CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214652Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 214652 (Atropine Sulfate Injection)

Integrated Quality Expedited Review

Recommendation: Approval

Drug Name	Atropine Sulfate Injection
Dosage Form; Type of Product	Parenteral (Injection, for intravenous use)
Indication	Indicated for temporary blockade of severe or life-threatening muscarinic effects
Strength	0.4 mg/mL, and 1 mg/mL
Route of Administration	For intravenous use
Rx/OTC Dispensed	Rx
Applicant	Accord Healthcare, Inc.
Submissions (s) Reviewed	NDA 214652, DMF (b) (4) and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ben Zhang	OPQ/ONDP/DNDAPI/NDB3
Drug Product/Environmental Assessment (EA)	Akm Khairuzzaman	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Allison Aldridge	OPQ/OPMA/DPMAIV/PMB12
Biopharmaceutics	Joan Zhao	OPQ/ONDP/DB/BB3
Microbiology	Dacie Bridge	OPQ/OPMA/DMAII/MAB4
RBPM	Grafton Adams	OPRO DRBPMI/RBPMBI
Application Technical Lead	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 214652 (Atropine Sulfate Injection) is recommended for approval. An expiration period of 24 months is granted for the product when stored at 20°C–25°C (68°F–77° F) in the proposed commercial container closure system. Excursions are permitted between 15°C and 30°C (59°F and 86°F).

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

I. Background

The applicant, Accord Healthcare, Inc., has sought U.S. marketing approval for NDA 214652 in accordance with Section 505(b)(2) of the FD&C Act. The proposed product, Atropine Sulfate Injection, is 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. This NDA refers to the Listed Drug (LD), Atropine Sulfate Injection, USP 0.5mg/5mL and 1 mg/10mL (i.e., Atropine Sulfate Ansyr™ plastic syringe 0.5 mg/5 mL (0.1 mg/ml) and 1 mg/10 mL (0.1 mg/mL); Hospira's NDA 021146). Due to potential drug shortage related to current Covid-19 pandemic, this NDA has been reviewed under a 6-month expedited review clock.

II. Quality Assessment Summary

A. Drug Substance (Atropine Sulfate, USP) Quality Summary

Regarding the drug substance atropine sulfate, USP, the applicant has cross-referenced all CMC information to DMF (b) (4) which has been previously reviewed and found adequate. Quality attributes of the drug substance that might have an impact on the drug product, such as polymorphism and particle size distribution, are not critical for the proposed injection formulation. The release specification for the drug substance, involving testing of critical quality attributes (CQAs), is adequate. The specification conforms to the USP monograph for atropine sulfate. Bacterial endotoxin levels are controlled to a total limit of NMT (b) (4) EU/mg in accordance with USP <85>. Microbial limits are controlled to a limit of NMT (b) (4) CFU/g in accordance with USP<61>. The stability data support the proposed retest period of (b) (4) months for the drug substance stored at (b) (4)

B. Drug Product (Atropine Sulfate Injection USP) Quality Summary

B.1. Product Design, Release Specification and Packaging:

The applicant's product design and development seem to have been geared towards characterizing the similarity between the test product and the LD, identifying key quality attributes of the target formulation and their relationship with incoming material attributes, manufacturing process variables and excipient variables. The proposed product, a sterile injectable solution, (b) (4) and complies with USP monograph. None of the excipients used in the formulation is classifiable as novel excipient or of human or animal origin. 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 strength is expressed in terms of the monohydrate salt, which is in accordance with the USP monograph. There is no overage and (b) (4) complies with the USP <1151> monograph. 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.

B.2. Manufacturing: The drug product is (b) (4) The listed critical material and process parameters are adequate. The proposed batch formulas are consistent with the proposed commercial master batch records and the executed exhibit batch record. Based on the control strategy, including in-process controls, the manufacturing process is acceptable.

B.3. Biopharmaceutics Aspects: Biopharmaceutics review evaluated the data supporting the bridge between the proposed drug product and the LD. 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 qualitative and quantitative composition of Accord's Atropine Sulfate for injection and LD product are similar, with the exception of the amount of sodium chloride at the point of patient contact. The difference of sodium chloride amount is unlikely to affect the *in vivo* disposition of the proposed product. The applicant has also provided comparative physicochemical data, which show comparable pH, osmolality, viscosity, and specific gravity between the proposed and the LD products. The applicant has provided sufficient information to support the bridge between the proposed drug product and the LD under 21CFR 320.24 (b) (6).

B.4. Microbiological Aspects: The proposed drug product is preservative-free and is packaged in single-dose vials. The provided information and data concerning sterilization, environmental monitoring, process validation and container/closure integrity testing are adequate. Sterility and bacterial endotoxins are tested at release and on stability in accordance with USP <71> and USP <85>, respectively. The product specification meets regulatory expectations for a sterile drug product.

B.5. Expiration Date & Storage Conditions: The current stability data, which include long-term and accelerated stability data, support a shelf-life of 24 months for the product when stored at

20°C–25°C (68°–77° F) in the proposed commercial container closure system. Excursions are permitted between 15°C and 30°C (59°F and 86°F).

