CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209260Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

I. GENERAL INFORMATION

NDA: 209260
Drug: Atropine sulfate injection, USP
Dosage strength: 0.4mg/mL in a 20 mL multi-dose glass vial
Class: Antimuscarinic agent
Applicant: Fresenius Kabi USA, LLC
Proposed Indication: Temporary blockade of severe or life threatening muscarinic effects
Date of submission: March 28, 2017
PDUFA date: January 28, 2018

II. REVIEW TEAM

Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Product

Clinical Team Leader: Martin Rose
Medical Reviewer: Melanie Blank
Pharmacology & Toxicology: William Link
Regulatory Health Project Manager: Sabry Soukehal

Office of Pharmaceutical Quality

Cross-Discipline Team Leader: Ta-Chen Wu
Application Technical Lead: Mohan Sapru
Drug Product / Environmental Assessment (EA): Thomas Wong
Drug Substance: Ramsharan Mittal
Microbiology: Valerie Huse
Process: Ziyang Su
Facility: Rose Xu
Biopharmaceutics: Qi Zhang, Gerlie Gieser

Office of Clinical Pharmacology

Xiaolei Pan

Office of Biostatistics

Jialu Zhang

Office of Surveillance and Epidemiology

DPV: Mohamed Mohamoud
DMEPA: Sarah Thomas
DRISK: Mona Patel

Office of Prescription Drug Promotion

Zarna Patel

Division of Pediatric and Maternal Health

Kristie Baisden

III. BACKGROUND

Fresenius Kabi USA, LLC (Fresenius, the Applicant) submitted a New Drug Application to seek approval of a 0.4 mg/mL, multiple-dose, glass-vial presentation for Atropine Sulfate via the 505(b)(2) pathway. The Reference Listed Drug (RLD) for the drug substance was Atropine Sulfate Ansyr™ Plastic Syringe (NDA 021146 manufactured by Hospira, Inc.). The Applicant also relied on NDAs 18800 (Bacteriostatic Sodium Chloride 0.9% in Plastic Container, manufactured by Hospira, Inc.) and 18802 (Bacteriostatic Water for Injection in Plastic Container, manufactured by Hospira, Inc.) for the benzyl alcohol levels.

The Applicant's original plan was to seek this NDA's approval through the 505 (j) pathway. However, the Division of Filing Review within the Office of Generic Drugs determined that the proposed product does not meet the RLD's condition of use: single use for RLD vs. multi-dose for the Applicant's product. This difference was not permissible under 505(j)(2)(C) and 21 CFR 314.93. The Applicant was advised to seek approval of the NDA through the 505(b)(2) pathway.

Atropine inhibits the muscarinic-like actions of acetylcholine. It is an anti-cholinergic indicated for the temporary blockade of severe or life-threatening muscarinic effects.

The active moiety, Atropine Sulfate, was initially approved in the U.S. for prescription use in 1960 and has been marketed as Atropine Sulfate Injection since 2001 (Ansyr™ Plastic Syringe, NDA 21146, the RLD).

Atropine Sulfate Injection, USP is a sterile nonpyrogenic isotonic solution administered parenterally by intravenous, intramuscular, subcutaneous, intraosseous or endotracheal injection. It differs in excipients from the RLD by the inclusion of benzyl alcohol (0.9%) as a preservative. Systemic exposure to benzyl alcohol has been associated with serious adverse reactions including death in neonates and low birthweight infants. There is no known minimum amount of benzyl alcohol at which this toxicity may occur. The proposed formulation is not recommended to be given to pre- and full-term neonates.

The Applicant relied on the nonclinical information from the approved RLD label and provided published literature to support the pharmacodynamics, pharmacokinetics and safety of the proposed Atropine Sulfate Injection formulation. The Applicant has not conducted *in vivo* pharmacology studies and relied upon the clinical pharmacology, safety, and efficacy data of the RLD. As the proposed Atropine Sulfate Injection formulation is intended solely for administration by injection, the Applicant expected no difference in the systemic exposure, safety, or efficacy of their product compared with the RLD and requested a BA/BE waiver because they believed that the BA/BE of the proposed product is self-evident.

IV. APPLICATION REVIEW

1. Regulatory Timeline

- NDA Receipt Date: March 28, 2017
- Filing Day 60: May 27, 2017
- Filing 74-Day: June 10, 2017
- Mid-cycle Communication Meeting: N/A
- Late-cycle Meeting: N/A
- Advisory Committee: N/A
- PDUFA Date: January 28, 2018

2. User Fee

The user fee for this application was paid in full on March 6, 2017 (User Fee ID 3016709).

3. Advisory Committee

There was no Advisory Committee meeting for this NDA because the application did not raise significant issues regarding the safety or effectiveness of the drug.

4. Pediatric Review Committee (PeRC)

Since the Applicant did not propose a new active ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration, the Pediatric Research Equity Act did not apply to this NDA. The Applicant requested a full waiver of pediatric studies. A review by the PeRC was not deemed necessary.

5. Trade name

At the time of NDA submission, the Applicant did not submit a proposed proprietary name for review. On May 15, 2017, the Division of Medication Error Prevention and Analysis asked the Applicant if they intended to have a proprietary name for atropine sulfate injection (memo-to-file reference ID 4097947). On May 22, 2017, the Applicant confirmed that they did not intend to submit a proprietary name for review (memo-to-file reference ID 4201020).

6. Facilities Inspections

The below facilities were deemed acceptable based on their inspectional histories and their demonstrated manufacturing capabilities.

- Fresenius Kabi USA, LLC (FEI 1450022): For Drug Product manufacturing.
- [redacted] (b) (4) For API manufacturing.
- [redacted] (b) (4): For Drug Substance and Drug Product release and stability testing.
- [redacted] (b) (4): [redacted] (b) (4) [redacted] (b) (4) testing.

7. Reviews

Below are the conclusions reached by the atropine sulfate injection, USP team members.

a) Division Memorandum – January 26, 2018

Dr. Stockbridge documented his concurrence with Dr. Wu's memo and supported approval of atropine sulfate injection, USP 0.4 mg/mL for the temporary blockade of severe or life threatening muscarinic effects.

b) Cross-Discipline Team Leader Memorandum – January 26, 2018

Dr. Wu summarized the reviews provided by each discipline and recommended an approval action.

