

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-306

CHEMISTRY REVIEW(S)

MEMORANDUM

To: NDA 22-306
From: Thomas M. Wong, Ph.D., Chemist
Date: 22-May-2009
Drug: So-Aqueous (sotalol hydrochloride) injection
Route of administration: Intravenous injection
Strength: 150 mg/10 ml (15 mg/ml)
Subject: **“Approval”** recommendation for NDA 22-306

The office of Compliance (OC) has now provided an overall acceptable recommendation for the manufacturing sites. The Bioniche facility used for packaging operation is actually a part of the manufacturing facility. The manufacturing facility has an acceptable recommendation which was based on the earlier inspection of the manufacturing and packaging parts of the Bioiche facility.

The application is recommended for “Approval” from CMC perspective. Attached is the final EES summary report.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 22306/000 Sponsor : ACADEMIC PHARMS
 Org Code : 110 1400 SOUTH ORANGE AVE
 Priority : 3 ORLANDO, FL 32806

Stamp Date : 02-NOV-2007 Brand Name : SO-AQUEOUS
 PDUFA Date : 25-MAY-2009 Estab. Name:
 Action Goal : Generic Name: SOTALOL HYDROCHLORIDE
 District Goal : 26-MAR-2009 Dosage Form: (INJECTION)
 Strength : 15 MG/ML

FDA Contacts: S. GOLDIE Project Manager 301-796-2055
 T. WONG Review Chemist (HFD-810) 301-796-1608
 K. SRINIVASACHAR Team Leader 301-796-1760

Overall Recommendation: ACCEPTABLE on 22-MAY-2009 by M. STOCK (HFD-320) 301-796-4753
 WITHHOLD on 21-MAY-2009 by M. STOCK (HFD-320) 301-796-4753

Establishment : CFN : 9612724 FEI : 3002806521
 BIONICHE TEORANTA
 INVERIN
 COUNTY GALWAY, , EI

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER
 FINISHED DOSAGE STERILITY TESTER

Profile : SVS OAI Status: NONE
 Last Milestone : OC RECOMMENDATION
 Milestone Date : 08-OCT-08
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
b(4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
 Last Milestone : OC RECOMMENDATION
 Milestone Date : 19-MAY-09
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
b(4)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER
 FINISHED DOSAGE STERILITY TESTER

Profile : CTL OAI Status: NONE
 Last Milestone : OC RECOMMENDATION
 Milestone Date : 10-SEP-08
 Decision : ACCEPTABLE
 Reason : BASED ON PROFILE

Establishment : CFN : _____ FEI : _____

b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER
 FINISHED DOSAGE STERILITY TESTER

Profile : CTL OAI Status: NONE
 Last Milestone : OC RECOMMENDATION
 Milestone Date : 06-NOV-08
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

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/s/

Thomas M Wong
5/22/2009 01:58:15 PM
CHEMIST

Ramesh Sood
5/22/2009 02:05:18 PM
CHEMIST

MEMORANDUM

To: NDA 22-306
From: Thomas M. Wong, Ph.D., Chemist
Date: 22-May-2009
Drug: So-Aqueous (sotalol hydrochloride) injection
Route of administration: Intravenous injection
Strength: 150 mg/10 ml (15 mg/ml)
Subject: CMC recommendation for NDA 22-306

The office of Compliance (OC) has provided an overall WITHHOLD recommendation for the manufacturing sites. The reason for the withhold is that the Bioniche facility used for packaging could not be inspected because of scheduled facility shut down. From CMC perspective, we do not recommend approval for this application until an acceptable recommendation from the Office of Compliance for the manufacturing sites is obtained. Attached is the EES summary report.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 22306/000 Sponsor : ACADEMIC PHARMS
 Org Code : 110 1400 SOUTH ORANGE AVE
 Priority : 3 ORLANDO, FL 32806

Stamp Date : 02-NOV-2007 Brand Name : SO-AQUEOUS
 PDUFA Date : 25-MAY-2009 Estab. Name:
 Action Goal : Generic Name: SOTALOL HYDROCHLORIDE
 District Goal : 26-MAR-2009 Dosage Form: (INJECTION)
 Strength : 15 MG/ML

FDA Contacts: S. GOLDIE Project Manager 301-796-2055
 T. WONG Review Chemist (HFD-810) 301-796-1608
 K. SRINIVASACHAR Team Leader 301-796-1760

