CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214652Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	28-September-2020
From	Mohan Sapru, M.S., Ph.D. CMC Lead, Division of Cardiology and Nephrology
Through	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiology and Nephrology
Subject	CDTL Review
NDA	214652 (Atropine Sulfate Injection)
Type of Application	505(b)(2)
Applicant	Accord Healthcare, Inc.
Date of Receipt	31-March-2020
PDUFA Goal Date Expedited Action Goal Date	31-January-2021 30-September-2020
Established/Proper Name	Atropine Sulfate Injection
Dosage forms; Strength	Injection; 0.4 mg/mL, and 1 mg/mL
Route of Administration	Intravenous (IV)
Proposed Indication(s)	Indicated for temporary blockade of severe or life-threatening muscarinic effects
Regulatory Action	**Approval**

This CDTL review is based on the primary reviews, memos and documented review input, as listed below:

Material Reviewed/Consulted	Review Team
OPQ's Integrated Quality Review (DARRTS, dated 09-September-2020)	Ben Zhang, Akm Khairuzzaman, Allison Aldridge, Joan Zhao, Dacie Bridge, and Mohan Sapru (ATL)
Non-Clinical Review (DARRTS, dated 09-August-2020)	Xi Yang, and Jean Wu
DMEPA Review (DARRTS, dated 16-September-2020 and 18-August-2020)	Maximilian Straka, and Hina Mehta
OPDP Labeling Consult Review (DARRTS, dated 24-August-2020)	Zarna Patel, James Dvorsky
DPMH Labeling Consult Review (DARRTS, dated 18-August-2020)	Kristie Baisden, Tamara Johnson

OPQ: Office of Pharmaceutical Quality; DPMH: Division of Pediatric and Maternal Health; DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion.

1. Background

The Applicant, Accord Healthcare, Inc., has sought U.S. marketing approval for Atropine Sulfate Injection, for intravenous use, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Atropine is a muscarinic antagonist indicated for temporary blockade of severe or life-threatening muscarinic effects. For the approval of this NDA, the applicant relies on FDA's previous finding of safety and efficacy for the Listed Drug (LD) i.e., Hospira, Inc.'s Atropine Sulfate Injection, USP in ANSYR™ Plastic Syringe (0.1 mg/mL; NDA 021146). The proposed formulation is almost identical to the RLD, except the intended higher product strengths (0.4 and 1 mg/mL) compared to the LD (0.05 mg/mL and 0.1 mg/mL). Due to current drug shortage, this NDA has been reviewed under a 6-month expedited review clock.

2. Product Quality

2.1. Drug Substance (Atropine Sulfate, USP)

Atropine is an antimuscarinic agent since it antagonizes the muscarine-like actions of acetylcholine and other choline esters. All CMC information about the drug substance atropine sulfate monohydrate is cross-referenced to DMF (b) (4) which has been reviewed and found adequate. The additional details provided in the NDA, including the release specification, which involves testing of critical quality attributes, are adequate.

2.2. Drug Product (Atropine Sulfate Injection USP)

The proposed drug product, Atropine Sulfate Injection, USP, is a sterile, nonpyrogenic isotonic solution of atropine sulfate monohydrate in water for injection with sodium chloride sufficient to render the solution isotonic. Each milliliter (mL) contains 0.4 mg or 1 mg of atropine sulfate monohydrate (equivalent to 0.332 mg or 0.83 mg of atropine) and 9 mg of sodium chloride. The product strength is expressed in terms of the monohydrate salt, which is in accordance with the USP monograph. The solution contains no bacteriostat, antimicrobial agent or added buffer (except for pH adjustment) and is intended for use only as a single-dose injection. All excipients are USP/NF compendial grade. The inactive ingredients used are within the IIG limits. The drug product is packaged in 2 mL USP (b) (4) Glass vial for both strengths. The container closure/packaging has been shown to be adequate for the intended purpose. The proposed product release specification, which includes testing the critical quality attributes such as appearance, identity, assay, degradants, content uniformity of dosage units (USP<905>), foreign particulates (USP<788>), sterility (USP<71>), bacterial endotoxins (USP<85>), and elemental impurities (in compliance with ICH Q3D, USP <232>, and USP<233>), is acceptable. The analytical methods have been validated.