He agreed with the Applicant's request to waive the requirement to conduct *in vivo* bioavailability or bioequivalence studies and concurred with the Biopharmaceutics reviewer that the benzyl alcohol level in the drug product (0.9%) is expected to be safe for use by adults but not in pediatric patients, pregnant women, and lactating mothers. His benefit-risk assessment indicated that the labeling adequately describes the risks and benefits associated with the use of atropine sulfate USP 0.4mg/mL.

c) Clinical review – January 2, 2018

Recommendation: Approval.

Dr. Blank's memo summarized her labeling recommendations based on a thorough literature review. Her proposed changes were mainly in Sections 1 (INDICATION AND USAGE) and 2 (DOSAGE AND ADMINISTRATION). She noted that the Applicant's proposed label (b) (4) .

In Section 1, she recommended to replace (b) (4), (b) (4) no longer supported by the Current American Heart Association guidelines for advanced cardiac life support, with *symptomatic bradycardia*.

She noted that Section 2 included sparse dosing recommendations for adults and no proposed dosing recommendations for pediatric patients despite a plenitude of published literature addressing atropine dosing in both populations and therefore proposed several changes.

Other recommendations were made throughout the label.

d) Clinical Pharmacology (No review)

A review was not deemed necessary as pertinent clinical pharmacology data were not provided in the application. However, the Office of Clinical Pharmacology provided labeling recommendations.

e) Pharmacology/Toxicology review – December 14, 2017

Recommendation: Approval.

Dr. Link noted that the inactive ingredients of the proposed drug product were the same as that of the RLD, except the addition of benzyl alcohol as a preservative and sulfuric acid as a pH adjuster. He stated that all excipients used in the manufacture of the drug product met the requirements of the current USP/NF including current USP< (b) (4) > for (b) (4). As preclinical studies were not conducted by the Applicant, Dr. Link's only concern was the

addition of benzyl alcohol to the drug product and the resultant risk in the pediatric population. However, he stated that these concerns were adequately described in the product's labeling.

f) Statistical memo – December 8, 2017

Dr. Zhang indicated that a statistical review was not performed because the submission did not contain clinical data and was based solely on published literature.

g) Office of Pharmaceutical Quality integrated review – December 31, 2017

Recommendation: Approval. A summary from each review discipline can be found below.

Drug Substance: Atropine Sulfate, USP is very soluble in water and is chemically designated as (C17H23N03)2•H2S04•H20. Atropine, a naturally occurring belladonna alkaloid, is a racemic mixture of equal parts of d- and 1-hyocyamine, whose activity is due almost entirely to the levo isomer of the drug. The CMC details concerning the drug substance have been cross-referenced to Type II DMF # (b) (4), which was found to be adequate. The proposed specifications meet the current USP requirements and are adequate to control the identity, strength, quality, physical and chemical purity, and potency.

Drug Product: Atropine Sulfate Injection, USP is a sterile, nonpyrogenic isotonic solution of atropine sulfate in water for injection with sodium chloride sufficient to render the solution isotonic. Each mL contains atropine sulfate, 0.4 mg (equivalent to 0.33 mg of atropine); benzyl alcohol, 9 mg; and sodium chloride, 9 mg. All excipients used in the proposed product meet the requirements of the current USP/NF. The difference in inactive ingredients of the proposed drug product compared to the listed drug (addition of benzyl alcohol as a preservative and sulfuric acid as the only pH adjuster) is considered irrelevant in the context of having a potential effect on the therapeutic equivalence or stability of the product.

Manufacturing: The manufacturing process, which involves (b) (4) was found to be acceptable.

Microbiology: Details concerning the microbiological monitoring of the environment have been cross-referenced to Type V DMF (b) (4), which was found adequate. The Applicant has adequately demonstrated the antimicrobial effectiveness for the proposed drug product. Furthermore, the release specification includes sterility and bacterial endotoxins testing. The stability data support the drug product's microbiological quality throughout the shelf life period.

Biopharmaceutics: Based on 21 CFR 320.24(b)(6), the Applicant's request to waive the requirement to conduct an *in vivo* bioavailability (BA) or bioequivalence (BE) studies to bridge the proposed drug product to the RLD was granted. The proposal to market 0.4 mg/mL was deemed unlikely to pose any safety and efficacy concerns because this strength falls between two strengths of already approved products: 0.1 mg/ml (Ansyr™, the RLD) and 2 mg/0.7 ml (Abbvie's discontinued product; ANDA 71295). Furthermore, the higher strength drug product permits administration of reduced volumes of the injectable solution, which is an advantage over the RLD, especially when administered via the intramuscular or subcutaneous routes.

Container Closure System: Atropine Sulfate Injection will be filled into (b) (4) 20 mL glass vials, closed with 20 mm (b) (4) rubber stoppers and capped with aluminum crimped flip-off seals. The Applicant's proposed specification is consistent with the requirements to confirm that the vial and closure provide a complete seal to maintain sterility.

Expiration Date and Storage Conditions: The stability data support a shelf-life of 24 months when stored at room temperature (20°C – 25°C; 68°F – 77°F). In addition, the in-use stability data support 24-hour use period after the initial puncture with storage at 20°C to 25°C.

Assessment of Manufacturing Facilities: Overall approval of all listed manufacturing facilities was recommended.

Environmental Assessment: Pursuant to 21 CFR § 25.31(a), the Applicant has claimed a categorical exclusion from the requirements of an environmental impact analysis statement. The Applicant's claim was found to be adequately justified.

The OPQ team concluded that the NDA can be approved and that Post-Marketing Commitments are not necessary.

8. Consults

a) Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (DMEPA) – November 8, 2017, and December 11, 2017

DMEPA performed a risk assessment of the proposed Atropine Sulfate Injection, USP container label, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and areas for improvement. DMEPA concluded that the proposed labeling could be improved to promote the safe use of the product. DMEPA's recommendations were conveyed to the Applicant during the labeling discussions.

b) Office of Prescription Drug Promotion (OPDP) – January 4, 2018

OPDP reviewed the draft prescribing information sent to the Applicant on December 23, 2017 and the draft carton and container labeling submitted by the Applicant on December 6, 2017 and had no comments.

c) Division of Pediatric and Maternal Health (DPMH) – October 4, 2017

DPMH reviewed the proposed prescribing information for compliance with the Pregnancy and Lactation Labeling Rule (PLLR). Revisions to subsections 5.6, 8.1, 8.2, 8.4, and 17 were made and communicated to the Division prior to the final labeling discussions with the Applicant.

9. Labeling

Labeling (prescribing information, carton and container labels) was thoroughly reviewed throughout the review cycle. Several labeling discussions occurred with the Applicant. The final agreed-upon labeling was attached to the approval letter.