Overall Recommendation:

Establishment : CFN : 9612724 FEI : 3002806521
 BIONICHE TEORANTA
 INVERIN
 COUNTY GALWAY, , EI

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER
 FINISHED DOSAGE STERILITY TESTER

Profile : SVS OAI Status: NONE
 Last Milestone : OC RECOMMENDATION
 Milestone Date : 08-OCT-08
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
 BIONICHE TEORANTA
 CASLA
 COUNTY GALWAY, , EI

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : SVS OAI Status: NONE
 Last Milestone : OC RECOMMENDATION
 Milestone Date : 19-MAY-09
 Decision : WITHHOLD
 Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

b(4)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 19-MAY-09
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
 └

b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
FINISHED DOSAGE STERILITY TESTER
Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :
 └

b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
FINISHED DOSAGE STERILITY TESTER
Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :
 └

b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
FINISHED DOSAGE STERILITY TESTER

22-MAY-2009

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 3 of 3

FINISHED DOSAGE STERILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 06-NOV-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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/s/

Thomas M Wong
5/22/2009 10:01:10 AM
CHEMIST

Ramesh Sood
5/22/2009 10:03:27 AM
CHEMIST

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-306
From: Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date: 11-May-2009
Drug: So-Aqueous (sotalol hydrochloride) injection
Route of administration: Intravenous injection
Strength: 150 mg/10 ml (15 mg/ml)
Subject: "Approval" recommendation for NDA 22-306 pending OC recommendation for manufacturing sites

Introduction: So-Aqueous (sotalol hydrochloride) injection is being developed for the treatment of ventricular arrhythmias and for the maintenance of normal sinus rhythm. Sotalol hydrochloride is an antiarrhythmic drug with class II (beta-adrenoreceptor blocking) and class III (cardiac action potential duration prolongation) properties. It is currently approved for oral administration under the tradename Betapace and Betaface AF along with several generic tablet formulations. The current 505(b)(2) submission will provide an injection formulations for the patients who are unable to take oral medication. This product must be diluted with saline or 5% dextrose in water (D5W) or ringer lactate and administered by a volumetric infusion pump over _____ hours at a constant infusion rate.

b(4)

Drug Substance: The drug substance is a white to almost white, fine crystalline powder which is freely soluble in water but practically insoluble in methylene chloride. Chemically, sotalol hydrochloride is N-(4-[(1RS)-1-Hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl]methanesulfonamide hydrochloride. The molecular formula is $C_{12}H_{21}ClN_2O_3S \cdot HCl$. It has one stereogenic center and is synthesized as a racemate. The drug substance will be manufactured and supplied by _____. The manufacturing and control information for the drug substance is referenced to DMF _____. There are also USP and EP monographs for sotalol hydrochloride. The DMF was found adequate to support the current NDA. The applicant has provided acceptable specification for the drug substance to ensure its suitability for the product manufacture. The specification include tests and acceptance criteria for solubility, color, appearance, identification (IR, HPLC and UV), identification of _____.

b(4)

Drug product: The drug product is a sterile, clear solution in 10 ml vial. The formulation contains sotalol hydrochloride, glacial acetic acid, acetic acid, sodium hydroxide and water for injection. All excipients are compendial. The manufacturing includes solution compounding under _____. The in-process tests control the individual manufacturing operations. The final drug product specification includes tests and acceptance criteria for appearance, assay (HPLC), impurities (HPLC), pH, clarity of the solution, visible and sub-visible particulate matter, volume of injection, bacterial endotoxin, identification (IR) and sterility. All analytical methods have been adequately validated. The product is packaged in 10 ml glass vials, each containing 10 ml of the solution (150 mg/10ml).

b(4)

Each vial is individually packaged in a carton. The drug product is to be stored at 25°C (77°F) with excursion permitted to 15°-30° C (59°-86°F). The product should be protected from freezing and light.

A 24 month expiration period has been assigned to the drug product based on the submitted stability data.

The microbiology reviewer has also provided "approval" recommendation on 5-May-09.

The office of Compliance (OC) has not provided an overall recommendation for the manufacturing sites at the time of this memorandum. The CMC reviewer will write a final recommendation after the OC has provided their recommendation.

