CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-146

Chemistry Review(s)

D. Willard

OCT 18 2000

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO RENAL DRUG PRODUCTS
Chemistry, Manufacturing, and Controls

NDA #: 21-146 DATE RECEIVED/REVIEWED October 16, 2000
REVIEW #: 3 REVIEWER: Kathleen E. Jongedyk

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	16-Dec-99	7-Dec-99	14-Jan-00
AMENDMENTS	Received and Reviewed from facsimile transmittals		
	29-Sep-00	02-Oct-00	02-Oct-00
	13-Oct-00	13-Oct-00	13-Oct-00

NAME & ADDRESS OF APPLICANT: Abbott Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-6156

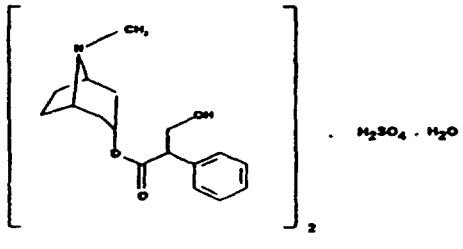
DRUG PRODUCT NAME
Proprietary: None
Established: Atropine Sulfate Injection
Code Name/#:CAS No. CAS-5908-99-6 (monohydrate): CAS-55-48-1 (anhydrous)
Chem.Type/Ther.Class: Type 3 S

PHARMACOLOGICAL CATEGORY/INDICATION:
Anti muscarinic agent (antagonizes the muscarine -like actions of acetylcholine and other choline esters. An antisialogogue for preanesthetic medication to prevent or reduce secretions of the respiratory tract.

DOSAGE FORM: Injection
STRENGTHS: 0.1mg/mL (5 and 10 mL); 0.05 mg/mL (5 mL)
ROUTE OF ADMINISTRATION: IV, IM, SC
Rx/OTC: _X_ Rx __ OTC
SPECIAL PRODUCTS: __ Yes _X_ No
If yes, fill out the form for special products deliver to TIA through team leader/ for data entry.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT, FORMULA
Molecular Weight: 694.8 Molecular Formula: $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4$

1- Benzeneacetic acid, a- (hydroxymethyl)- 8-methy-8-azabicyclo [2,3]oct-3-yl ester, endo (±)-, sulfate (2:1(salt), monohydrate
2- **1aH, 5aH-Tropan-3a-ol (±)tropate(ester), sulfate (2:1)) (salt) monohydrate**



REMARKS

Chemist Review #3 Abbott Laboratories responds (13-Oct-00) to FDA requests made in the 05-Oct-00 T.con. Abbott provides acceptable responses and revised draft documents for FDA requests.

1- Updated Atropine Sulfate API impurity tests to be the same as provided by ( ) in DMF( )

2- Updated the API Drug Code Summary for Atropine Sulfate USP Powder to add specifications for identification and quantification for three impurities and provided complete laboratory test methods tests that are equivalent to (, in DMF( ) Spec. Single impurity NMT ( ) NMT ( )%, individual unspecified impurity NMT( )%, total impurities NMT %.

3- Revised the retest date for Atropine Sulfate USP Powder API to be ( ) months after storage in Abbott Laboratories warehouse deleting the pervious month retest date.

4- Provided a new test method and specifications for degradation products for the finished drug product including Tropic Acid NMT(%, Atropic Acid NMT %, Apoatropine NMT ( )% and total impurities NMT(%.
This method was provided in the original NDA submission as a research method with limits for information only and was not included either in the specifications for the finished drug product or the marketed drug product stability protocol.

5- Revised the finished drug product and marketed stability protocols to include the new(test method and specifications limits for Tropic Acid, Atropic Acid, Apoatropine and Total Impurities

6- Abbott Laboratories provides a commitment to continue development work on a (for the finished drug product and submit to the method to the NDA when completed.

7- Abbott Laboratories will exert influence on with( )o complete the deficiencies.(as responded to FDA requests.