III. Assessment of Manufacturing Facilities: Regarding the listed manufacturing and testing facilities, 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.

IV. Environmental Exclusion:

The applicant's claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(a) is acceptable.

V. Life Cycle Knowledge Information

On the next page:

Final Risk Assessment

NDA 214652 (Atropine Sulfate Injection)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H (High)**	Drug product release specification includes sterility (USP <71>) testing. Container closure integrity studies indicate that the container closure system remains integral and maintains the sterility of the product.	Acceptable	
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M (Moderate)**	The endotoxin levels are controlled on release per USP <85>.	Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels may need to be evaluated based on the proposed maximum daily dose
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)	Assay is tested via product release specification. Stability of the API and the drug product, and suitability of commercial container closure system have been well demonstrated. Product manufacturing process is reasonably well-controlled.	Acceptable	
Uniformity of Dose - Fill/ Deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	**L (Low)**	Per release specification, the product must meet the the requirement of USP <1> for Injections and USP monograph for Atropine Sulfate injection. Container content for injection is monitored on release (USP <791>.	Acceptable	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation or Aggravation**	**Final Risk Evaluation**	**Comments**
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	(b) (4) [redacted] Thus, omission of routine testing of osmolality has been justified.	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	Controlled via release specification.	Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	M (Moderate)	Monitored on release per USP <788>.	Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	The extractables and leachables studies indicate no product quality risk from container closure system used to package the drug product	Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)	Routinely monitored on release.	Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 214652 (Atropine Sulfate Injection) is recommended for approval. An expiration period of 24 months is granted for the product when stored at 20°C–25°C (68°F–77° F) in the proposed commercial container closure system. Excursions are permitted between 15°C and 30°C (59°F and 86°F).

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Division of Cardiology and Nephrology
ONDP/DNDPIII/NDPB5

Mohan K. Sapru -S

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Items	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Atropine Sulfate Injection, USP	Acceptable
Established name(s)	Atropine Sulfate Injection, USP	Acceptable
Route(s) of administration	IV infusion	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	IV injection, 0.4 mg/mL, and 1 mg/mL	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single dose in not mentioned in the proposed package inert.	FDA Recommended to use the wording "single dose vial"
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	None	Acceptable
Available dosage form(s)	IV injection	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Follows approved USP product for the LD. Additionally, FDA recommended to use equivalence statement	Acceptable

	of “equivalent to 0.332 mg of atropine” and “equivalent to 0.83 mg of atropine”.	

1.2.3 Section 11 (DESCRIPTION)

Items	Information Provided in the NDA	Assessor’s Comments
DESCRIPTION section		
Proprietary and established name(s)	Atropine Sulfate Injection, USP	Acceptable
Dosage form(s) and route(s) of administration	injection, IV route	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Follows approved USP product for the LD.	Acceptable
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided	Acceptable
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Provided	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	Acceptable
Statement of being sterile (if applicable)	Yes	Acceptable
Pharmacological/ therapeutic class	Not provided	Acceptable
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	Not Applicable	Acceptable
Other important chemical or physical properties (such as pKa or pH)	0.308 mOsmol/mL pH 3.0 to (b) (4)	FDA corrected the pH range from 3-5 to 3-4.5

		to reflect the drug product specification
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity	None present	Acceptable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Items	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	IV Injection	Acceptable
Strength(s) in metric system	Not applicable	Acceptable
Available units (e.g., bottles of 100 tablets)	Both strengths will be available as 1 vial pack, 10 vial pack and 25 vial pack	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient use). Other package terms include pharmacy bulk package and imaging bulk package.	Single dose	Acceptable
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4) Once opened, the bag can be stored at room temperature (b) (4)	Acceptable

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature [20° to 25°C (68° to 77°F)], excursions permitted to 15° to 30°C (59° to 86°F)	Acceptable
Include information about child-resistant packaging	Not Acceptable	Acceptable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Items	Information Provided in the NDA	Assessor's Comments
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: Intas Pharmaceuticals Limited, Plot No.: 457, 458, Village – Matoda, Bavla Road, Ta. - Sanand, Dist.- Ahmedabad – 382 210.	Acceptable