V. CONCLUSION

The review team recommended approval. An approval letter was signed by Dr. Stockbridge on January 26, 2018.

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/s/

SABRY SOUKEHAL
01/26/2018

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

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

Memorandum

Date: January 4, 2018

To: Sabry Soukehal, Regulatory Health Project Manager
Division of Cardiovascular and Renal Products (DCRP)

Michael Monteleone, Associate Director for Labeling, (DCRP)

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

CC: James Dvorsky, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for BIVALIRUDIN in 0.9% Sodium Chloride Injection, for intravenous use

NDA/BLA: 209260

In response to DCRP's consult request dated April 10, 2017, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for ATROPINE SULFATE injection, for intravenous, intramuscular, subcutaneous, or endotracheal use.

PI: OPDP has reviewed the attached draft PI and we do not have any comments. OPDP's review is based on the draft PI received by electronic mail from DCRP on December 26, 2017.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 6, 2017, and we do not have any comments.

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

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

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/s/

ZARNA PATEL
01/04/2018

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:	December 11, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209260
Product Name and Strength:	Atropine Sulfate Injection, USP, 8 mg per 20 mL
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC (Fresenius)
Submission Date:	December 6, 2017
OSE RCM #:	2017-649-1
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label and carton labeling for Atropine Sulfate (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

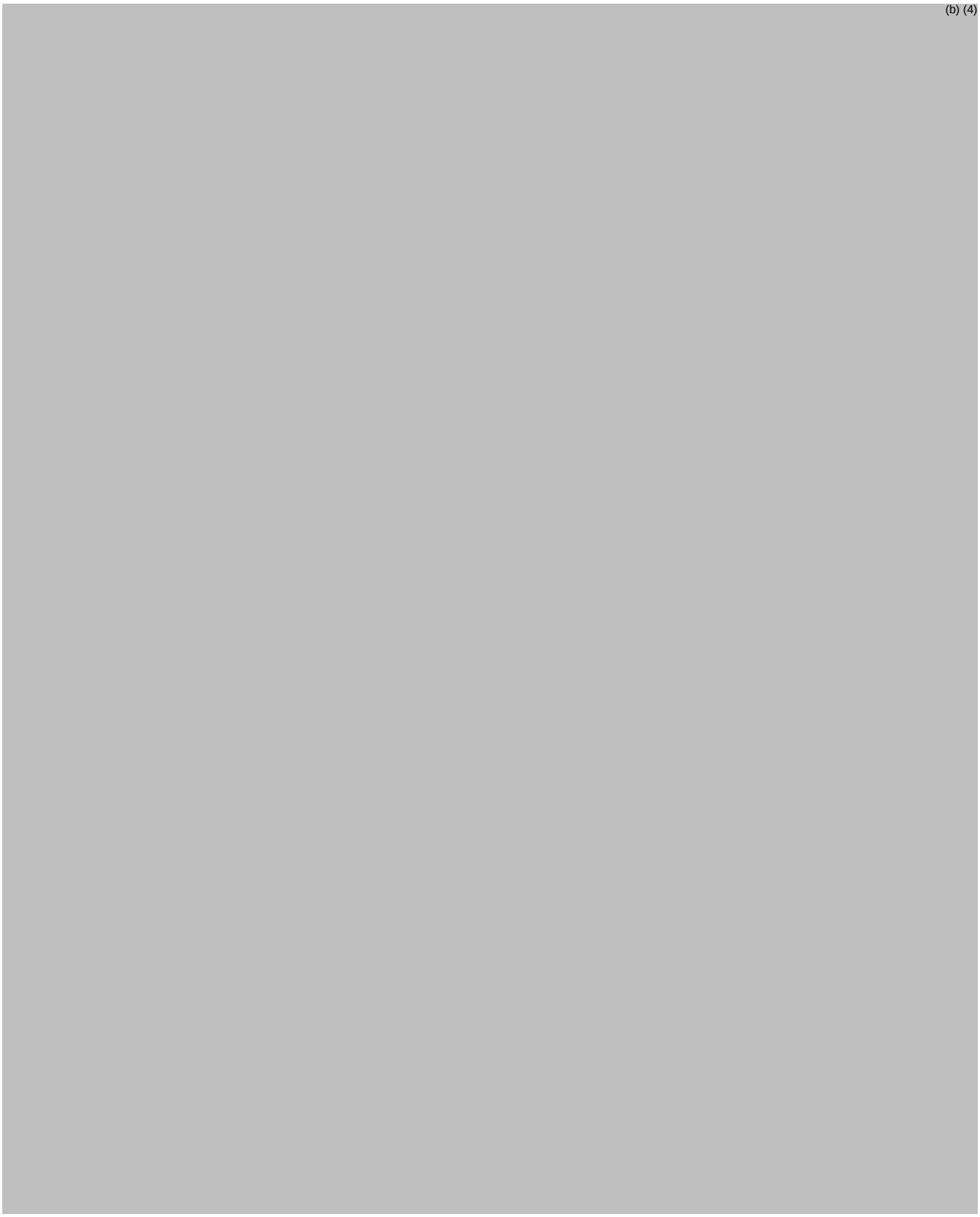
We note that Fresenius incorporated all of our recommendations except for the recommendation dealing with expiration date format on the container label and carton labeling. Fresenius responded that their "intended format for the expiration date is MMYY (e.g. 01/17). This is the expiration date format that is used for all FK USA product labels." We find their proposed, alternative expiration date format acceptable. The revised container label and carton labeling for Atropine Sulfate are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Thomas S. Label and Labeling Review for Atropine Sulfate (NDA 209260). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 8. RCM No.: 2017-649.

APPENDIX A. LABEL AND LABELING SUBMITTED ON DECEMBER 6, 2017

Container label

(b) (4)



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/s/

SARAH E THOMAS
12/11/2017

CHI-MING TU
12/11/2017

LABEL AND LABELING REVIEW

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

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

Date of This Review:	November 8, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209260
Product Name and Strength:	Atropine Sulfate Injection, USP, 8 mg per 20 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC
Submission Date:	October 31, 2017
OSE RCM #:	2017-649
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

Fresenius Kabi USA, LLC (Fresenius) submitted this 505(b)(2) NDA to seek approval of an 8 mg per 20 mL (0.4 mg per mL) multiple-dose vial presentation for Atropine Sulfate. The Listed Drug (LD) is Atropine Sulfate Ansyr™ Plastic Syringe (NDA 021146).

