CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-306

MEDICAL REVIEW(S)

Cross-Discipline Team Leader Review

Date	5/1/2009
From	Mehul Mehta, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-306
Applicant	The Academic Phrmaceuticals
Date of Submission	7/25/08
PDUFA Goal Date	5/25/09
Proprietary Name / Established (USAN) names	So-Aqueous (Sotalol Hydrochloride)
Dosage forms / Strength	Injection / 15 mg/ml
Proposed Indication(s)	1. Substitution for oral sotalol in patients who are unable to take sotalol orally: initiation and/or maintenance of sotalol therapy. Also indicated for the initiation of therapy in those patients, who have clear indications for sotalol therapy, but unable to take it orally. Oral sotalol is indicated for: a) maintenance of normal sinus rhythm in patients with history of highly symptomatic atrial fibrillation/flutter; b)Treatment of documented life-threatening ventricular arrhythmias
Recommended:	*Complete Response*

1. Introduction

As stated above, So-Aqueous NDA 22-306 is an intravenous formulation of sotalol meant for patients who are unable to take sotalol orally. The sponsor requested, and received orphan-drug designation status on July 25, 2008. This is a 505(b)(2) submission. The listed drug specified by the sponsor for reliance of safety and efficacy is NDA 19-865 for Betapace Tablets by Berlex Labs.

The waiver of user fees for this NDA, as a result of orphan-drug designation, was granted by the Agency on 8/6/2008 (see Edward Fromm memo in DFS). In the same memo, the Agency agreed upon the filing date for this submission as July 25, 2008 and gave it the standard (S) review priority classification.

505(b)(2) assessment was made, and agreed upon, by the Agency on 11/17/2008 (see Russell Fortney memo in DFS).

The NDA filing review was done on 11/17/2008 and all disciplines agreed that this NDA can be filed. (See Russell Fortney memo in DFS).

The submission primarily consists of a relative bioavailability (BA) study that compared the systemic exposure of sotalol via oral (Betapace AF Tablet) and IV (So-Aqucous) infusion routes and assessment of this study will be the major focus of this memo.

2. Background

Oral sotalol hydrochloride is indicated for the maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm. Because sotalol hydrochloride can cause life-threatening ventricular arrhythmias, it should be reserved for patients in whom AFIB/AFL is highly symptomatic. Patients with paroxysmal AFIB whose AFIB/AFL is easily reversed (by Valsalva maneuver, for example) should usually not be given sotalol hydrochloride. In general, antiarrhythmic therapy for AFIB/AFL aims to prolong the time in normal sinus rhythm. Recurrence is expected in some patients.

Oral sotalol is indicated for the treatment of documented life-threatening ventricular arrhythmias. Because of the proarrhythmic effects of sotalol including a 1.5 to 2% rate of Torsade de Pointes or new VT/VF in patients with either NSVT or supraventricular arrhythmias, its use in patients with less severe arrhythmias, even if the patients are symptomatic, is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided. In life-threatening ventricular arrhythmias, the response to treatment should then be evaluated by a suitable method (e.g., PES or Holter monitoring) prior to continuing the patient on chronic therapy. Antiarrhythmic drugs may not enhance survival in patients with ventricular arrhythmias.

Information relevant from Betapace label for this submission is that sotalol Tmax ranges from 2.5 – 4 hours, its half-life is 12 hours, and its absolute bioavailability is in the range of 90-100%.

As mentioned earlier, the only clinical study conducted and submitted in this application is the clinical pharmacology study 12103. This study failed to achieve its primary objective of demonstration of similar sotalol systemic exposure from the oral and the IV infusion route and this will be discussed at length in this memo.

In addition, other disciplines that have written a review for this submission are Chemistry and Microbiology. It was determined by Drs. Karkowsky and DeFelice, the assigned medical reviewer and pharmacology/toxicology reviewer respectively that there will be no clinical and no pharm/tox review for this submission. This was conveyed by these reviewers at the team meeting on 3/13/2009.

3. CMC/Device

The following information is obtained from the 2/27/09 review of Drs. Wong and Sood.

"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

b(4)

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 —— 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 —— material and infusion tubing made from [ ] 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 the unused portion will be discarded. b(4)

The composition of the drug product is a simple one. Acetic acid is [ ] to maintain the pH of solution in the range of 6.0 - 7.0. Water for injection is used as ——. The product is filled into 10 ml glass vials, sealed with a —— stopper, and a flip caps with aluminum skirt. The commercial batch size is —— however, depending on market-needs, the commercial batch size may be changed to a size within the range of ——, 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 support the proposed 24 month shelf-life when stored at 25°C, protected from light." b(4)

The recommendations from the Chemistry review are:

"The drug product, So-Aqueous TM (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.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None at this time."

