# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-306**

## OTHER REVIEW(S)

**NDA 22-306 Sotalol Hydrochloride Injection**
**RHPM Overview**
**July 1, 2009**

**Sponsor:** **Academic Pharmaceuticals, Inc.**
**Type:** **505(b)(2)/3S**
**Receipt Date:** **July 25, 2009**
**Goal Date:** **May 25, 2009**

**Action:** **Approval**
**Action Date:** **July 1, 2009**

**Background**
Sotalol oral tablets have been approved for a number of years. Academic Pharmaceuticals, Inc. is seeking approval of an injectable sotalol product that can be used when patients are unable to use the oral product (because of surgery, intubation, acute illness, etc.). This application was originally submitted on November 2, 2007. The sponsor claimed both orphan and 505(b)(2) user fee exclusions. However, at the time the application was submitted the 505(b)(2) user fee exclusions had expired (FDAAA now requires user fees for 505(b)(2) applications) and orphan designation had not yet been granted. Therefore, an UN letter was issued. The sponsor was granted orphan designation on July 25, 2008, and that became the official receipt date of the application, with a PDUFA goal date of May 25, 2009.

**Division Director's Memo (5/22/09)**
**Reviewer: Norman Stockbridge, M.D., Ph.D.**
**Recommendation: Approval**
**Summary:** The clinical pharmacologists, Dr. Mehta, and I are all in complete agreement that the IV portion of the one comparative bioavailability study was flawed. Dr. Mehta's and the clinical pharmacologists propose an in vitro study of the IV administration of sotalol to confirm the accounting for drug in the tubing. Secondly, they recommend a DSI audit of the original study. I conclude that our reliance upon the sponsor's comparative PK study was minimal. It confirmed the PK following oral administration, and that suffices to describe dosing instructions that will produce fairly similar plasma profiles of sotalol following oral and IV administration of about the same dose over about [ ] Given the lack of dosing adjustment recommendations for Betapace by weight or for the modest dependence of kinetics on meals, these instructions seem sufficient. Consequently, I do not believe that further inquiry into the sponsor's flawed study will be useful. The site does not appear to have performed the study well, and I will suggest an inspection, but this does not need to be conducted prior to approval.

b(4)

**CDTL Review (5/20/09)**
**Reviewer: Mehul Mehta, Ph.D.**
**Recommendation: Complete Response**
**Summary:**
In my opinion, this application cannot be approved based on the data submitted in this application for the following two reasons:

1. For study 12103, the sponsor has not provided any data to explain why the IV arm (75 mg So-Aqueous) failed to show similar exposure (AUC) to the oral arm (80 mg Betapace). Until this is satisfactorily addressed by the sponsor, this study is of limited usefulness.
2. There are some useful data from study 12103, namely the similar Tmax and half-life of oral sotalol from this study compared to those reported in the Betapace label. However, before this information can be relied upon, this study has to be audited by DSI so that we are assured of the authenticity of these data. The study has not been audited yet.

Therefore, in my opinion, this should be a 'Complete Response' action and the following needs to occur so that the application can be further evaluated:

- To prove that indeed the infusion pump's failure to deliver the right volume of drug is the reason for lack of similar exposure of the IV arm to the oral arm, the sponsor needs to perform an in-vitro pump study with sotalol solution for IV infusion where a) the procedures used in study 12103 are applied, and; b) the IV tubing is adequately flushed after administration of sotalol. In both cases, the volume and the amount of sotalol delivered should be measured. The difference in amount of sotalol delivered under these two conditions should help justify the results of study 12103.
- Study 12103 needs to be audited by DSI

**Clinical Pharmacology and Biopharmaceutics Review (12/18/08)**
**Reviewer: Elena Mishina, Ph.D., and Christopher Tornoe, Ph.D.**
**Recommendation: Complete Response**
**Summary:** The Office of Clinical Pharmacology has reviewed the information submitted under NDA 22-306 for sotalol injection and finds the results from bioequivalence study No. 12103 not acceptable. However, taking into account that the study was not properly powered to demonstrate bioequivalence and also that a critical protocol's violation occurred during the infusion of the drug, OCP considers that the sponsor should be given the opportunity to provide additional data to support the approval of their product.

According to CFR 320.24, there are different types of evidence that can be submitted to establish bioavailability or bioequivalence. The selection of the method depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. In general, the following two approaches (*in vivo* or *in vitro*) are acceptable for determining the bioavailability or bioequivalence of a drug product:

(i) An in vivo study in humans in which the concentration of the active ingredient in an appropriate biological fluid is measured as a function of time. This approach is particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body; or
(ii) An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data.

Although, an acceptable in vivo BE study can be considered the "Gold Standard" choice to support the approval of this product, in this particular case there is an alternative in vitro approach that also can be used to support the approval of this product. The in vitro approach is supported by the reviewer's PK population-simulated data predicting the concentration-time profiles for sotalol.
The following comments should be properly addressed by the sponsor.