T.con. 17-Oct-00 Jonathan Dohnalek (Abbott) agreed that Abbott laboratories upon request would revise the labeling recommended storage statement to

"Store at 25°C (77° F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]"

Container closure Rubber stopper and Ansyr syringe. Labeling components which are directly onto the Ansyr syringe barrel consist of(were found to be acceptable,(Chemist review #1 dated 10-29-98 D. Lewis, Ph. D. reviewer.

The EER is acceptable for all sites for the API, intermediates, and drug product.
The microbiological review is acceptable for the injectable finished drug product.
Method validation of the Abbott Laboratories methods is pending requiring completion..

RECOMMENDATIONS AND CONCLUSIONS

The NDA 21-146 may be approved from the CMC standpoint There are no CMC issues pending.
Recommend that the applicant revise the storage statement on all labeling to the following:

"Store at 25°C (77° F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]"

cc: Org. NDA 21-146
HFD-110/Division File
HFD-810/KJongedyk/17-Oct-00 to team leader
HFD- PM
HFD-810/DIVISION DIRECTOR (JSimmons)

/S/
Kathleen E. Jongedyk

/S/ 10-18-00
Kasturi Srinivasachar, Team Leader

D Willard

OCT 16 2000

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO RENAL DRUG PRODUCTS
Chemistry, Manufacturing, and Controls

NDA #: 21-146 DATE RECEIVED/REVIEWED October 2, 2000
REVIEW #: 2 REVIEWER: Kathleen E. Jongedyk

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	16-Dec-99	7-Dec-99	14-Jan-00
AMENDMENTS	29-Sep-00	02-Oct-00	02-Oct-00

NAME & ADDRESS OF APPLICANT: Abbott Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-6156

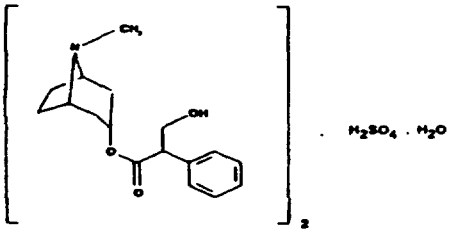
DRUG PRODUCT NAME
Proprietary: None
Established: Atropine Sulfate Injection
Code Name/#:CAS No. CAS-5908-99-6 (monohydrate): CAS-55-48-1 (anhydrous)
Chem.Type/Ther.Class: Type 3 S

PHARMACOLOGICAL CATEGORY/INDICATION:
Anti muscarinic agent (antagonizes the muscarine -like actions of acetylcholine and other choline esters. An antisialogogue for preanesthetic medication to prevent or reduce secretions of the respiratory tract.

DOSAGE FORM: Injection
STRENGTHS: 0.1mg/mL (5 and 10 mL); 0.05 mg/mL (5 mL)
ROUTE OF ADMINISTRATION: IV, IM, SC
Rx/OTC: _X_ Rx __ OTC
SPECIAL PRODUCTS: __ Yes _X_ No
If yes, fill out the form for special products deliver to TIA through team leader/ for data entry.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT, FORMULA
Molecular Weight: 694.8 Molecular Formula: $(C_{17}H_{23}NO_3)_2 . H_2SO_4$

1- Benzeneacetic acid, a- (hydroxymethyl)- 8-methy-8-azabicyclo [2,3]oct-3-yl ester, endo (±)-, sulfate (2:1(salt), monohydrate
2- 1aH, 5aH-Tropan-3a-ol (±)tropate(ester), sulfate (2:1)) (salt) monohydrate



REMARKS **Abbott Laboratories responds to FDA requests made in the 22-Sep-00 T.con. See NDA review #1.**

1- **Abbott commits to use three API test methods**

- Upon verification and or completion of method transfer
- To convert the three methods into Abbott Standard test methods (STMs) which requiring their performance for API QC release
- To file a prior approval supplement if different API analytical procedures for QC release are established

2- **Abbott commits to include degradation products testing in their commercial stability protocol.**

Standard Test Methods (STM). Abbott requires STM methods to be performed prior to release of the commercial lots to market.