The Division of Cardiovascular and Renal Products consulted us to review the proposed Atropine Sulfate container label and carton labeling, as well as the proposed Atropine Sulfate Prescribing Information (PI) for areas of vulnerability that could 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 Label and Labeling 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
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Although approved Atropine sulfate injections are supplied in concentrations of 0.05 mg/mL and 0.1 mg/mL packaged in Ansyr Plastic Syringe, Atropine sulfate injection, USP, in a 0.4 mg/mL concentration has been marketed as an unapproved product since 1971 in a multiple-dose vial by West-ward Pharmaceuticals Crop.[a] The proposed Atropine sulfate injection, USP, 8 mg/20 mL has the same 0.4 mg/mL concentration and is also packaged in a vial just like the currently marketed 0.4 mg/mL Atropine sulfate injection products. We are not aware of any medication errors from our routine post-marketing surveillance associated with concentration confusion between the currently marketed 0.05 mg/mL, 0.1 mg/mL, and 0.4 mg/mL

[a] Atropine Sulfate. Online from DailyMed at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5d45eb2f-b964-4f64-b277-eef807520466. Accessed September 20, 2017.

concentrations; thus, we do not anticipate that the proposed Atropine sulfate injection, USP, 8 mg/20 mL from Fresenius will introduce any new risk of error.

DMEPA performed a risk assessment of the proposed Atropine Sulfate Injection, USP container label, carton labeling, and PI to identify deficiencies that may lead to medication errors and areas for improvement.

We note the route of administration of "endotracheal" is provided in the proposed prescribing information, but this route is not provided on the container label or carton labeling. We clarify this discrepancy in Section 4 below. We also note that the lot number and expiration date are missing from the proposed carton labeling, which are required in accordance with 21 CFR 201.10(i) and 21 CFR 201.17. In addition, we note the storage temperature after initial use was not specified on the labels and labeling. Per communication with OPQ, OPQ confirmed the storage temperature after initial use is between 20° to 25°C (68° to 77°F). We provide a recommendation related to this noted omission and other recommendations in section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Atropine Sulfate Injection, USP container label, carton labeling, and PI can be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on our review, we recommend the following changes to the PI be implemented prior to the approval of this NDA:

A. Prescribing Information (PI)
    1. General Comments
        a. We recommend removing the mL dose amounts noted in the Dosage and Administration sections of the Highlights and Full PI. We are concerned that providing both the mg and mL dose amounts may cause confusion and lead to dosing errors.
    2. Highlights, Dosage Forms and Strengths
        a. Add the dosage form injection so the statement reads "Injection: 8 mg per 20 mL (0.4 mg per mL) multiple dose glass vial".
    3. Full PI, Sections 3 and 16
        a. Add the appropriate information to facilitate identification of the injection dosage form (e.g., color of injection solution and other identifying characteristics).
    4. Full PI, Section 16
        a. We note the use of the same numbers for the commercial package size (last 2 digits) of the NDC numbers for the 8 mg per 20 mL (0.4 mg per mL) multiple dose vial container label and the carton labeling for the carton containing ten 20 mL multiple dose vials. Because the two entities have

different quantities (container with 1 vial versus carton containing 10 vials), we recommend revising the last 2 digits of the NDC numbers to differentiate between the 2 package sizes and provide the two NDC numbers in Section 16 of the full PI.

b. We note the [redacted] (b) (4) provided in Section 16 of the PI. We are uncertain of what this number represents, and are concerned that it may be misinterpreted as the lot number. We recommend removing the [redacted] (b) (4) from Section 16, or for the Applicant to provide an explanation for what the number represents and a rationale for including this number in the PI.
c. We recommend revising the quantity statement in Section 16 to improve clarity as follows: "20 mL multiple dose vial, packaged in a carton containing 10 vials."
d. Revise the discard statement after initial use to include the storage temperature, as follows: "After initial use, store between 20° to 25°C (68° to 77°F) and discard within 24 hours."

4.2 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

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

A. Container Label and Carton Labeling
    1. We note the route of administration of "endotracheal" is provided in the proposed prescribing information, but this route is not provided on the container label or carton labeling. Clarify whether or not the endotracheal route will be a route of administration for the proposed atropine injection product, and maintain consistency in the provision of routes of administration across labels and labeling.
    2. Revise the "Usual Dose" statement to read: "Usual Dose: See prescribing information."
    3. We note the use of the same numbers for the commercial package size (last 2 digits) of the NDC numbers for the multiple dose vial container label and the carton labeling for the carton containing 10 multiple dose vials. Because the two entities have different quantities (container with 1 vial versus carton containing 10 vials), we recommend revising the last 2 digits of the NDC numbers to differentiate between the 2 package sizes.
    4. Revise the discard statement after initial use to include the storage temperature, as follows: "After initial use, store between 20° to 25°C (68° to 77°F) and discard within 24 hours."
    5. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors,

identify the format you intend to use. We recommend using a format like either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).[b]

B. Container Label

1. We note that the lot number and expiration date are located in close proximity to the number "403301" on the container label. We recommend relocating or removing the number "403301" so that its current location does not cause confusion with the printed lot number or expiration date.[c]

C. Carton Labeling

1. We did not identify a placeholder ("LOT" or "EXP") for the lot number and expiration date on the proposed carton labeling. Ensure the lot number and expiration date are presented on the carton labeling in accordance with 21 CFR 201.10(i) and 21 CFR 201.17, and ensure that they are clearly differentiated from one another.[d] 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.[e]

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

[c] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

[d] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert A cute Care. 2014;19(23):1-4.

[e] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Atropine Sulfate Injection that Fresenius Kabi USA, LLC submitted on October 31, 2017, and the listed drug (LD).

