CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-306

PHARMACOLOGY REVIEW(S)

A. DeFelice, Ph.D.
HFD-110 DCaRP
June 15, 2009

NDA 22-306 (505(b)2)

Toxicology Study Review

SUBMISSION:
The material reviewed is a report (Evaluation of Sotalol (So-Aqueous) Potential for Hemolysis) of a study evaluating effect of So-Aqueous Sotalol HCl, at up to 100 ng/ml, on release of hemoglobin from isolated human red blood cells.

SUBMISSION RECEIPT DATE: August 20, 2008

REVIEW COMPLETION DATE: June 9, 2009

REVIEWER: A. De Felice, Ph.D.
Supervisory Pharmacologist
Division of Cardiovascular and Renal Drug Products (HFD-110; DCaRP)

SPONSOR: Academic Pharmaceuticals, Inc.

DRUG PRODUCT: So-Aqueous™ Intravenous Sotalol HCl

RELATED APPLICATIONS: IND 66,955 (So-Aqueous)
This NDA, submitted under 505(b) 2),largely relies upon safety and effectiveness of Betapace tablets (NDA 19-865; Bayer).

DRUG SUBSTANCE: Sotalol Hydrochloride: N-(4-[(1RS)-1-Hydroxy-2-[(1-methylethyl) amino] ethyl] phenyl] methanesulfonamide hydrochloride. MW: 308.83

PHARMACOLOGIC CATEGORY: Anti-Arrhythmic (classes II and III)

PROPOSED INDICATION: To prolong the time to recurrence of life-threatening ventricular arrhythmias and highly symptomatic atrial fibrillation in patients unable to take oral sotalol.

FORMULATION AND ROUTE OF ADMINISTRATION: 10 ml vials containing 150 mg Sotalol HCl i.e., 15 mg/ml for constant rate intravenous infusion.

PROPOSED DOSAGE: 75 mg infused over — hrs. b(4)

Summary of Results, and Conclusions:

Based on the analytical method used [ ] there was no evidence of any appreciable exposure-related hemolysis of human red blood cells incubated *in vitro* in the presence of So-Aqueous formulation. At sotalol concentrations of 1, 10, and 100 ng/ml, hemolysis was 1.1%, 1.2%, and 1.2%, respectively, of that produced by distilled water. The hemolysis produced by distilled water was defined as 100%. Normal saline and working buffered NaCl solution produced 0% and 0.5% hemolysis, respectively. b(4)

The high sotalol concentration is only approximately 1/6 th the maximum that would be achieved clinically after 80 mg are infused at a constant rate for 3.5- 4 hrs. The maximum clinical concentration was calculated from simulations performed by Sponsor using PK-parameters and constants derived from clinical study protocol 12103 (Table 2, Clin Pharmacol and Biopharm Review: P. Hinderling; Nov. 2, 2005; IND 66955). Dr. John Somberg, representing Academic Pharmaceutical, informed this reviewer, in a telephone conversation of 6/12/2009 that Sponsor intends to repeat the subject *in vitro* study at higher sotalol concentrations. In that conversation, Dr. Somberg also noted that only pre-infusion serum K^+ was monitored in protocol 12103, and accordingly, does not provide any serum [K+]-based insight into important hemolysis.
It is noted that the rate of infusion of So- Aqueous in protocol 12103 was carefully chosen to assure to asure that the maximum blood level achieved in a single intravenous infusion scenario of 80 mg/4 hrs would not exceed, based on simulations, that afforded by an oral dose of 80 mg. Reviewer is not aware of any hemolytic potential of the approved oral dosage formulation of sotalol (Betapace).

Sponsor asserts, based on a meta-analysis (Protocol 12103a) of clinical experience with subject and other intravenous sotalol formulations that there was no evidence of what would probably be of more concern to this reviewer - namely, potential for thrombosis, phlebitis, or thrombophlebitis. Sponsor's conclusion from the meta-analysis was that sotalol does not have the potential to cause such.

TOXICOLOGY STUDY REVIEWED:

Evaluation of Sotalol (So-Aqueous™) Potential for Hemolysis

[An associated report number, if any, was not provided.[
Methodology and Results of procedure are taken *verbatim* from study report:

Study dates: March 25, 2008- April 8, 2008.
Laboratory site: [redacted] b(4)
Name and Affiliation of Investigator: Vasant Ranade, PhD. Director of Chemistry, Academic Pharmaceuticals. 21 N. Skokie Hwy, Lake Bluff, Illinois. 6004

Study purpose: To evaluate So-Aqueous, as well as other pharmaceuticals including two formulations of amiodarone, and other marketed products to determine the extent of hemolysis of human red blood cells in vitro in presence of pharmacologic concentrations of these agents.
Drug lot: Bioniche: Lot # 050806

Method:
Preparation of reagents:
Report asserts that the procedure was adapted from Hematology Principles and Procedure by Barbara A. Brown. 1988 Lea & Febiger. Philadelphia, p 139-142.
Buffered sodium chloride stock solution was made from 100 ml of saline solution to which was was added 1.376 g of dibasic sodium phosphate (Na_2HPO_4) and 0.243 g of monobasic sodium phosphate NaH_2PO_4) . The Buffered sodium chloride working solution consisted of 20 ml of buffered sodium chloride stock solution (#1 as above) to which was added 180 ml of distilled water. The pH of this solution was 7.51.