4. Nonclinical Pharmacology/Toxicology

There is no pharm/tox review for this NDA.

5. Clinical Pharmacology/Biopharmaceutics

As stated earlier, this submission rests primarily on the clin. pharm. study 12103. This was reviewed by Drs. Mishina, Dorantes, Tornoe and Jadhav of the Office of Clinical Pharmacology and the review was placed in DFS on 4/21/09. This review was amended on 5/14/09. Summarized below are the key features, and limitations, of this study.

Study 12103 Methods:

This was a randomized, two-dose, two-period, single dose, crossover study comparing systemic exposure of sotalol when given via Betapace 80 mg tablet and So-Aqueous (15 mg/ml), 75 mg IV infusion administered over 2.5 hours with a constant infusion rate. The primary objective of the study was to assess So-Aqueous infusion rate that would give exposure similar to that of an 80 mg oral dose of Betapace. The study was conducted in sotalol naïve healthy subjects. Eighteen subjects were recruited and usable data was obtained only from 15 subjects. After completion of the study, the sponsor realized that the systemic exposure (AUC) of sotalol from the IV arm was significantly lower than expected. The sponsor then used the data generated from this study and conducted simulations to estimate an infusion duration that would give similar Cmax and AUC as compared to that from 80 mg Betapace.

Study 12103 Results:

Table 3: The individual pharmacokinetic parameters of sotalol

		C max		T max		$AUC_{0-48\ hrs}$		$AUC_{0-\infty}$	
Subject	Initials	IV	Oral	IV	Oral	IV	Oral	IV	Oral
1		459	1538	2.50	2.00	3535	7343	3602	7425
2		622	410	2.00	3.50	4614	4460	4742	4703
3		593	326	2.50	2.50	4197	3225	4304	3317
4		356	635	2.50	3.00	3177	6893	3249	7241
5		607	795	3.00	3.00	3630	7816	3685	8165
6		532	812	2.50	2.50	3690	6802	3811	9335
8		617	748	3.00	3.50	4979	8991	5075	7730
9		523	591	2.00	2.50	4198	8311	4242	6656
10		591	845	2.50	2.00	5146	8933	5291	9150
11		1848	626	2.50	1.50	9944	5979	10134	6246
12		465	508	2.50	2.00	3650	4935	3727	5226
14		962	649	2.50	3.50	8640	8315	8948	9862
16		764	683	2.00	1.50	7342	8403	7444	9763
17		675	548	2.50	2.00	5622	8635	5749	6910
18		1467	1126	2.00	1.00	7018	7821	7146	8114
	Mean	739	723	2.43	2.40	5292	6891	5410	7323
	SD	405	296	0.32	0.78	2048	1694	2097	1897
	Median	600	642	2.50	2.50	4406	8942	4523	7333
	Min	356	326	2	1	3177	3225	3249	3317
	Max	1848	1538	3	4	9944	8933	10134	9862
	CV	0.55	0.41	0.13	0.33	0.39	0.25	0.39	0.26

b(6)

The mean plasma concentrations of sotalol after one administration of 80 mg oral sotalol and a 2.5-hr infusion of intravenous sotalol is shown below.

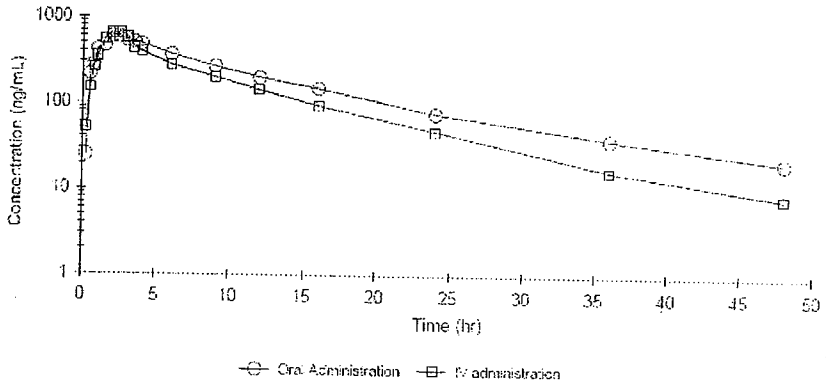

Figure 3. Sponsor's plot of the mean plasma concentrations of sotalol after the administration of 80 mg Oral Sotalol and a 2.5-hr infusion of "75" mg IV Sotalol.

Recommendations and comments from Drs. Mishina, Dorantes, Tornoe and Jadhav:

"The Office of Clinical Pharmacology has reviewed the information submitted under NDA 22-306 for So-Aqueous™ 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.