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

Product Name	**Atropine Sulfate, USP (NDA 209260)** [Proposed]	**Atropine Sulfate, USP (NDA 021146)**
Initial Approval Date	N/A	July 9, 2001
Active Ingredient	Atropine Sulfate	Atropine Sulfate
Indication	Muscarinic antagonist indicated for temporary blockade of severe or life threatening muscarinic effects, e.g., as an antisialagogue, an antivagal agent, an antidote for organophosphorus or muscarinic mushroom poisoning, and to treat (b) (4) .	Muscarinic antagonist indicated for temporary blockade of severe or life threatening muscarinic effects, e.g., as an antisialagogue, an antivagal agent, an antidote for organophosphorus or muscarinic mushroom poisoning, and to treat bradyasystolic cardiac arrest.
Routes of Administration	Intravenous, intramuscular, subcutaneous, or endotracheal	Intravenous, intramuscular, subcutaneous, or endotracheal
Dosage Form	Injection	Injection
Strength	8 mg per 20 mL (0.4 mg per mL)	Adult: 1 mg/10 mL (0.1 mg/mL), Pediatric: 0.25 mg/5 mL (0.05 mg/mL)
Dose and Frequency	(b) (4) -Adult dosage: • Antisialagogue or other antivagal: Initial single dose of 0.5 mg to 1 mg. May repeat in (b) (4) hours. • Antidote for organophosphorus or muscarinic mushroom poisoning: Initial single dose of (b) (4) mg to (b) (4) mg, repeated every (b) (4) minutes.	-Titrate according to heart rate, PR interval, blood pressure and symptoms. -Adult dosage: • Antisialagogue or other antivagal: Initial single dose of 0.5 mg to 1 mg. May repeat in 1-2 hours. • Antidote for organophosphorus or muscarinic mushroom poisoning: Initial single dose of 2 mg to 3 mg, repeated every 20-30 minutes.

	• [redacted]: [redacted] mg dose, repeated every 3-5 minutes [redacted], with 3 mg maximum total dose. -Patients with Coronary Artery Disease: Total dose should not exceed 0.03 mg/kg to 0.04 mg/kg. -Pediatric dosage: [redacted].	• Bradyasystolic cardiac arrest: 1 mg dose, repeated every 3-5 minutes [redacted] 3 mg maximum total dose. -Patients with Coronary Artery Disease: Total dose should not exceed 0.03 mg/kg to 0.04 mg/kg. -Pediatric dosage: dosing has not been well studied. Usual initial dose is 0.01 to 0.03 mg/kg.
How Supplied	8 mg per 20 mL (0.4 mg per mL) multiple dose glass vial, packaged in a quantity of 10 vials	Ansyr Plastic Single-Dose Syringe: Adult 1 mg/10 mL (0.1 mg/mL), Pediatric 0.25 mg/5 mL (0.05 mg/mL)
Storage	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].	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.]
Container Closure	Atropine Sulfate Injection will be filled into [redacted] glass vials [redacted] The vials are closed with [redacted] rubber, [redacted] stoppers [redacted] and capped with aluminium crimped flip-off seals [redacted]. The filled, stoppered, capped and labeled vials are then placed into [redacted] paperboard covered trays.	Stopper, Plunger, Blue Rubber; [redacted], 10 mL

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 18, 2017, we searched the L:drive and AIMS using the terms, "atropine" and NDA# "209260" to identify reviews previously performed by DMEPA and related to this label and labeling review.

Our search identified 3 previous, relevant reviews for the Atropine Sulfate Injection, USP Ansyr and (b) (4) syringes under NDA 021146 (LD for NDA 209260).[f,g,h] We considered applicable recommendations from our previous reviews for the proposed Atropine Sulfate Injection, USP vial.

[f] Thomas, S. Label and Labeling Review for Atropine Sulfate Injection NDA 021146/S-016. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 16. RCM NO.: 2016-2041.

[g] Thomas, S. Label and Labeling Review Memo for Atropine Sulfate Injection NDA 021146/S-016. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 20. RCM NO.: 2016-2041-1.

[h] Thomas, S. Label and Labeling Review for Atropine Sulfate Abboject Injection NDA 021146/S-018. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 11. RCM NO.: 2017-862.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On August 18, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. Of note, we completed a similar search on July 11, 2017[i], and so we mainly focused on identifying additional newsletters since the last ISMP Atropine search.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Searched the Acute Care, Community, and Nursing Newsletters.
Search Strategy and Terms	Match Exact Word or Phrase: atropine

D.2 Results

Our search retrieved 28 newsletters, and all 28 newsletters were published prior to our last search on July 11, 2017. Thus, no new newsletters or relevant medication errors were identified.

[i] Thomas, S. Label and Labeling Review for Atropine Sulfate Abboject Injection NDA 021146/S-018. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 11. RCM NO.: 2017-862.

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,[j] along with postmarket medication error data, we reviewed the following Atropine Sulfate Injection label and labeling submitted by Fresenius Kabi USA, LLC on October 31, 2017.

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container Label

(b) (4)

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

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/s/

SARAH E THOMAS
11/08/2017

CHI-MING TU
11/08/2017

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
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: September 14, 2017 **Date Consulted:** July 31, 2017

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

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

To: Sabry Soukehal, Regulatory Project Manager (RPM)
Division of Cardiovascular and Renal Products (DCaRP)

Drug: Atropine Sulfate Injection

NDA: 209260

Indication: Temporary blockade of severe or life-threatening muscarinic effects

Applicant: Fresenius Kabi USA, LLC

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- NDA 209260 submitted on March 28, 2017.
- Applicant's revised label and literature review submitted June 30, 2017

Consult Question: DCaRP requests DPMH assistance with reviewing the applicant's PLLR updated labeling

INTRODUCTION

On July 31, 2017, DCaRP consulted DPMH to provide input on the appropriate format and content of the pregnancy and lactation sections of ATROPINE SULFATE INJECTION labeling to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

REGULATORY HISTORY

- On March 28, 2017, Fresenius Kabi USA, LLC submitted a new NDA 209260 via the 505 (b) (2) regulatory pathway for Atropine Sulfate Injection.
- The applicant is relying on the FDA-approved drug Atropine Sulfate Injection in Ansyr Plastic Syringe NDA 021146, Hospira Inc. as the reference listed drug (RLD) which was approved based on the published literature on July 9, 2001.
- The active moiety, Atropine Sulfate, was initially approved in the U.S. in 1960.
- Atropine is an anti-cholinergic indicated for temporary blockade of severe or life-threatening muscarinic effects, e.g., as an antisialagogue, antivagal agent, antidote for organophosphorus or muscarinic mushroom poisoning, and to treat bradyasystolic cardiac arrest.
- On June 7, 2017, the Agency sent the Applicant an information request at the time of the filing that requested the prescribing information be resubmitted in PLLR format and to provide a review and summary of published literature regarding atropine use in pregnancy and lactation.
- On June 30, 2017, the Applicant submitted revised labeling and the requested supporting information which was adequate.