-To revise the Market stability protocols to include R&D method

-To require monitoring of the three identified degradation products, tropic acid, atropic acid, and apoatropine, in addition to total degradation products, at each test interval.

-To develop a more sensitive analytical method for the degradation products of the drug product.

Not Acceptable The new STM and revised Marketed Product Stability protocol will be sent in the annual reports.

Abbott Laboratories does not provide a response to the following:

3-Revision of drug product specifications to include specification for degradation product if appropriate.

4- A justification for the poor sensitivity of the current method for degradation products.

Abbott Laboratories provides a commitment to develop a more sensitive impurity method but not the time for completion.

Acceptable The DMF for atropine sulfate DMF(chemist review #2 lists deficiencies conveyed to the DMF holder 8-Sep-00 who has provided a commitment (28-Sep-00 facsimile transmission) that they will fulfill the requests if required but need additional time to complete this work.

RECOMMENATIONS AND CONCLUSIONS

From the standpoint of CMC information recommend the NDA be approved with the following requests to be added to the letter to the applicant.

Recommend the storage statement be revised on all labeling

"Store at 25°C (77° F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

Inform Abbott Laboratories that prior to distribution of the drug product the following information should be submitted as correspondence to NDA 21-146.

1- Incorporation into the Abbott API Quality Standard Specification three impurity methods,

2- Revised marketed product stability protocols that include degradation product tests and acceptance criteria.

3- Revise the drug product regulatory specifications that include tests / acceptance criteria for degradation products.

Abbott Laboratories should be reminded of their commitment to develop a more sensitive analytical method for monitoring degradation products

/S/
Kathleen E. Jongedyk

/S/ 16-00
Kasturi Srinivasachar, Team Leader

cc:
Org. NDA 21-146
HFD-110/Division File
HFD-810/KJongedyk/02-Oct-00 to team leader
HFD- PM
HFD-810/KSrinivasachar
HFD-810/DIVISION DIRECTOR (JSimmons)
R/D Init. by: Ksrinivasachar

D. Willard

OCT 13 2000

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO RENAL DRUG PRODUCTS

Fc Chemistry, Manufacturing, and Controls

NDA #: 21-146 DATE REVIEWED: April 26, 2000
REVIEW #: 1 REVIEWER: Kathleen E. Jongedyk

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL 16-Dec-99	27-Dec-99	14-Jan-00	
AMENDMENTS	14-Jan-00	19-Jan-00	24-Jan-00
	21-Jul-00	24-Jul-00	27 - Jul-00
	28-Aug-00	31-Aug-00	06-Sep-00

NAME & ADDRESS OF APPLICANT: Abbott Hospital Products Division
Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-6156

DRUG PRODUCT NAME
Proprietary: None
Established: Atropine Sulfate Injection
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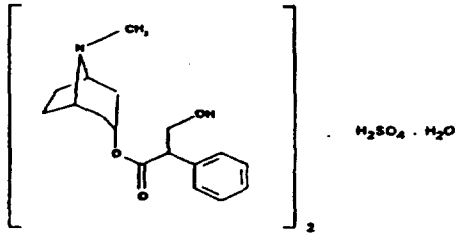
1- 1aH, 5aH-Tropan-3a-ol (±)tropate(ester), sulfate (2:1)) (salt) monohydrate



2- SUPPORTING DOCUMENTS:

ype/ Numbe	Subject	Holder	Status	Review Date	Letter Date
	Atropine Sulfate		Not Acceptable	16-Aug-00DMF Subm/Rec 24-Aug-00 Review Date 8-Sep-00	8-Sep-00
	Plastic for Syringe		Acceptable	Based on chemist review dated 09-May-00 and NDA 21-146 and	None
	Rubber Stopper		Acceptable	Based on DMF review 10-27-98 of formulation and NDA information for USP Testing results for toxicity**	None

*Abbott Laboratories tested the material according to the current USP Biological and Physico-chemical test for plastic. The material passed all tests.