COMMENTS:

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."

My Conclusions of Study 12103:

1. The reason sponsor chose 75 mg of So-Aqueous dose to compare with 80 mg Betapace dose is probably based on the fact that sotalol absolute bioavailability (BA) is about 90-100%.
2. As can be seen clearly from the above results, the IV arm produced a significantly lower (30%) AUC_{0-48} compared to the oral dose. Thus, this study failed to achieve its primary objective.
3. The sponsor's explanation is that the infusion pump failed to deliver the full volume of the infusate. The sponsor estimated that about 13 ml of solution got left behind in the infusion set and so effectively, only about 62 mg was delivered.
4. **The sponsor did not provide any data to verify the explanation in #3.**
5. In addition to loss due to volume not infused, the drug can be lost due to binding to the infusion bag and the tubing also. However, the sponsor did submit adequate data to address this issue which were evaluated in the CMC review. Dr. Mishina (clinical pharmacology reviewer) also assessed these data and came to the same conclusion that sotalol did not bind to the bag or the tubing.
6. Another troubling aspect of these results is the difference in the variability in the PK parameters from the IV and the oral arms. Typically, less variability is seen through IV administration compared to the oral administration since the former bypasses the sources of variability involved with the process of absorption and the 'first pass' metabolism effect through gut and liver. However, in this study, the findings are just the opposite. The %CV was 55% and 41% for the Cmax, and was 39% and 26% for AUC, for the IV and oral arms respectively! Thus, the variability in the IV arm is significantly greater than that from the oral arm. This could partly be due to the issue identified in #3.
7. Even with this problematic infusion, two subjects showed a much higher Cmax with the IV arm than the oral arm. In subject #14, the Cmax was 48% higher with the

infusion (962 vs. 649) while in subject #11, the Cmax was 195% higher (1848 vs. 626)!!

8. Even though it failed on its primary objective, this study did provide the following useful information:
    a. The Tmax and half-life of sotalol following Betapace administration, i.e., the oral arm, were 2.5 hours and 10 hours respectively.
    b. The half-life of sotalol following So-Aqueous was 10 hours.
9. The findings highlighted in #8 are similar to those reported in the Betapace label, which reports sotalol Tmax to range from 2.5 to 4 hours and the half-life of 12 hours. Similar PK characteristics have been reported in the literature also (Am J Cardiol. 1993 Aug 12; 72(4):19A-26A).
10. The infusion duration of 2.5 hours was not appropriate. Pharmacometrics reviewer, Dr. Chris Tornoe, used the sponsor generated data from the IV and the PO arms to create a PK model using which he carried out simulations to identify the infusion duration that would give nearly identical Cmax and AUC of sotalol following 80 mg Betapace administration. These simulations suggest the infusion duration to be in the range of 4 to 5 hours. The sponsor's estimate was - hours. b(4)

6. Clinical Microbiology

The following information is obtained from the 5/5/09 review of Drs. Metcalfe and Langille.

"I. Recommendations

A. Recommendation on Approvability – NDA 22-306/N-000 is recommended for approval on the basis of product quality microbiology.
B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - The bulk drug solution is compounded and then filtered through — filters in series prior to being — filled into — glass vials and sealed with — stoppers. b(4)
B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.
C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable."

7. Clinical/Statistical- Efficacy

The only clinical trial conducted and submitted in this NDA is the clinical pharmacology study 12103 which has been reviewed by the Office of Clinical Pharmacology, as detailed in #5 above. Therefore, there is no clinical review for this NDA.

8. Safety

There is no additional safety assessment for this NDA.

9. Advisory Committee Meeting

An AC was not held for this 505(b)(2) NDA

10. Pediatrics

Not Applicable.

11. Other Relevant Regulatory Issues

- The only human study submitted in this NDA, i.e., study #12103 has not been audited by DSI. The validity of useful data from this study needs to be established by a satisfactory DSI audit before final action can be taken on this application.
- The overall site approval from the Office of Compliance is pending.

12. Labeling

- Proprietary name – *NOT RESOLVED YET*

Sponsor's proposed labeling has not been evaluated yet.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action:

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:

1. 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.
2. Study 12103 needs to be audited by DSI

If the above two requirements are satisfactorily met, then only can this application rely on the findings of safety and efficacy of Betapace. This is assuming that the overall site inspection from Office of Compliance is satisfactory.

- **Recommended Comments to Applicant**

1. 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 amount of sotalol delivered should be measured. The sponsor may have conducted such a study but no details about the study design, conduct and resulting data have been provided.

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/s/

Mehul Mehta
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