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Not applicable

3.0 CARTON AND CONTAINER LABELING

3.1 Vial Label

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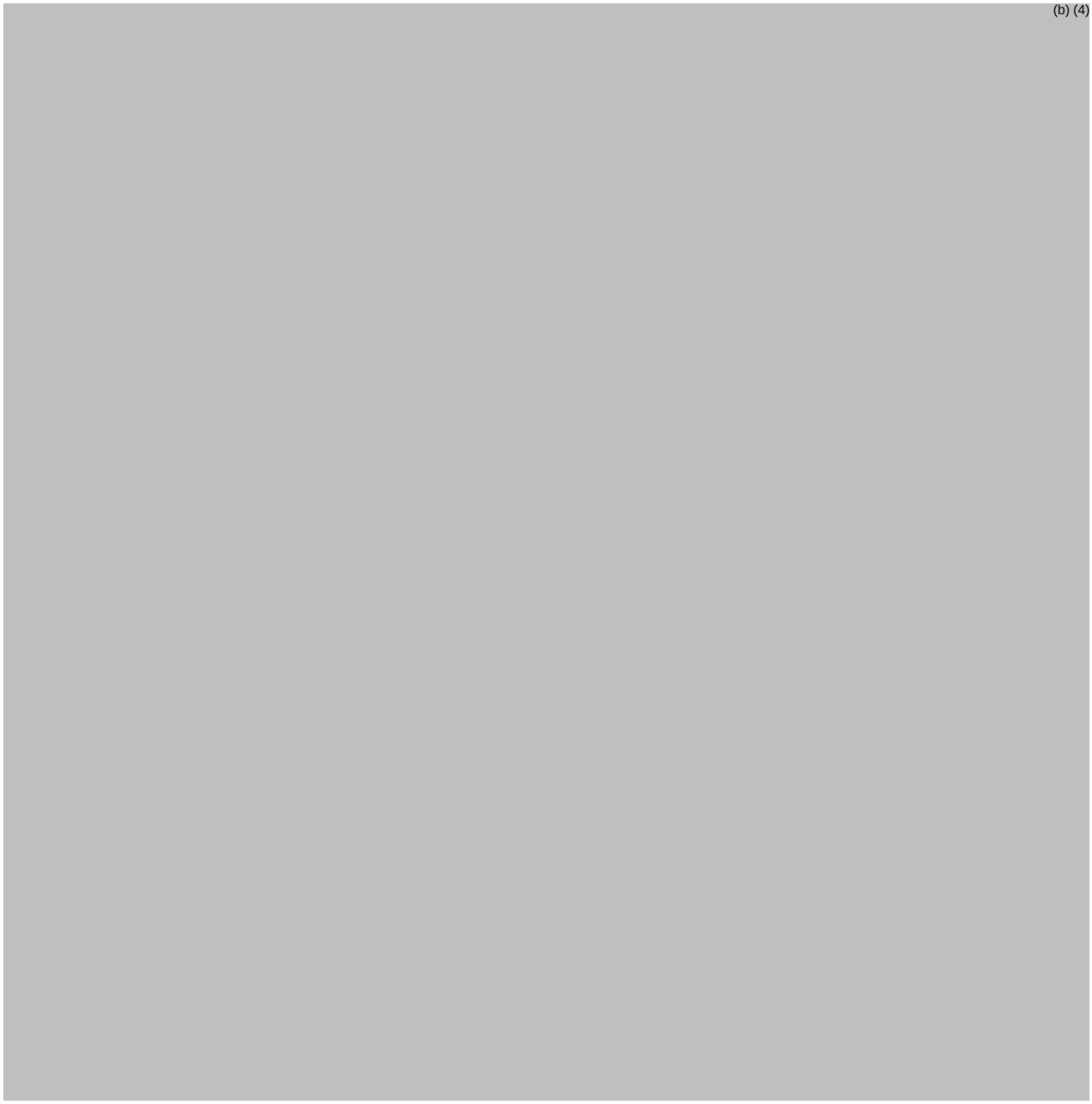

Reviewer's note: *Identical vial label and outer packaging has been provided for the higher strength.*

Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	Atropine Sulfate Injection, USP	Acceptable
Dosage strength	0.4 mg/mL, and 1 mg/mL	Acceptable
Route of administration	Intravenous Infusion	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Follows approved USP product for the LD	Acceptable
Net contents	1 ml per single dose vial	Acceptable
"Rx only" displayed on the principal display	yes	Acceptable
NDC number	yes	Acceptable
Lot number and expiration date	yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature [20° to 25°C (68° to 77°F)]	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use)	Single dose	Acceptable
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Not applicable	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Acceptable	Acceptable
Name of manufacturer/distributor	Manufactured by:	Acceptable

	Intas Pharmaceuticals Limited, Plot No.: 457, 458, Village – Matoda, Bavla Road, Ta. - Sanand, Dist.- Ahmedabad – 382 210.	
Medication Guide	Not Applicable	Acceptable
No text on Ferrule and Cap Overseal	Not Applicable	Acceptable
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Follows approved USP product for the LD.	Acceptable

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

1. In the dosage form and strength section of the package insert, FDA recommended to use "single dose container"
2. In section 3 of the package insert, FDA suggested to use equivalence statement
3. In the description section of the package insert, FDA recommended to use correct pH range (3-4.5) to reflect the drug product specification.
4. On the final carton/container labels, the pH range need to be corrected from 3-5 to 3-4.5

Overall Assessment and Recommendation: **Adequate after the above deficiencies are fulfilled.**

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 8/21/2020.
Secondary Assessor Name and Date (and Secondary Summary, as needed): David Claffey, Ph.D., 8/21/2020.

Akm Khairuzzaman

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David Claffey

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