1. The sponsor should perform an in vitro pump study with sotalol solution for IV infusion where 1) the procedures used in study 12103 are applied, and 2) the IV tubing is adequately flushed after administration of sotalol. In both cases, the amount delivered should be measured to verify that the intended amount of sotalol was delivered. The sponsor should evaluate in vitro a possible binding of sotalol to the _____ tubing. If the in vitro studies confirm the administered amount of the IV dose, this information may be used for the approval consideration. If the in vitro pump study cannot resolve the discrepancies found in the data, the sponsor may have to repeat the in vivo study using IV and oral formulations. b(4)
2. The agency should conduct site inspection to verify the validity of the records.

**Chemistry Review (2/27/09)**

**Reviewer: Thomas Wong, Ph.D.**
**Recommendation: Approval**
**Summary:** The drug product, sotalol hydrochloride for injection, 150 mg/10 ml, is recommended as APPROVAL from a CMC perspective.

**Microbiology Review (5/7/09)**
**Reviewer: John Metcalfe, Ph.D.**
**Recommendation: Approval**
**Summary:** NDA 22-306 is recommended for approval on the basis of product quality microbiology.

**DSI:** There were no inspections of the clinical study sites.

**Pediatric Rule:** PREA does not apply as this application does not include a new dosage form, indication, route of administration or dosing regimen.

**Labeling:** The Package Insert is similar to the most recently approved Betapace label, with modifications made to account for the change in route of administration, and the change to the PLR format.

**Tradename:** The sponsor's requested tradename of So-Aqueous was rejected by DMEPA for the following reasons:

[redacted]

b(4)

The sponsor has submitted a rebuttal to DMEPA's objections, and has also submitted an alternate tradename for review, [redacted] but at this time the issue has not been resolved. The application will be approved without a tradename.

b(4)

**Advisory Committee:** N/A

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

# Maternal Health Team Label Review

**Date:** June 30, 2009 **Date Consulted:** May 28, 2009

**From:** Leyla Sahin, M.D.
Medical Officer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

**Through:** Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

**To:** Division of Cardiorenal products (DCRP)

**Drug:** Sotalol; NDA 22-306

**Subject:** Pregnancy and Nursing Mothers labeling

**Materials Reviewed:** Pregnancy and Nursing Mothers subsections of sotalol labeling.

**Consult Question:** Please review sections of the proposed label as they relate to pregnancy and lactation.

## INTRODUCTION

On August 19, 2008, Academic Pharmaceuticals, Inc. submitted a new drug application (NDA) to the Division of Cardiorenal Products for a new intravenous formulation of sotalol. Sotalol is

an antiarrythmic drug that blocks beta adrenergic receptors and prolongs cardiac action potential duration. It is indicated for the treatment of atrial fibrillation and flutter. The sponsor's proposed indication for intravenous sotalol is for substitution for oral sotalol in patients who are unable to take sotalol orally; initiation and/or maintenance of sotalol therapy.
On May 28, 2009, the DCRP consulted the Maternal Health Team (MHT) to review the pregnancy and nursing mothers section of the sotalol package insert, and provide comment. This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of iv sotalol labeling.

## BACKGROUND

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of iv sotalol labeling.

### MATERIALS REVIEWED

**1. Sponsor's Proposed Pregnancy and Nursing Mothers Labeling**

**----------USE IN SPECIFIC POPULATIONS----------**

[redacted] b(4)

**8.1 Pregnancy**

[redacted] b(4)

b(4)

## 8.3 Nursing Mothers

b(4)

2. **Published Literature**

**A. Sotalol use during pregnancy:**

In the clinical setting, sotalol is used during pregnancy to treat fetal arrhythmias by administering drug to the mother. Published studies demonstrate efficacy and no adverse outcomes related to sotalol administration are reported. Published data on the use of sotalol during pregnancy to treat maternal cardiac arrhythmias is limited to a few case reports[1,2,3].

**B. Sotalol use during lactation:**

There are published data on the levels of sotalol in human milk. In five mothers[4] whose mean sotalol dose was 433 mg/day, sotalol concentrations in milk ranged from 4.8 to 20.2 mg/L (mean=10.5 mg/L), with a milk:plasma ratio of 5.5:1 (range 2.2-8.8). Using an average milk intake of 500 ml of milk per day, the calculated infant dose was 0.8-3.4 mg/kg, which is similar to recommended therapeutic doses in neonates[5]. Two other case reports showed similar findings. One woman[3] taking sotalol 160 mg/day had milk sotalol levels of 5 and 4.4 mg/L at 3 hours after the dose on days 5 and 7 postpartum, with a milk plasma ratio of 3.57 and 2.75. Another woman[6] taking sotalol 240 mg/day had milk:plasma ratios that ranged from 2.43-5.64.