BACKGROUND

Drug Characteristics[1]

- Atropine Sulfate Injection, USP is a sterile nonpyrogenic isotonic solution administered parenterally by intravenous, subcutaneous, or intramuscular injection.
- The proposed drug strength is 0.4mg/mL which differs from the RLD 0.1mg/mL and 0.05mg/mL. This multi-dose vial formulation contains the preservative benzyl alcohol (0.9%) as an inactive ingredient which is not present in the single dose syringe RLD.
- Atropine inhibits the muscarinic-like actions of acetylcholine.
- Elimination half-life is (b) (4) hours in adults but more than doubled in children < 2 years old.
- Molecular weight of ≈289 Daltons.
- Plasma protein binding is about 44%.
- Common adverse reactions are dry mouth, blurred vision, photophobia, tachycardia, heat intolerance, constipation and difficulty with micturition.

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.[2] The case fatality rate in women is >15%. [3]AOPP is life-threatening for the pregnant woman and fetus due to placental transfer of organophosphates. Early recognition and

[1]Atropine Sulfate Injection (NDA 021146) package insert

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

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

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.

- *Bradyasystyolic Cardiac Arrest:*

Cardiac arrest in pregnancy is rare, approximately 1:12,000 delivery admissions.[4] The estimated rate of survival to hospital discharge is 58.9%.[5] 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.[6] Atropine was removed from the 2010 AHA guidelines for ACLS cardiac arrest algorithm and is indicated only for bradycardia cases.[7]

Current State of the Labeling[1]

- Atropine Sulfate Injection (NDA 021146), the RLD for this submission, currently approved labeling is from October 30, 2015 and is not in PLLR format.
    - There are no Boxed Warnings
    - Warnings and Precautions are listed for tachycardia, glaucoma, pyloric obstruction, urinary retention, and viscus plugs.
    - No significant interactions with hormonal contraceptives are noted.
    - Section 8.1 Pregnancy states: Category C**.** Animal reproduction studies have not been conducted with atropine. It also is not known whether atropine can cause fetal harm when given to a pregnant woman or can affect reproduction capacity.
    - Section 8.3 Nursing Mothers states: Trace amounts of atropine were found in breast milk. The clinical impact of this is not known.

REVIEW

PREGNANCY

Nonclinical Experience

A sub-study of mice in a single publication reported exposure to atropine was associated with an increase in skeletal anomalies including one axial skeletal fusion and one soft tissue anomaly, exencephaly. However, given the low incidence of each anomaly and inadequate study design, a definitive conclusion regarding teratogenicity cannot be reached. For further details, refer to the Nonclinical Review by Aaron Ruhland, Ph.D.[8]

Review of Literature

-Applicant's Review: the literature search parameters were not specified. The applicant noted animal studies have not been performed and no adequate well-controlled studies are available in pregnant women, thus it is not known whether atropine can cause fetal harm. The submitted published literature data is summarized in **Table 1**.

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

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

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

[7] 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.

[8] Ruhland A, Ph.D. Pharmacology Toxicology Review in DARRTS April 3, 2014. Reference ID: 3482794.

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[9]	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[10]	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[11]	*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[12]	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[13]	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[14]	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.
Dow et al., 1978[15]	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.

*Indicates the referenced author's comments and conclusions.

-DPMH's Review: A literature search was performed in PubMed, Embase, Micromedex[16], TERIS[17], Reprotox[18], and Briggs[19], using the terms "atropine and pregnancy," "atropine and

[9]Heinonen OP et al. Birth Defects and Drugs in Pregnancy. Littleton, MA: Published Sciences Group, 1977.
[10]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.
[11]Siebert et al. Ebstein's anomaly and extracardiac defects. Am J Dis Child 1989; 143:570-2.
[12]Onnen et al. Placental transfer of atropine at the end of pregnancy. Eur J Clin Pharmacol 1979; 15:443-6
[13] Kanto et al. Placental transfer and Pharmacokinetics of atropine after single maternal intravenous and intramuscular administration. Acta Anaesth Scand. 1981; 25, 85-88.
[14] Abboud et al. Fetal and maternal CV effects of atropine and glycopyrrolate. Anesth Analg. 1983; 62(4):426-30
[15]Dow et al. The effect of atropine on the LESP in late pregnancy. Obstet Gynecol 1978; 51(4):426-30.
[16]Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 8/16/17.

pregnant women," "atropine and pregnancy and birth defects," "atropine and pregnancy and congenital malformations," "atropine and pregnancy and stillbirth," "atropine and spontaneous abortion" and "atropine and pregnancy and miscarriage." No adequate well-controlled studies of atropine use in pregnancy were reported. One additional surveillance study, one retrospective study, and multiple case reports are summarized in **Table 2**.

Table 2: Additional Pregnancies Exposed to Atropine Reported in the Published Literature

Reference	Drug, Dose, Route	Study Design	Pregnant Subjects	Exposure Timing	Exposure Duration	Results/Outcomes
Boston Collaborative Jick et al., 1981[20]	*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[21]	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[22]	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[23]	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[24]	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[25]	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[26]	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[27]	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.

[17]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 8/16/17.
[18]Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 8/16/17.
[19]Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[20]Jick H et al. First-trimester drug use and congenital disorders. JAMA 246:343-346, 1981.
[21]Adhikari et al., Organophosphate poisoning in pregnancy. Journal of Obst. and Gynaecology. 2011, 31:4, 290-292.
[22]Solomon et al. Acute chlorpyrifos poisoning in pregnancy. Clinical Toxicology 2007. 45:4, 416-419.
[23] Rayyan et al. Neonatal cholinesterase inhibitor poisoning. J Paediatr. Child Health. 2005, 41, 152-153.
[24]Kamha et al. Organophosphate Poisoning in Pregnancy. Basic & Clinical Pharm & Toxicology 2005, 96, 397-398.
[25]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.
[26]Shah et al.Neonatal mydriasis due to effects of atropine maternal Tik-20 poisoning Postgrad Med.1995; 41:21.

Micromedex notes atropine as "Category C" by the FDA. Atropine crosses the placenta but amount of transfer is variable based on maternal drug concentration. There has been no evidence of human teratogenicity with atropine use during pregnancy. Use in pregnancy may effect fetal heart rate.

TERIS database states atropine use during pregnancy is unlikely to pose a substantial risk, but the data are insufficient to state there is no risk.

Reprotox reports human fetal exposure to atropine was not associated with developmental adverse effects or fetal toxicity when exposure occurred early in pregnancy or before delivery.

Briggs notes although human data describing pregnancy outcomes with atropine use are limited; there is no evidence of embryo or fetal harm. Atropine does cross the placenta and has been used to test placental function in obstetric patients by producing fetal blockade and subsequent tachycardia.[28] In another study, IV atropine (0.05mg) caused a decrease in fetal breathing in 13/15 fetuses after 2 minutes lasting 5-10 minutes, but no fetal hypoxia was observed.[29]

Reviewer's Comment
The 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.