2.2.1. Manufacturing: The drug product is (b) (4) The Applicant has demonstrated that the drug product can be manufactured with consistent quality and purity. Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

2.2.2. Microbiological Aspects: The proposed drug product is [redacted] (b) (4). The product sterility is the key critical quality attribute of the proposed product. Manufacturing of the drug product is adequately controlled for microbiological attributes at various stages of the process. Microbiology tests, i.e. sterility, and bacterial bioburden testing are performed as per USP <71> and USP <85>, respectively, as part of the release testing of the finished product.

2.2.3. Biopharmaceutics Aspects: The proposed product is intended for the same indications and has the same active ingredient, dosage form, dose, dosing regimen, and route of administration as the LD. The Applicant has provided comparative physicochemical data, which show comparable pH, osmolality, viscosity, and specific gravity between the proposed and the LD products. The difference in sodium chloride amount between the proposed product and the LD is unlikely to affect the *in vivo* disposition of the proposed product. In summary, the Applicant has provided sufficient information to support the bridge between the proposed drug product and the LD under 21CFR 320.24 (b) (6).

2.3. Assessment of Manufacturing Facilities: Regarding the listed manufacturing and testing facilities for this NDA, there are no outstanding cGMP issues and are deemed acceptable. Specifically, both the drug product and drug substance facilities have been approved based on inspection history and manufacturing experience of the concerned facilities.

2.4. Expiration Date & Storage Conditions: Based on stability data, an expiration period of 24 months is granted for the product when stored at 20°C - 25°C (68°F - 77°F) in the commercial packaging. Product excursions are permitted to 15-30°C (59-86°F).

2.5. Integrated Quality Assessment Conclusion: From the chemistry, manufacturing, and controls (CMC)/quality perspective, the NDA is recommended for approval.

3. Non-Clinical Pharmacology/Toxicology

No pivotal Pharmacology/Toxicology studies have been submitted and are not required for this NDA. The nonclinical information is mainly referred to the findings from the LD. GLP-compliant *in vitro* hemolytic assay and *in vivo* local tolerance study in rabbits have been performed to address the safety concerns associated with the higher strengths. Based on *in vitro* assay, atropine (1 mg/mL) is non-hemolytic to human whole blood. Based on results from *in vivo* study, atropine is well-tolerated without any local effects at the site of injection in New Zealand rabbits at an IV dose of 0.16 mg/kg (concentration of 1 mg/mL), which is equivalent to the MRHD based on body surface area (BSA). In conclusion, the NDA is approvable from a nonclinical perspective.

4. Clinical Pharmacology

N/A

5. Statistical-Evaluation

N/A

6. Clinical Studies/Financial Certification Disclosure

No clinical studies have been performed in support of this 505(b)(2) NDA. Hence, there is no financial information to disclose.

7. Advisory Committee Meeting

N/A

8. Pediatrics, and Other Relevant Regulatory Issues

None of the PREA criteria apply to this application. Hence, the Applicant is exempt from this requirement.

9. Labeling

Based on multidisciplinary review, the Division's labeling recommendations have been accepted by the Applicant and are reflected in the most recent version of the product labeling.

10. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

  All the reviews of this application recommended approval, and I concur with the reviewers. Based on the OPQ's Integrated Quality Review, an expiration period of 24 months is granted for the product when stored at 20°C - 25°C (68°F - 77°F) in the commercial container closure system. Product excursions are permitted to 15°C -30°C (59°F -86°F).

- **Risk Benefit Assessment**

  The current NDA relies on FDA's previous finding of safety and efficacy for the LD i.e., Hospira, Inc.'s Atropine Sulfate Injection, USP in ANSYR™ Plastic Syringe (0.1 mg/mL; NDA 021146). The proposed indication for the proposed drug product has been previously approved for the LD. The applicant's proposed to-be-marketed drug product is essentially similar to the LD as it has the same active moiety, dosage form, dose, dosing regimen, and route of administration as the LD. The differences in inactive ingredient sodium chloride between the proposed product and the LD have been adequately justified by the Applicant and is not expected to impact disposition, safety, or efficacy of the proposed drug product. Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for currently marketed LD. The non-clinical, and clinical information concerning clinical efficacy and safety available in published literature does not warrant any change in current assessment of the risk-benefit profile of atropine.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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