

Trace amounts of atropine have been reported in the published literature in lactating women after oral intake. However, atropine levels in human milk after intravenous administration have not been studied. The amount of atropine absorbed by the breastfed infant and the potential effects of such are not known. Since the elimination half-life of atropine is doubled in children less than 2 years of age, DPMH recommends including a Clinical Consideration in subsection 8.2 of labeling for lactating women to consider pumping and discarding breastmilk for 24 hours (based on approximately 5-6 half-lives) following the last dose of Atropine Sulfate Injection to minimize potential infant exposure.

There are no available data regarding the effect of short-term use of intravenous atropine on milk production. Considering atropine is an anticholinergic drug, long-term use may reduce milk production; however, a single systemic dose is not likely to interfere with breastfeeding. Therefore, DPMH recommends including a statement in subsection 8.2 of Atropine Sulfate Injection labeling that there are no available data on the effects of atropine on milk production. DPMH recommends omitting the risk/benefit statement from subsection 8.2 of labeling, considering Atropine Sulfate Injection is indicated for acute life-threatening emergencies and should not be withheld due to lactation.

Fertility

DPMH recommends (b) (4)

DPMH did not identify any clinical data to suggest atropine use has an adverse effect on fertility. Pregnancy testing and contraception headings will not be included because the available human data on atropine use in pregnancy do not suggest an increased risk of major congenital malformations or miscarriage.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of Atropine Sulfate Injection labeling for compliance with the PLLR (see below). DPMH discussed the labeling recommendations below with DCN at the August 18, 2020 labeling meeting. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Atropine Sulfate Injection Pregnancy and Lactation Labeling
FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary

There are risks to the mother and fetus associated with untreated severe or life threatening muscarinic events *(see Clinical Considerations).* Available data from published observational studies on atropine use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data).* Animal reproduction studies have not been conducted with atropine.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Severe or life-threatening muscarinic events such as acute organophosphate poisoning and symptomatic bradycardia are medical emergencies in pregnancy which can be fatal if left untreated. Life-sustaining therapy for the pregnant woman should not be withheld due to potential concerns regarding the effects of atropine on the fetus.

Data

Human Data

Atropine crosses the placenta *[see Clinical Pharmacology (12.3)]*. No adequate and well-controlled studies are available regarding use of atropine in pregnant women. In a cohort study of 401 pregnancies in the first trimester and 797 pregnancies in the second or third trimester, atropine use was not associated with an increased risk of congenital malformation. In a surveillance study, 381 newborns were exposed to atropine during the first trimester; 18 major birth defects were observed when 16 were expected. No specific pattern of major birth defects was identified. In another surveillance study of 50 pregnancies in the first trimester, atropine use was not associated with an increased risk of malformations. Methodological limitations of these observational studies including the inability to control for the dosage and timing of atropine exposure, underlying maternal disease, or concomitant maternal drug use, cannot definitively establish or exclude any drug associated risk during pregnancy.

8.2 Lactation

Risk Summary

Trace amounts of atropine have been reported in human milk after oral intake. There are no available data on atropine levels in human milk after intravenous injection, the effects on the breastfed infant, or the effects on milk production.

Clinical Considerations

Minimizing exposure

The elimination half-life of atropine is more than doubled in children less than 2 years of age *[see Clinical Pharmacology (12.3)]*. To minimize potential infant exposure to Atropine Sulfate Injection, a woman may pump and discard her milk for 24 hours after use before resuming to breastfeed her infant.