Summary
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 DCaRP Pharm/Tox team. Atropine crosses the placenta and may affect fetal heart rate and breathing though no adverse outcomes are reported.

LACTATION
Nonclinical Experience
There is no information regarding the presence of atropine in animal milk.

Review of Literature
-Applicant's Review: Two published review articles are cited noting trace amounts of atropine (<0.1 mg/100ml) were detected in milk when therapeutic doses of 600 mg were taken orally by lactating women in a study from 1939.[30,31] The applicant references **Briggs** which states

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[27]Karalliedde et al. Acute Organophosphorus Insecticide Poisoning During Pregnancy. Human Toxicol. 1988, 7, 363-364.
[28]Mellin GW. Drugs in the first trimester of pregnancy and fetal life of Homo sapiens. Am J Obstet Gynecol 90:1169-80, 1964.
[29]Roodenburg PL et al. Effect of maternal intravenous administration of atropine (0.5mg) on fetal breathing and heart pattern. Contrib Gynecol Obstet 1979; 6:92-97.
[30] Vorherr, H. Drug Excretion in Breast Milk. Postgraduate Medicine. 1974; 56:4, 97-104

"Limited human data-probably compatible," noting it has not been adequately documented whether measurable amounts of atropine are present in milk or how it may affect the nursing infant. Neonates are particularly sensitive to anticholinergic agents; however no adverse effects have been reported in nursing infants whose mothers were taking atropine. The American Academy of Pediatrics considers atropine to be compatible with breast feeding.[32]

-DPMH's Review: A published literature search was performed in *Medications and Mother's Milk*[33], LactMed[34], Micromedex[16], PubMed and Embase using the search terms "atropine and lactation" and "atropine and breastfeeding." No adequate and well-controlled studies for atropine use in lactating women were found.

In *Medications and Mothers' Milk*, the author states there is "No data, probably compatible," noting only small amounts of atropine are believed to be present in milk, but the effects may be highly variable. Caution is recommended as slight absorption together with enhanced neonatal sensitivity creates hazardous potential. "Avoid if possible, but definitely not contraindicated."

The **LactMed** database states no information is available on the use of atropine during breastfeeding. Long-term use might reduce milk production or letdown, but a single systemic dose is not likely to interfere with breastfeeding. No information was found regarding maternal and infant drug levels of atropine during lactation or the effects of atropine in breastfed infants. Anticholinergic drugs can reduce prolactin in nonnursing women, but the prolactin level in a mother with established lactation may not affect her ability to breastfeed.[35]

Micromedex notes "Infant risk cannot be ruled out." No human studies of neonatal outcomes after exposure to atropine via breast milk have been published. The World Health Organization rates atropine as compatible with breastfeeding, but recommends monitoring the nursing infant for side effects such as drying of secretions, temperature elevations, and CNS disturbances.[36]

Summary

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 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.

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[31] Knowles, J. Excretion of drugs in milk-a review. Pediatric Pharmacology and Therapeutics. 1965;66:1068-82

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

[33]Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas. Hale Publishing.

[34]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 8/15/17.

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

[36] Anon: Breastfeeding and Maternal Medication. World Health Organization, Geneva, Switzerland, 2002.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Available animal reproduction studies with atropine are minimal, not GLP, have low subject numbers (≤ 6), and are limited in regards to establishing a definitive effect on function. For further details, refer to the Nonclinical Review by Aaron Ruhland, Ph.D.[8]

Review of Literature

-Applicant's Review: literature search parameters were not provided. Published animal studies summarized in the nonclinical review above were cited by the applicant which note atropine was associated with decreased fertility in male rats and changes in uterine parameters in female rats. However, the limitations of these non-GLP studies preclude establishment of risk, thus will not be included in labeling. No human data was reported regarding the effect of atropine on fertility.

-DPMH's Review of Literature: A search of published literature was performed in PubMed, Embase, Reprotox[18] using the terms, "atropine and fertility", "atropine and contraception", "atropine and oral contraceptives" and "atropine and infertility." No reports were found related to atropine and fertility in humans or interaction with hormonal contraceptives. **Reprotox** states no reports have been located on reduced fertility in men treated with atropine.

Summary

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 theses studies cannot be evaluated. Therefore, the data from these nonclinical studies will not be in labeling as per discussion with the DCaRP Pharmacology/Toxicology team. DPMH recommends section 8.3 Females and Males of Reproductive Potential be omitted.

OTHER RELEVANT CONSIDERATIONS-Benzyl Alcohol

The applicant's formulation of Atropine Sulfate Injection differs from the RLD by the inclusion of benzyl alcohol 9 mg/mL in a 20 mL multi-dose vial. Benzyl alcohol with systemic exposure has been associated with serious adverse reactions including death in neonates and low birth-weight infants. Cases of "gasping syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-404 mg/kg/day). However, there is no known minimum amount of benzyl alcohol at which this toxicity may occur.

Nonclinical Experience and Benzyl Alcohol: **Reprotox** cites a study in which maternal toxicity with decreased fetal weight was noted in the offspring of pregnant mice dosed by gavage with benzyl alcohol 750 mg/kg/day on gestational days 7-14.[37,38]. **Micromedex** notes a study where rats and rabbits were given benzyl alcohol subcutaneously at doses up to 500 and 400 mg/kg/day, respectively.[39] There was no evidence of teratogenicity, but maternal toxicity and reduced fetal weights were noted at the highest doses. **Shepard's** cites an early study where benzyl alcohol

[37]Hazelden et al. 1983 Screening of priority chemicals for potential reproductive hazard. NIOSH, Public Health Service, US Dept Health, Education and Welfare, Cincinnati, OH. Contract No. 20-81-6005. 135p.
[38]Hardin et al. 1987. Eval of 60 chemicals in a preliminary developmental toxicity test. Terat Carci Mut 7:29-48.
[39]PI: Ulesfia topical lotion, benzyl alcohol topical lotion. Contract Pharmaceuticals Limited, Mississauga, ON, 2010

was injected into the yolk sac of the chick, from before incubation up to day 7, in which meningoceles and skeletal defects were produced.[40]

Pregnancy and Benzyl Alcohol: There are no adequate and well-controlled studies of systemic benzyl alcohol use during pregnancy. **Briggs** recommends benzyl alcohol injectable products be contraindicated during pregnancy. The author states it is not known if benzyl alcohol crosses the placenta or if embryo-fetal risk exists, although the molecular weight (108 Daltons) is low enough for placental transfer. A report of benzyl alcohol exposure is cited in a 22-year-old pregnant woman who was treated with dalteparin injections from a multiple-dose vial for the first 4 months.[41] The patient was switched to a benzyl alcohol-free formulation for the rest of pregnancy and the outcome was a healthy infant. Another case report is cited describing a postpartum woman who received a 1.5% benzyl alcohol-containing normal saline epidural injection and developed flaccid paralysis.[42] The patient fully recovered at 16 months.