** Abbott Laboratories tested the l rubber according to the current specifications and methods described in the USP, General Chapter's <381> " Closures for Injections" and <87> and <88> "Biological Reactivity Tests, in-vitro and in-vivo." Test results were reviewed and found adequate. The is described in DMF which has been reviewed and found adequate for use with Ansyr®, syringes (DMF review #3, dated 10-27-98, David Lewis Ph.D. reviewer)

RELATED DOCUMENTS (if applicable): None

CONSULTS: A microbiology review was requested 14-Jan-00. Completed Acceptable

REMARKS:

Atropine Sulfate Injection USP was on the market in 1938 and grandfathered under the 1938FDA 1962 Desi. Abbott Laboratories currently markets Atropine Sulfate Injection in an Abboject® glass container.

NDA 21-146 provides for Abbott laboratories to market the drug product in plastic syringes with a rubber stopper and luer tip cover. The formulation, manufacturing procedure, quality assurance testing, and personnel provided for the plastic syringe product is identical to that of the product in glass.

The USP monographs for Atropine Sulfate and Atropine Sulfate Injection and Abbott Laboratories API and drug product do not have an impurity degradation test method.

Abbott Laboratories quality control release standards do not provide a
Product specifications for the drug substance, drug product, and stability studies for the drug product.

Abbott Laboratories provides for only the USP monograph specifications that do not include impurity specifications for API and drug product. The USP specifications for the API includes a non specific turbidity precipitation test for other alkaloids.

Abbott Laboratories claims that atropine sulfate is a plant derived natural product, and is therefore excluded by the ICH guidelines from limits on impurities. This ICH guideline applies only to crude extracts of natural plant products which is not the case for atropine sulfate preparation that provides for chemical synthetic steps.

T.con. 15-Sept-00 Abbott has received
methods (LOQ[%) dated 1997 and 2000. Abbott states that eports their method can quantitatively determine impurities at the % and detected at the %.

T.cons 6-May-00, Jul-00, and 15-Sep-00 Abbott Laboratory will provide a more sensitive impurity method ; not received as 1-Oct-00.

Abbott stability studies for the reference standard reports impurities for test values at initial time of %, % at months, and % at months. The method was not described and no details were provided. provided, initial NDA submission, volume 1.2, pages 2-17.

Abbott Laboratories proposes at months retest data for the API. The retest specifications do not include impurities. T.Con 15-Sep-00 Abbott they do not have any stability data to support the API retest date.

The method lacks sensitivity and did not identify or report individual impurities. Abbott method validation data for linearity for the three identified impurities indicated that the method should detect and possibility quantify below %

Abbott Laboratories proposes a -month expiration date for the drug product in Ansyr® plastic syringes.

Abbott Laboratories provides supportive evidence for use of the ANSYR plastic syringe by listing the approved NDA drug products that provide for this container closure system.

50% Dextrose, Iopoamidol (51%, 61%, 76%), 50 mg/ml Bretylium Tosylate, Sterile Water for Injection USP (5 ml and 10 ml), 5% Dextrose USP, Lidocaine 2% and 1% USP, and 2.5 mg/ml, Verapamil HCl USP, 25% Dextrose USP, and 0.9% Sodium Chloride USP.

CONCLUSIONS & RECOMMENDATIONS:

An acceptable review for NDA 21-146 provided by the Division of Microbiology.

Acceptable EERs for NDA 21-146 (Abbott's manufacturing site) and DMF manufacturing site for API) were provided by Compliance.

Acceptable Abbott Laboratories request for a waiver from preparing the Environmental Assessment Report.