Details of Procedure:

1. Five ml of venous blood was collected from 2 subjects in heparinized (green top) tubes.
2. The green top tubes were centrifuged at 1,300 xg (~2930 rpm) for 10 min and the supernatant fluid was removed.
3. To RBC's in each tube, 2 ml of normal saline was added and the tubes were centrifuged (1300 g's) three times, each time for 5 minutes. The supernatant fluid was removed.
4. To 0.1 ml of each of the drug solution, 0.1 ml of RBC's was added. The contents of the tubes were left at room temperature for 15 min. To this, 5 ml of buffered sodium chloride working solution was added and left at room temperature for 15 min. The tubes were then centrifuged for 10 min. The supernatant fluid (ea 200 µl) [redacted] b(4)

   The results were obtained in triplicate and expressed as optical densities (OD's) and calculated as % hemolysis. Using the formula given below. By convention, normal saline is assumed to cause no hemolysis, since normal saline is isotonic. The extent of hemolysis was then compared to normal saline by the formula:

   $$\frac{\text{OD of drug solution} - \text{OD of normal saline}}{\text{OD of water} - \text{OD of normal saline}} \times 100$$

Results.

It is asserted that over the concentration range of 1 to 100 ng/ml, there was very low hemolysis (≤ ca. 1% of that of dist. water) based on change in optical density i.e., light absorption at [redacted] Distilled water was the positive control, and normal saline the b(4)
carrier and the negative control. Diphenhydramine and atropine, each at concentrations of 1, 10 and 100 ug/ml, caused ca. 5% and 4%, respectively, of the hemolysis seen with dist. water. The maximum concentration tested was only approx. 1/6 the maximum achieved clinically after 75 -80 mg are infused at a constant rate for 3.5- 4 hrs, based on simulations performed by Sponsor using PK-parameters and constants derived from Protocol 12103 (Table 2: Clin Pharmacol and Biopharm Review; P. Hinderling; Nov. 2, 2005; IND 66955). The report is silent on whether there was any hemolysis apparent to the naked eye, even in the positive control (pure distilled water). There is no statement regarding whether sotalol absorbs at [redacted] light as a source of potential interference in the analytical method.

Evaluation:

Results *prima facie* reveal no evidence of hemolysis. Using distilled water as the positive control seems entirely adequate, although [redacted] which also uses a spectrophotometric analysis of absorption at [redacted] adds saponin (3% w/v) to the distilled water. The buffer is standard 0.05M acetate at pH 6.5, maintaining b(4)
the solution in the pH range of 6.0-7.0. It is not clear how the methodology used in the subject study - which is asserted to be based on published referenced methodology - conforms to that used by [redacted] The method used by [redacted] depends on the quantitative

conversion of oxyhemoglobin to cyanmethemoglobin upon addition of Drabkin's solution. Furthermore, it is not obvious whether there was any interference from the test article i.e., whether sotalol itself absorbs at —— and, if so, whether any correction for such was necessary. b(4)

This study exclusively addresses the hemolytic potential of the formulation *in vitro,* and at up to a concentration of 100 ng/ml. Beyond the fact that the max. concentration tested is only about 1/6th the maximum expected after a 4 -4.5 hr infusion of a total dose of approx. 75 mg, there are other shortcomings in the conduct and reporting of this *in vitro* study: the methodology is not clear i.e., whether sotalol itself absorbs at —— the report is silent as to whether it was performed according to GLP; and it is not signed). This study does not inform (nor was it intended to inform) any potential for effects on RBC agglutination or plasma protein flocculation, or on platelet activity. Although a pre-clinical study was not performed to look at local peri-infusion venous toxicity, there is appreciable clinical experience with the intravenous use of this formulation to provide re-assurance, if not equipoise, with respect to any hemolytic activity, or to local venous bioincompatability. Sponsors Clinical study report of protocol 12103a (Evaluation of the Incidence and Severity of Thrombophlebitis, Phlebitis, and Venous Irritation with Intravenous Administration of Sotalol. Amendment module 5, Vol 2.1), asserts that there were adverse venous effects vis a vis thrombosis or thrombophlebitis either in the parent bioequivalence study, protocol no. 12103; or as gleaned from a meta-analysis of, reportedly, all published English language studies of intravenous sotalol (75 eligible publications; 1842 subjects exposed to stalol; no consideration given to study design, diagnosis, or inclusion criteria). b(4)

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/s/

Albert Defelice
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PHARMACOLOGIST