Lactation and Benzyl Alcohol: There are no adequate and well-controlled studies of systemic benzyl alcohol use during lactation. **Micromedex** notes "infant risk cannot be ruled out." It is not known if benzyl alcohol is present in human milk or whether it can cause harm in the breastfed infant. **Briggs** recommends injectable products preserved in benzyl alcohol be contraindicated in breastfeeding, but states no reports describing use during lactation were found. The molecular weight (108 Daltons) is low enough for transfer into breastmilk. The author notes "although a dose-response relationship has not been determined, it appears unlikely a nursing infant's exposure to benzyl alcohol from breast milk would be high enough to cause toxicity." **LactMed** reports benzyl alcohol may enter breastmilk and be absorbed by the infant.

Summary
Human data are not available regarding the use of benzyl alcohol in pregnancy and lactation. There are no known adverse outcomes associated with fetal or neonatal exposure to benzyl alcohol through maternal drug administration; however, benzyl alcohol can cause serious adverse events and death when administered intravenously to neonates and infants. DPMH recommends using benzyl alcohol-free formulations if Atropine Sulfate Injection is needed in pregnancy or lactation. A contraindication is not advised, as potential life-saving treatment for a pregnant or lactating woman should not be withheld in emergency situations when a preservative-free formulation of Atropine Sulfate Injection is not readily available.

CONCLUSIONS
The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of Atropine Sulfate Injection labeling were structured to be consistent with PLLR, as follows:

- **Warnings and Precautions, Subsection 5.6**
  - "The "Warnings and Precautions" section of labeling was updated to correspond with changes made to the Highlights and subsection 8.4 of labeling.
- **Pregnancy, Subsection 8.1**

[40] Duraiswami, PK: Experimental teratogenesis with benzyl alcohol. Johns Hopkins Hospital Bull. 95: 57-67,1954.
[41] Moll S. A low-molecular-weight heparin preparation contraindicated during pregnancy. Am J Obstet Gynecol 2001; 184:1046.
[42] Craig et al. Flaccid paraparesis following obstetrical epidural anesthesia: possible role of benzyl alcohol. Anesth Analg 2977; 56:219-21.

- The "Pregnancy" subsection of labeling was formatted in the PLLR format to include: "Risk Summary", "Clinical Considerations", and "Data", sections.

- **Lactation, Subsection 8.2**
  - The "Lactation" subsection of labeling was formatted in the PLLR format to include: "Risk Summary" and "Clinical Considerations" sections.
- **Pediatric Use, Subsection 8.4**
  - The "Pediatric" subsection of labeling was added using the labeling review tool format for benzyl alcohol.
- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of labeling was updated to correspond with changes made to subsection 8.2 of labeling.

LABELING RECOMMENDATIONS
DPMH revised subsections 5.6, 8.1, 8.2, 8.4, and 17 of labeling for compliance with the PLLR. The Labeling Review Tool was used to guide standard labeling language for subsections 5.6 and 8.4 regarding the use of benzyl alcohol-containing drug products in pediatric patients. DPMH discussed our labeling recommendations below with DCaRP on 10/4/17. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Atropine Sulfate Injection Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------WARNINGS AND PRECAUTIONS ----------
- Benzyl Alcohol Toxicity: Use preservative-free formulation in neonates, infants, pregnant women, and lactating women. (5.6, 8.1, 8.2, 8.4)

FULL PRESCRIBING INFORMATION
5 WARNINGS AND PRECAUTIONS
5.6 Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative
Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including ATROPINE SULFATE INJECTION in multiple-dose vials. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.

When Prescribing ATROPINE SULFATE INJECTION in multiple-dose vials in infants consider the combined daily metabolic load of benzyl alcohol from all sources including ATROPINE SULFATE INJECTION in multiple-dose vials (contains 9mg of benzyl alcohol per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known *[see Use in Specific Populations (8.1, 8.2, 8.4)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
This ATROPINE SULFATE INJECTION contains benzyl alcohol. Benzyl alcohol may cross the placenta. If available, preservative-free ATROPINE SULFATE INJECTION is recommended when atropine therapy is needed during pregnancy. There are no known adverse outcomes

associated with fetal exposure to the preservative benzyl alcohol through maternal drug administration; however benzyl alcohol can cause serious adverse events and death when administered intravenously to neonates and infants *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.4)]*.

Limited available data with ATROPINE SULFATE INJECTION use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes *(see Data).* There are risks to the mother and fetus associated with untreated severe or life-threatening muscarinic events *(see Clinical Considerations).* Animal reproduction studies have not been conducted with ATROPINE SULFATE INJECTION.

The estimated 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 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Severe or life-threatening muscarinic events such as acute organophosphate poisoning and bradysystolic cardiac arrest 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

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

This ATROPINE SULFATE INJECTION contains benzyl alcohol. Benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant. If available, preservative-free ATROPINE SULFATE INJECTION is recommended when atropine therapy is needed during lactation *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.4)]*.

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. The lack of clinical data during lactation

precludes a clear determination of the risk of atropine to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ATROPINE SULFATE INJECTION and any potential adverse effects on the breastfed infant from ATROPINE SULFATE INJECTION or from the underlying condition.

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.

8.4 Pediatric Use

Serious adverse reactions including fatal reactions and the "gasping syndrome" occurred in premature neonates and infants in the neonatal intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

When prescribing ATROPINE SULFATE INJECTION in multiple-dose vials in infants consider the combined daily metabolic load of benzyl alcohol from all sources including ATROPINE SULFATE INJECTION in multiple-dose vials (ATROPINE SULFATE INJECTION in multiple-dose vials contains 9 mg/mL of benzyl alcohol) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known *[see Warnings and Precautions (5.6)]*.

17 PATIENT COUNSELING INFORMATION

Lactation

Advise a woman to pump and discard her milk for 24 hours after ATROPINE SULFATE INJECTION use before resuming to breastfeed her infant *[see Use in Specific Populations (8.2)]*.

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/s/

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