---

[1] Auzelle MP et al: [In utero treatment of fetal tachycardias with a digitalis-beta blocker combination. Apropos of 2 cases]. J Gynecol Obstet Biol Reprod (Paris) 16:383-91, 1987.

[2] Babin JP et al: [Possible embryofetopathy caused by a beta-blocker (sotalol) taken throughout the pregnancy]. Pediatrie 40:129-36, 1985.

[3] Wagner X, Jouglard J, Moulin M et al. Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. Am Heart J. 1990; 119:700-2.

[4] O'Hare MF, et al. Sotalol as a hypotensive agent in pregnancy. Br J Ob Gyn 1980;87(9):814-820.

[5] Laer S, et al. Development of a safe and effective pediatric dosing regimen for sotalol based on population pharmacokinetics and pharmacodynamics in children with supraventricular tachycardia. J of the American College of Cardiology. 2205;46(7);1322-30.

[6] Hackett LP, Wojnar-Horton RE, Dusci LJ et al. Excretion of sotalol in breast milk. Br J Clin Pharmacol. 1990;29:277-8.

## DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule published May 2008. While the final rule is being written and cleared, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians. Sotalol is used during pregnancy to treat fetal cardiac arrhythmias but data about the use of sotalol to treat maternal arrhythmias is limited. There are published data on milk levels of sotalol that can inform the nursing mothers section of labeling.

The MHT recommends the following changes regarding pregnancy and nursing to the sotalol label:

1. Add published data on milk levels, which show that high levels of sotalol are excreted in milk.

2. Remove the weight based multiples of the human dose, as body surface area is the best basis for calculating human dose multiples when AUC is not available. Removing unnecessary information from the label makes it easier for the clinician to understand the outcomes from these studies and use them in prescribing decisions.

3. Remove the one case report regarding sotalol exposure during pregnancy. This limited information is not useful for the prescriber in assessing or communication the risks and benefits of sotalol use. There are other more extensive published data[7] that report normal fetal weights following use of sotalol during pregnancy to treat fetal arrhythmias.

4. Remove Pregnant Women from Highlights, as the proposed language is contrary to the information that appears in 8.1 Pregnancy.

The MHT's recommended labeling for iv sotalol is provided below.

## RECOMMENDATIONS

Provided below are the MHT's recommended revisions to the sponsor's proposed labeling. A track changes version of labeling that highlights all changes made was sent to the DCRP by e-mail on June 11, 2009.

**Highlights of Prescribing Information:**

**----------USE IN SPECIFIC POPULATIONS----------**

[7] Oudijik M, et al. Treatment of fetal tachycardia with sotalol: transplacental pharmacokinetics and pharmacodynamics. J Am Coll Cardiol 2003;42:765-70.

Nursing Mothers: Sotalol is excreted in milk in large amounts; potential harm to the infants. Discontinue nursing or discontinue the drug (8.3).

### 8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. Sotalol crosses the placenta. In animal studies there was no increase in congenital anomalies, but an increase in early resorptions occurred at sotalol doses 18 times the maximum recommended human dose (MRHD, based on body surface area). Because, animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Reproduction studies in rats and rabbits during organogenesis at sotalol doses (9 and 7 times the MRHD (based on body surface area), respectively, did not reveal any increase in congenital anomalies. In rabbits, a sotalol dose 6 times the MRHD produced a slight increase in fetal death, but this was associated with maternal toxicity. This effect did not occur at a sotalol dose 3 times the MRHD. In rats, a sotalol dose 18 times the MRHD, increased the number of early resorptions, while a dose 2.5 times the MRHD produced, no increase in early resorptions.

### 8.3 Nursing Mothers

Sotalol is excreted in human milk in high levels. In five mothers whose mean sotalol dose was 433 mg/day, sotalol concentrations in milk ranged from 4.8 to 20.2 mg/L (mean=10.5 mg/L), with a milk:plasma ratio of 5.5:1 (range 2.2-8.8). The calculated infant dose was 0.8-3.4 mg/kg, which is similar to recommended therapeutic doses in neonates. Two other case reports showed similar findings. Because of the potential for adverse reactions in nursing infants from sotalol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

# SEALD LABELING REVIEW

| | |
|---|---|
| APPLICATION NUMBER | NDA 22-306 |
| APPLICANT | Academic Pharmaceuticals |
| DRUG NAME | SO-AQUEOUS (sotalol hydrochloride) |
| SUBMISSION DATE | July 25, 2008 |
| SEALD REVIEW DATE | May 22, 2009 |
| SEALD REVIEWER(S) | Kimberly A. Shiley, RN, BSN |
| | This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57. |

# 12 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Other Review(s) -* 1

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

Kimberly Shiley
5/22/2009 11:19:45 AM
CSO
SEALD comments sent to Review Division on 5-22-09.
Please sign off

Laurie Burke
5/26/2009 03:01:51 PM
INTERDISCIPLINARY