Recommendation: The final "approval" recommendation for this NDA from CMC perspective is contingent upon a final recommendation from the Office of Compliance for the manufacturing sites. All other CMC issues have been resolved.

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/s/

Ramesh Sood
5/11/2009 09:47:52 AM
CHEMIST



NDA 22-306

So-AqueousTM (Sotalol Hydrochloride) Injection

Academic Pharmaceuticals, Inc.

Thomas M. Wong, Ph.D.

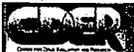
**Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment**

**Division of Cardiovascular and Renal Products
Review of Chemistry, Manufacturing, and Controls**



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CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-306
2. REVIEW #: 1
3. REVIEW DATE: February 27, 2009
4. REVIEWER: Thomas M. Wong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

25 July 2008

CMC Amendment # 0003:

5 Sep 2008 and 8 Oct 2008

CMC Amendment # 0004:

5 Dec 2008

CMC Amendment # 0005:

18 Dec 2008

CMC Amendment # 0006:

15 Jan 2009

CMC Amendment # 0007:

29 Jan 2009

CMC Amendment # 0008:

9 Feb 2009

7. NAME & ADDRESS OF APPLICANT:

Name: Academic Pharmaceuticals, inc.

Address: 21 N. Skokie Valley Highway
Lake Bluff, IL 60044

Representative: Not Applicable

Telephone: (847) 735-1170

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: So-Aqueous™
- b) Non-Proprietary Name (USAN): Sotalol Hydrochloride, USP
- c) Code Name/#: N/A



CHEMISTRY REVIEW



Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) Sotalol Hydrochloride Injection, 15 mg/ml

10. PHARMACOL. CATEGORY: Treatment of ventricular arrhythmias

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 15 mg/ml

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN Name: Sotalol Hydrochloride, USP

Chemical name: N-(4-[(1R,S)-1-Hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl]methanesulfonamide hydrochloride

Other chemical name: None

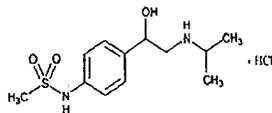
CAS registry number: 959-24-0

Company or lab code: None

Molecular Weight: 308.83

Structural formula: $C_{12}H_{21}ClN_2O_3S \cdot HCl$

Structure:





CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	II	┌	—	1	Adequate	August 25, 2008	Annual update submitted on December 17, 2007
—	III	└	—	4	N/A	N/A	There is enough data in the application.
—	III	┌	—	4	N/A	N/A	There is enough data in the application.

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	66,955	Commercial IND

18. STATUS:

ONDC:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMFPA	N/A		
EA	Acceptable/categorical exclusion	February 27, 2009	T.M. Wong
Microbiology	Pending		John Metcalfe

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____
Yes ____ No If no, explain reason(s) below:



CHEMISTRY REVIEW



Executive Summary Section

The Chemistry Review for NDA 22-306

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product, So-Aqueous™ (sotalol hydrochloride for injection), 150 mg/10 ml, is recommended as APPROVAL from a CMC perspective, pending on overall site approval from Office of Compliance and satisfactory microbiology review. A final memo will be deposited in the DFS once both the overall site approval from Office of Compliance and recommendation from microbiology review are obtained.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product:

So-Aqueous™, Sotalol hydrochloride, injection is developed to substitute oral sotalol therapy for the maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter) and for the treatment of documented life-threatening ventricular arrhythmias. The product contains 15 mg/ml racemic sotalol hydrochloride dissolved in [redacted] with a final pH of approximately [redacted]. The injection is supplied as a sterile, clear solution in 10 ml vial, for intravenous administration. Each vial contains 150 mg racemic sotalol hydrochloride and 29 mg glacial acetic acid in water for injection as inactive ingredient. So-Aqueous™ must be diluted for infusion with saline, or with 5% dextrose in water (D5W), or with Ringer lactate and administered by a volumetric infusion pump over [redacted] hours. Compatibility study results indicated that the drug product is compatible with these diluents. Compatibility study results also indicate that the drug product is compatible with infusion bags made from [redacted] material and infusion tubing made from [redacted] material. These diluents as well as the materials for the infusion system are specified in the package insert. The vial is a single use vial and unused portion will be discarded.

b(4)