APPENDIX A

Table 1: Pregnancies Exposed to Atropine Reported in the Published Literature

Reference	Drug, Dose, Route	Study Design	Pregnant Subjects	Exposure Timing	Exposure Duration	Results/Outcomes
Collaborative Perinatal Project (1959-1974) Heinonen et al., 1977[22]	Atropine (dose not reported)	Prospective Cohort	401 797	1st trimester 2nd or 3rd trimester	Not reported	No evidence for an association with atropine and major or minor malformations in any trimester. *Possible association with parasympatholytic class (2,323 exposures) and minor malformations. *Reviewer's comment: details on the type of minor malformations are not provided by author.*
Michigan Medicaid Study (1985-1992) Rosa 1993[23]	Atropine (dose not reported)	Surveillance	381	1st trimester	Not reported	18 (4.7%) major birth defects in the atropine exposed population versus 16 (4.2%) expected in the general population. Details available for 6 defects (observed/expected) 4/4 cardiac defects, 0/0.5 clefts, 1/0 spina bifida, 2/0 polydactyly, 1/1 hypospadias, 2/0 limb reduction defects. *Only with limb defects was there a possible association, but factors such as mother's disease, other drug use, and chance may be involved.
Siebert et al., 1989[24]	*Lomotil* Atropine and diphenoxylate	Case Report	1	10th week gestation	Not reported	Female infant born at 36w with Ebstein's anomaly, hypertelorism, epicanthal folds, low-set posteriorly rotated ears, cleft uvula, medially rotated hands, deafness, and blindness. *Timing of exposure was beyond the susceptible stages of development for these defects.
Onnen et al., 1979[25]	12.5ug/kg IV Atropine	Prospective: Atropine placental transfer	73	3rd trimester in labor	Single Dose	-Placental transfer of atropine noted in all cases. -Fetal/maternal blood concentration ratio was 1.2+/-0.5 at 5-15 min -Fetal tachycardia (12+/- 5 beats/min from baseline) after 15 min which lasted 25-50 min.
Kanto et al., 1981[26]	0.01 mg/kg IV or IM Atropine	Prospective: Atropine placental transfer	44 n=32 IV n=12 IM	3rd trimester prior to C-section	Single Dose	Placental transfer with apparent fetal uptake noted after both IV and IM atropine. -Atropine was detected in umbilical cord blood -No atropine was noted in the amniotic fluid.
Abboud et al., 1983[27]	0.01mg/kg IV Atropine	Prospective: Effects of Atropine vs. Glycopyrrolate	10 per group	3rd trimester in labor	Single Dose	-Maternal heart rate increased in both groups. -No change in maternal blood pressure. -No statistically significant changes were noted in fetal heart rate or variability for either group.

[22]Heinonen OP et al. Birth Defects and Drugs in Pregnancy. Littleton, MA: Published Sciences Group, 1977.

[23]F. Rosa, Personal communication, FDA, 1993. Cited in: Briggs GG et al. Drugs in Pregnancy and Lactation:
A Reference Guide to Fetal and Neonatal Risk, 7th ed. Philadelphia, PA: Lippincott Williams&Wilkins, 2005.

[24]Siebert et al. Ebstein's anomaly and extracardiac defects. Am J Dis Child 1989; 143:570-2.

[25]Onnen et al. Placental transfer of atropine at the end of pregnancy. Eur J Clin Pharmacol 1979; 15:443-6

[26] Kanto et al. Placental transfer and Pharmacokinetics of atropine after single maternal intravenous and intramuscular administration. Acta Anaesth Scand. 1981; 25, 85-88.

[27] Abboud et al. Fetal and maternal CV effects of atropine and glycopyrrolate. Anesth Analg. 1983; 62(4):426-30