Not acceptable The DMF for atropine sulfate DMF)chemist review #2 lists deficiencies conveyed to the DMF holder 8-Sep-00 who has provided a commitment (28-Oct-00 facsimile transmission) that they will fulfill the requests if required but need additional time to complete this work. No time frame provided for completion of this work.

Abbott was requested (T.con 22-Sep-00) to amend the NDA 21-146 by providing the following information:

1-The impurity method they would use for acceptance testing of the drug substance.

2- Revision of the stability protocol for marketed batches to include monitoring of degradation products.

3- Revision of drug product specifications to include specification for degradation product if appropriate.

4- A justification for the poor sensitivity of the current method for degradation products or a commitment to develop a more sensitive method.

The NDA is approvable for CMC pending a satisfactory response to the DMF deficiencies and the four issues listed above.

cc:
Org. NDA 21-146
HFD-110/Division File
HFD-810/KJongedyk/26-Apr-00 to team leader
Returned &Revised 26-Sep-00and 29-Sept-00
HFD- PM
HFD-810/KSrinivasachar
HFD-810/DIVISION DIRECTOR (JSimmons)
R/D Init. by: KSrinivasachar filename: 21-146
Desktop 21-146FR

/S/ 10-13-00
Kathleen E. Jongedyk

/S/ 10-13-00
Kasturi Srinivasachar, Team Leader

Redacted 30

pages of trade secret and/or confidential commercial information

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21146/000**
Priority: **5S** Org Code: **110**
Stamp: **20-DEC-1999** Regulatory Due: **20-OCT-2000**
Action Goal: District Goal: **21-AUG-2000**
Applicant: **ABBOTT LABS**
1 ABBOTT PARK RD DEPT 389 AP30
ABBOTT PARK, IL 60064
Brand Name: **ATROPINE SULFATE INJ 0.1MG/ML(5/10ML)0.0**
Established Name:
Generic Name: **ATROPINE SULFATE INJ 0.1MG/ML(5/10ML)0.0**
Dosage Form: **FIJ (FOR INJECTION)**
Strength: **0.1 MG/ML FILL 5 & 10ML**

FDA Contacts:
D. WILLARD (HFD-590) 301-827-2387 , Project Manager
K. JONGEDYK (HFD-110) 301-594-5300 , Review Chemist
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation:

ACCEPTABLE on 06-JUN-2000 by M. GARCIA (HFD-322) 301-594-0095
ACCEPTABLE on 07-JAN-2000 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: [ ]
ABBOTT LABORATORIES
DMF No: [ ]
AADA No:

Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [ ]
DMF No: [ ]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-JUN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

ABBOTT

NDA CERTIFICATION REQUIREMENT

FOR ALL APPLICATIONS

FOR APPROVAL OF A DRUG PRODUCT

NDA 21-146 Atropine Sulfate Injection, USP, Plastic Syringe

List Number	Concentration	Fill Volume	Size/ Type Container	Manufacturing Facility
1630	0.1 mg/mL	10 mL	10 mL Plastic Syringe	
9629	0.1 mg/mL	5 mL	5 mL Plastic Syringe	
9630	0.05 mg/mL	5 mL	5 mL Plastic Syringe	

Per Section 314.94(d)(5) of the Final Rule, published in the Federal Register, September 8, 1993, page 47351, "The applicant shall submit a field copy of the abbreviated application...and a certification that the field copy is a true copy of the technical section...contained in the archival and review copies of the abbreviated application."

We certify that the field copy is a "true" copy of the technical section contained in the archival and review copies of the above-referenced application. We certify that a true copy has been sent (at the time of submission to the FDA) to the appropriate FDA district.

Jessie Y. Lee 12/15/99

Jessie Y. Lee, Ph.D. Date
Manager, Regulatory Affairs
Abbott Laboratories
D-389, AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

ATROPINENDA.jyl/182