The composition of the drug product is a simple one. Acetic acid is used as [redacted] to maintain the pH of solution in the range of 6.0 - 7.0. Water for injection is used as [redacted]. The product is filled into 10 ml glass vials, sealed with a [redacted] stopper, and a flip caps with aluminum skirt. The commercial batch size is [redacted] however, depending on market-needs, the commercial batch size may be changed to a size within the range of [redacted], depending on the demand of the product. The proposed scale up will use equipment of the same operating principles and design. The manufacturing is a typical parenteral drug manufacturing process and in-process controls are adequate. Drug product specification is in place and the testing items and their acceptance criteria are appropriate and adequate. The specification has been justified and the analytical methods have been adequately validated. Stability results supports the proposed 24 month shelf-life when stored at 25°C, protected from light.

b(4)

CHEMISTRY REVIEW

Executive Summary Section

Drug substance:

Detailed information of the drug substance is available in DMF — . Sotalol hydrochloride, USP, is a white crystalline solid with a molecular weight of 308.8. It is hydrophilic, soluble in water, propylene glycol and ethanol, but is only slightly soluble in chloroform. Chemically, sotalol hydrochloride is N-(4-[(1R)-1-Hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl) methanesulfonamide hydrochloride. The molecular formula is $C_{12}H_{21}ClN_2O_3S \cdot HCl$. Specification of the drug substance is in place and the testing methods have been validated. The available stability data supports a 5 year expiry dating.

b(4)

B. Description of How the Drug Product is Intended to be Used

So-Aqueous™ is an aqueous formulation of intravenous sotalol hydrochloride. Sotalol hydrochloride is an antiarrhythmic drug with Class II (beta-adrenoreceptor blocking) and Class III (cardiac action potential duration prolongation) properties. It is intended to substitute for oral sotalol in patients who are unable to take sotalol orally: initiation and/or maintenance of sotalol therapy. So-Aqueous™ must be diluted with saline or 5% dextrose in water (D5W) (or ringer lactate) and administered by a volumetric infusion pump over — hours at a constant infusion rate.

b(4)

So-Aqueous™ is supplied as a sterile, clear solution in 10 ml vials, each containing 150 mg sotalol hydrochloride (15 mg/ml). Each vial is individually packed in a carton. The drug product is to be stored at 25°C (77°F) with excursion permitted to 15°-30°C (59°-86°F). Protect from freezing and light. The NDC is 42919-176-10.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Academic Pharmaceuticals, Inc., has submitted sufficient and appropriate information to support the approval of the drug product, So-Aqueous™ (sotalol hydrochloride for injection).

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Thomas M. Wong, Ph.D.
Branch Chief Name: Ramesh Sood, Ph.D.
Project Manager Name:

C. C Block

See DFS.

53 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Thomas M Wong
2/27/2009 11:20:46 AM
CHEMIST

Ramesh Sood
2/27/2009 02:31:03 PM
CHEMIST

Initial Quality Assessment
Branch I

OND Division: Division of Cardiovascular and Renal Products
NDA: 22-306
Applicant: Academic Pharmaceuticals
Letter Date: 22 Oct 2007
Status Date: 25 July 2008
PDUFA Date: 25 May 2009
Tradename: So-Aqueous
Established Name: Sotalol hydrochloride
Dosage Form: Sterile solution (injection), 15 mg/mL
Route of Administration: Intravenous
Indication: Substitution for oral sotalol in patients unable to take oral medication
Assessed by: Kasturi Srinivasachar
ONDQA Fileability: Yes

Summary

This is a 505(b)(2) submission in paper CTD format for a parenteral formulation of sotalol hydrochloride. Sotalol hydrochloride, a beta-adrenoreceptor blocker, is currently approved for oral administration under the tradename Betapace and Betapace AF along with several generic tablet formulations for the treatment of life threatening ventricular arrhythmias and maintenance of sinus rhythm in patients with symptomatic atrial fibrillation. This is the first product for intravenous administration and is indicated for patients who are unable to take oral medication for various reasons (surgery, intubation, acute illness etc.). Clinical development was carried out under IND 66,955. No CMC specific or interdisciplinary meetings with a significant CMC component were held with the sponsor.