Reference	Drug, Dose, Route	Study Design	Pregnant Subjects	Exposure Timing	Exposure Duration	Results/Outcomes
Dow et al., 1978[28]	0.6mg IV Atropine	Prospective: Effect on the Lower Esophageal Sphincter	10 with heartburn 10 without heartburn 8 controls	3rd trimester	Single Dose	Atropine demonstrated an adverse effect on the competency of the LESP both in pregnancy and the nonpregnant state.
Boston Collaborative Jick et al., 1981[29]	*Lomotil* Atropine and Diphenoxylate	Surveillance	50	1st trimester	Not reported	Atropine was not associated with an increased risk of congenital malformations.
Adhikari et al., 2011[30]	2mg IV atropine, doubled every 5-10min until symptoms relieved	Retrospective: Organophosphate Poisoning	21	12-20wks (7 of 21) 21-28wks (5 of 21) >28wks (6 of 21)	Variable (min 24h)	*Maternal*: 15 women had no pregnancy or delivery complications, 2 died during acute stages of poisoning, 5 required ventilator care *Fetal*: 2 preterm births and 13 term births (all 15 infants were healthy with normal Apgars), 1 spontaneous abortion at 10 weeks, no congenital abnormalities. *3 patients were lost to follow up
Solomon et al., 2007[31]	2mg IV atropine every 10-15min (total 30mg IV atropine)	Case report: Organophosphate Poisoning	1	29 weeks	48 hours	*Maternal*: survived, went into preterm labor 2 days after event *Fetal*: premature birth at 29 weeks, Apgars 6/8, but died 2 days later from prematurity and hyaline membrane disease.
Rayyan et al., 2005[32]	2 boluses IV atropine, then infusion 0.015mg/kg/h	Case report: Organophosphate Poisoning	1	40weeks	40 hours	*Maternal*: full recovery Fetal: live infant, Apgars 5/7, admitted to NICU with pesticide poisoning, fully recovered. Both discharged home on day 11.
Kamha et al., 2005[33]	2mg atropine IV q 15min, (total 240mg)	Case report: Organophosphate Poisoning	1	26weeks	40 hours	*Maternal*: recovered in 7 days, followed by uncomplicated delivery 12 weeks later at term *Fetal*: healthy infant, Apgars 9/10
Pan et al., 2004[34]	1mg IV atropine	Case report: Asystole after Spinal-Epidural	1	34weeks	Single Dose	*Maternal*: full recovery, forceps delivery *Fetal*: preterm healthy infant, Apgars 8/8 Both discharged home in 2 days.
Shah et al., 1995[35]	Total 83 mg IV atropine	Case Report: Organophosphate Poisoning	1	3rd trimester	28hours	*Maternal*: full recovery, vaginal delivery *Fetal*: normal Apgars. Neonatal mydriasis at birth which resolved after 3 days.
Karalliedde et al., 1988[36]	Total 64 mg IV atropine Atropine dose not reported	2 Case Reports: Organophosphate Poisoning	1 1	36 weeks 16weeks	24hours Not reported	*Maternal*: mechanical ventilation x 6days then fully recovered. *Fetal*: healthy term infant, Apgar 8 at 1min *Maternal*: mechanical ventilation x 9days then fully recovered. *Fetal*: healthy term infant, Apgar 10 at 1 min.

[28]Dow et al. The effect of atropine on the LESP in late pregnancy. Obstet Gynecol 1978; 51(4):426-30.
[29]Jick H et al. First-trimester drug use and congenital disorders. JAMA 246:343-346, 1981.
[30]Adhikari et al., Organophosphate poisoning in pregnancy. Journal of Obst. and Gynaecology. 2011, 31:4, 290-292.
[31]Solomon et al. Acute chlorpyrifos poisoning in pregnancy. Clinical Toxicology 2007. 45:4, 416-419.
[32] Rayyan et al. Neonatal cholinesterase inhibitor poisoning. J Paediatr. Child Health. 2005, 41, 152-153.
[33]Kamha et al. Organophosphate Poisoning in Pregnancy. Basic & Clinical Pharm & Toxicology 2005, 96, 397-398.
[34]Pan et al. Severe maternal bradycardia and asystole after combined spinal-epidural labor analgesia in a morbidly obese parturient. Journal of clinical anesthesia.2004, 16: 461-464.
[35]Shah et al.Neonatal mydriasis due to effects of atropine maternal Tik-20 poisoning Postgrad Med.1995; 41:21.
[36]Karalliedde et al. Acute Organophosphorus Insecticide Poisoning During Pregnancy. Human Toxicol. 1988, 7, 363-364.

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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)

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

Date of This Review:	August 17, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214652
Product Name, Dosage Form, and Strength:	Atropine Sulfate injection, 0.4 mg/mL, 1 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Accord Healthcare Inc.
FDA Received Date:	March 31, 2020, July 8, 2020
OSE RCM #:	2020-636
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, and Prescribing Information (PI) for Atropine Sulfate (NDA 214652) for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Accord Healthcare Inc. submitted a new drug application (NDA) for Atropine Sulfate Injection, USP 0.4 mg/mL and 1 mg/mL (NDA 214652) on March 31, 2020, as a 505(b)(2) application.

