

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205108Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	10-16-2014
From	Kasturi Srinivasachar, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	205108
Supplement#	
Applicant	Arbor Pharmaceuticals
Date of Submission	Dec 23, 2013
PDUFA Goal Date	Oct 23, 2014
Proprietary Name / Established (USAN) names	Sotylize / sotalol hydrochloride
Dosage forms / Strength	Oral solution 5 mg/mL
Proposed Indication(s)	1. Treatment of documented life-threatening ventricular arrhythmias 2. The maintenance of normal sinus rhythm in patients with history of highly symptomatic atrial fibrillation/flutter
Recommended:	Approval

This secondary review is based on the primary reviews of:

- **CMC (Sherita McLamore-Hines), 09-26-2014 and 06-23-2014**
- **Quality Biopharmaceutics (Sandra (Suarez), 09-18-2014**
- **Microbiology (Bryan Riley), 02-04-2014**
- **DMEPA (Jean Olumba), 04-10-2014 and 03-19-2014**
- **DMPP (Karen Dowdy), 10-10-2014**
- **OPDP (Puja Shah), 10-8-2014**
- **505(b)(2) Assessment (Russell Fortney) 10-02-2014 and 10-16-2014**

1. Introduction

This is a 505(b)(2) NDA for sotalol hydrochloride oral solution, 5 mg/mL. This filing is based upon the reference listed drugs (RLD), Betapace tablets which was approved on Oct. 30, 1992 under NDA 19865 and Betapace AF tablets which was approved on Feb. 22, 2000 under NDA 21151. This product is being developed for patients who are unable to swallow tablets.

2. Background

Sotylize (sotalol hydrochloride) has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Sotalol hydrochloride is a racemic mixture of (b)(4) l-sotalol. Both isomers have similar Class III antiarrhythmic effects, while the l-isomer is responsible for virtually all of the beta-blocking activity. The beta-blocking effect of sotalol is non-cardioselective, half maximal at an oral dose of about 80 mg/day and maximal at doses between 320 and 640 mg/day. Sotalol does not have partial agonist or membrane stabilizing activity. Although significant beta-blockade occurs at oral doses as low as 25 mg, significant Class III effects are seen only at daily doses of 160 mg and above.

The current application relies on the Agency's determination of safety and efficacy for Betapace tablets and supporting relevant published literature and consequently there are no clinical or clinical pharmacology sections. The regulatory decision will be primarily based on the recommendations in the CMC, Quality Microbiology, Biopharmaceutics and the Division of Medication Error Prevention and Analysis (DMEPA) reviews of this application.

3. CMC

The reviewer recommends approval from a CMC perspective.

Drug Substance: The Applicant referenced DMF (b)(4) for complete information on the drug substance, sotalol hydrochloride. The reviewer states that the original DMF and all subsequent amendments were reviewed and found to be adequate.

Drug Product: The product will be marketed in one strength, 5 mg/mL. The excipients in the formulation include sodium citrate (b)(4), citric acid (b)(4), sucralose, sodium benzoate, grape flavor and purified water. The drug product is packaged in either 250 mL or (b)(4) mL amber (b)(4) bottles with an induction seal and a (b)(4) cap. An expiration dating period of 15 months has been requested by the Applicant and will be granted based on the stability data provided.

Facilities review/inspection: The drug substance and drug product manufacturing sites were submitted for inspection and the current overall Office of Compliance recommendation is "Acceptable".

4. Biopharmaceutics

The reviewer recommended approval based on a review of the BA/BE waiver request. The reviewer concluded that the biowaiver request was adequately supported by the high solubility and permeability of the drug substance and the high oral bioavailability of sotalol following administration of the tablets and the rapid dissolution of Betapace tablets.

5. Product Quality Microbiology

The reviewer recommended approval from a quality microbiology perspective based on the acceptability of the Microbial Limits specification for Sotylize.

6. Non-Clinical Pharmacology/Toxicology

N/A

7. Clinical/Statistical- Efficacy

N/A

8. Safety

N/A

9. Advisory Committee Meeting

N/A

10. Pediatrics

PeRC granted a full waiver from pediatric studies and agreed that the product is fully assessed for all pediatric populations down to birth.

11. Other Relevant Regulatory Issues

N/A

12. Labeling

The proposed proprietary name, Sotylize, was found acceptable by the Office of Medication Error Prevention and Risk Management from both a promotional and safety perspective. DCRP has not carried out a formal review of the labeling for this NDA since it basically follows the labeling for Betapace and Betapace AF with the exception of the obvious changes to dosage form and strength and sections 11 (Description) and 16 (How Supplied/ Storage and Handling) of the package insert. **I noted that there is a typographical error in the structure of sotalol (one of the double bonds of the benzene ring is missing) and recommend that this be corrected in the labeling attached to the NDA action letter.**

DMEPA has recommended some improvements to the container labels to promote safe use of the product and to mitigate any confusion. These include 1) relocation of the net quantity statement to the bottom of the principal display panel away from the NDC number; 2) revisions to the storage statement on the side panel to correspond to the storage condition statement in the package insert; 3) changing the presentation of the established name to ‘sotalol hydrochloride’ from the current (b) (4). These recommendations have been incorporated in the revised container labels submitted by the Applicant on 05-02-2014. DMPP and OPDP have several comments and recommendations for the PI and PPI and these will be incorporated in the labeling attached to the NDA action letter.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

All primary reviews of this application recommended approval and I concur with the reviewers. Sotylize (sotalol hydrochloride) oral solution, 5 mg/mL, may be approved with a shelf-life of 15 months when stored at room temperature.

- Risk Benefit Assessment

This is a 505(b)(2) application for sotalol hydrochloride oral solution which relies on the safety and efficacy established for the marketed products, Betapace and Betapace AF tablets. Consequently, the risk/benefit of this product is expected to be the same as Betapace.

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/s/

KASTURI SRINIVASACHAR
10/16/2014