Drug Substance

The drug substance is a white to almost white, fine crystalline powder which is freely soluble in water but practically insoluble in methylene chloride. It has one stereogenic center and is synthesized as a racemate [redacted] It is sourced from [redacted] who is the holder of DMF # [redacted] This DMF has been referenced for CMC information concerning the drug substance. There are also USP and EP monographs for sotalol hydrochloride. A copy of the specification sheet from [redacted] has been submitted to the QOS but is barely legible. The in-house testing performed by the drug product manufacturer is also listed. DMF # [redacted] was last reviewed on Oct. 3, 2007 and found to be adequate.

b(4)

Drug Product

Sotalol injection is a sterile solution containing 15 mg/mL sotalol hydrochloride with glacial acetic acid, acetic acid [redacted] sodium hydroxide and water for injection as excipients. Glacial acetic acid is used; [redacted] to maintain the pH between 6.0 and 7.0 [redacted] and sodium hydroxide [redacted] used for pH adjustment. It is stated that the formulation has been developed to correlate with the dosing regimen of the oral dosage forms. The manufacturing

b(4)

process is similar to that of other solution parenteral products. [redacted] sterilization was investigated and found not to be suitable because of an increase in impurity levels and [redacted] production was chosen. The [redacted] product is filled into 10 mL [redacted] glass vials with [redacted] stopper and flip caps with aluminum skirt [redacted]. Standard specifications are proposed for an injection product and impurity limits are based on USP/EP. There are different acceptance criteria for release and shelf-life for assay and impurities. Data have been submitted for 3 batches manufactured at [redacted] commercial scale at Bioniche Teoranta, Ireland. The commercial manufacturing will be at the same facility but in a different building. Data have also been provided for a Biobatch manufactured by the same process at [redacted]. A shelf-life of 24 months is proposed based on 18 months' long term and 6 months' accelerated data on 3 pilot scale batches. Since So-Aqueous is administered by slow infusion it must be diluted and compatibility studies have been carried out with 5% dextrose injection, 0.9% sodium chloride injection and Lactated Ringer's Injection. It was concluded that sotalol hydrochloride injection was compatible with these I.V. solutions at final concentrations ranging from [redacted] over a 24 hour period.

b(4)

Critical Review Issues

Drug substance

- All updates and amendments to the DMF for sotalol hydrochloride since the last review should be evaluated.
- From the synthetic scheme provided in the NDA, the intermediate named [redacted]. The DMF should be reviewed to see if this intermediate has been detected in the drug substance at levels above the EMEA threshold for genotoxicity.
- Are the limits for residual Pd in the drug substance specification in conformance with EMEA limits for an injection product?
- It is stated that microbiological limit tests are performed by Bioniche in addition to USP tests but this is not reflected in the specification. Are these tests performed on every batch of drug substance and what are the acceptance criteria?
- An expiration date of 5 years is claimed for the drug substance. Do the stability data support this? Is there a retest date in addition to this?

b(4)

Drug Product

- Since this is a parenteral dosage form, the major critical issue is sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life. These aspects are expected to be covered by the microbiology reviewer.
- USP has an assay acceptance criterion of 95-105% for sotalol tablets which should be valid over the shelf-life of the product. However, Academic Pharmaceuticals is proposing a shelf-life limit of [redacted] for sotalol injection. Is this justified?
- Are different release and shelf-life limits for impurities [redacted] justified? It is stated in the drug substance section of the QOS that impurities [redacted] are not degradants. What is the qualification threshold for this product?
- Is the total impurity limit of [redacted] acceptable given that the values from the stability studies after 18 months of long term storage are [redacted] ?
- Have appropriate tests been performed to show compatibility of the vial stoppers with the drug product?

b(4)

- No humidity controls have been specified for the stability studies under long term and accelerated temperatures. Is this acceptable?

Labeling

The package insert and container labels should state the quantitative amounts of all excipients. The labels state that vials should be stored with light protection yet there is no mention of cartons as a secondary container. If cartons are used their labels should also be provided.

Comments and Recommendations

The application is fileable. Manufacturing, testing and packaging facilities will be entered into EES and the reviewer should verify the accuracy and completeness of the entries. A consult request for the microbiology review of this NDA will be submitted. A single CMC reviewer is recommended for this application.

Kasturi Srinivasachar
Pharmaceutical Assessment Lead
Ramesh Sood, Ph.D.
Branch Chief

Aug.15, 2008
Date
Aug. 15, 2008
Date

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/s/

Kasturi Srinivasachar
8/15/2008 12:31:33 PM
CHEMIST

Ramesh Sood
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