The NDA refers to the Reference Listed Drug (RLD), Atropine Sulfate Injection, USP 0.5 mg/5 mL (0.1 mg/mL) and 1 mg/10 mL (0.1 mg/mL) available as Ansyr plastic syringe and LifeShield Abboject glass syringe under NDA 021146. The proposed product will be available as 0.4 mg/mL and 1 mg/mL single dose vials. In response to the Agency's recommendations dated June 29, 2020, Accord revised the labeling in accordance with the most recent labeling approved for atropine injection – NDA 21146 dated June 24, 2020.

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 – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS 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

We note that Atropine Injection has the same active ingredient, dosage form (injection), route of administration (intravenous), storage requirements, dosing regimen, and administration as the reference listed drug. As stated above the proposed product will be available in a single-dose vial presentation. We performed a risk assessment of the proposed container label, carton labeling, and PI, for Atropine Sulfate to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the proposed container label, carton labeling, and PI that could be revised to improve clarity and readability of important information.

For the Division, we note that the product description is listed as: “a clear, colorless solution” in Section 3: Dosage Forms and Strengths of the PI, however, this information is not included in Section 16: How Supplied/ Storage and Handling. For the applicant we recommend changes to the container label and carton labeling to improve readability and prominence of important information.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed carton labels, container labeling and prescribing information can be improved to promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Accord Healthcare Inc. to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. Dosage Form and Strengths

    a. As currently presented the dosage form information is redundant and unclear. We recommend revising to read “Injection: 0.4 mg/mL or 1 mg/mL as a clear, colorless solution in a single dose vial.”.

2. How Supplied/Storage and Handling Section

    a. As currently presented the table contains redundant information. We recommend removing the following columns: vials, fill volume, and total content. Revise as below:

Concentration (mg/mL)	NDC	Package size
0.4 mg/mL	16729-525-63	1 vial
	16729-525-03	10 vials
	16729-525-08	25 vials
1 mg/mL	16729-526-63	1 vial
	16729-526-03	10 vials
	16729-526-08	25 vials

4.2 RECOMMENDATIONS FOR ACCORD HEALTHCARE INC.

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

A. General Comments (Container labels & Carton Labeling)

1. We recommend revising the ‘0.4 mg/1 mL’ and ‘1 mg/1 mL’ concentration statements to ‘0.4 mg/mL’ and ‘1 mg/mL’ in accordance with USP General Chapter <7>.

B. The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 6666, 6667, and 6668). This can lead to wrong strength errors because healthcare providers use the middle digits (product code) to help verify a product's strength, dosage form, or formulation. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-**XXXX**-XX.

C. Container Labels

1. To ensure consistency with the Prescribing Information, revise the statement, "See insert for dosage" to read "Recommended Dosage: See prescribing information."

2. The expiration date is required on the immediate container and carton labeling per 21 CFR 211.137. As currently presented, the expiration date is not present on the container label. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends 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. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

3. As currently presented, the lot number is not present on the container label. The lot number statement is required on the immediate container and carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). Ensure the lot number is clearly differentiated from the expiration date.

D. Blister Foil

1. There are incomplete portions of the label present on the blister-pack carton labeling. We recommend that only one complete label is present on each blister to ensure that all of the required information is included and to avoid redundancy.

E. Carton Labeling

1. Consider moving the statement "Discard Unused Portion" to the principal display panel below the "1 mL Single-Dose vial" statement to ensure this important information is not overlooked. In addition, debold "1 mL" from the "1 mL Single-Dose Vial" statement to prevent confusion with the strength statement.

2. To ensure consistency with the Prescribing Information, revise the statement, "Usual Dose: See Insert" to read "Recommended Dosage: See prescribing information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Atropine Sulfate received on July 8, 2020 from Accord Healthcare Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Atropine Sulfate and the Listed Drug

Product Name	**Atropine Sulfate**	**Atropine Sulfate Ansyr Plastic Syringe[a]**
Initial Approval Date	N/A	July 9, 2001
Active Ingredient	Atropine Sulfate	Atropine Sulfate
Indication	Atropine is a muscarinic antagonist indicated for temporary blockade of severe or life-threatening muscarinic effects.	Atropine is a muscarinic antagonist indicated for temporary blockade of severe or life-threatening muscarinic effects.
Route of Administration	intravenous	intravenous
Dosage Form	injection	injection
Strength	0.4 mg/mL, 1 mg/mL	0.05 mg/mL and 0.1 mg/mL in Ansyr Plastic Syringes. 0.1 mg/mL in LifeShield Abboject Glass Syringes.
Dose and Frequency	**Use** / **Dose (adults)** / **Repeat** Antisialagogue or other antivagal: 0.5 to 1 mg: 1-2 hours Organophosphorus or muscarinic mushroom poisoning: 2 to 3 mg: 20-30 minutes Bradyasystolic cardiac arrest: 1 mg: 3-5 minutes; 3 mg maximum total dose	
How Supplied	Atropine Sulfate Injection, USP 0.4 mg/1 mL and 1 mg/1 mL are supplied in single-dose vial as follows: **(Proposed)** Concentration (mg/mL) / NDC / Package size	Atropine Sulfate Injection, USP is supplied in single-dose syringes as follows: **Syringes** / **Concentration (mg/mL)** / **Fill Volume** / **Total Atropine Content** / **NDC# (Unit of Sale)**

<table>
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<tr><td>0.4 mg/mL</td><td>16729-525-63</td><td>1 vial</td></tr>
<tr><td></td><td>16729-525-03</td><td>10 vials</td></tr>
<tr><td></td><td>16729-525-08</td><td>25 vials</td></tr>
<tr><td>1 mg/mL</td><td>16729-526-63</td><td>1 vial</td></tr>
<tr><td></td><td>16729-526-03</td><td>10 vials</td></tr>
<tr><td></td><td>16729-526-08</td><td>25 vials</td></tr>
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<table>
<tr><td>Ansyr Plastic Syringe</td><td>0.1 mg/mL</td><td>10 mL</td><td>1 mg</td><td>0409-1630-10 (Bundle of 10)</td></tr>
<tr><td>Ansyr Plastic Syringe</td><td>0.05 mg/mL</td><td>5 mL</td><td>0.25 mg</td><td>0409-9630-05 (Bundle of 10)</td></tr>
<tr><td>LifeShield Abboject Glass Syringe</td><td>0.1 mg/mL</td><td>5 mL</td><td>0.5 mg</td><td>0409-4910-34 (Bundle of 10)</td></tr>
<tr><td>LifeShield Abboject Glass Syringe</td><td>0.1 mg/mL</td><td>10 mL</td><td>1 mg</td><td>0409-4911-34 (Bundle of 10)</td></tr>
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<tr>
<td>Storage</td>
<td>Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature.]</td>
<td>Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature.]</td>
</tr>
<tr>
<td>Container Closure</td>
<td>2 mL USP (b) (4) Clear Glass vial with (b) (4) Grey rubber stopper and a 13 mm flip off plain turquoise blue seal.</td>
<td>Ansyr Plastic Syringes and LifeShield Abboject Glass Syringes.</td>
</tr>
</table>

[a] Atropine Sulfate Ansyr Plastic Syringe [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 JUN 24. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021146s022lbl.pdf.

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,[b] along with postmarket medication error data, we reviewed the following Atropine Sulfate labels and labeling submitted by Accord Healthcare Inc.

- Container label received on July 8, 2020
- Carton labeling received on July 8, 2020
- Unit-Dose Carton Labeling received on July 8, 2020
- Prescribing Information (Image not shown) received on July 8, 2020, available from \\CDSESUB1\evsprod\nda214652\0007\m1\us\final-labeling-text-pdf-0007.pdf

G.2 Label and Labeling Images

Container label

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

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

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