CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-306

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 22-306 (So-Aqueous; IV sotalol for symptomatic AF)

Sponsor: Academic Pharmaceuticals

Review date: 21 May 2009

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

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HFD-110/Fortney
OTS/OCP/Mehta

This memo conveys the Division's recommendation to approve IV sotalol to prolong the time to recurrence of life-threatening ventricular arrhythmias and highly symptomatic atrial fibrillation in patients unable to take oral sotalol. However, because the review team has not reviewed labeling, no action on this application can be taken before the action date.

This NDA, largely relying upon the safety and effectiveness of Betapace (505(b)2) is supported by reviews of CMC (Wong; 27 February 2009), Microbiology (Metcalfe; 5 May 2009), and clinical pharmacology and biopharmaceutics (Mishina and Tornoe; 21 April and 14 May 2009), and by Dr. Mehta's CDTL memo dated 20 May 2009).

The final CMC issue (a facility inspection) was resolved today (22 May 2009). There are no microbiology issues. There are no pre-clinical or clinical data and no reviews for those disciplines.

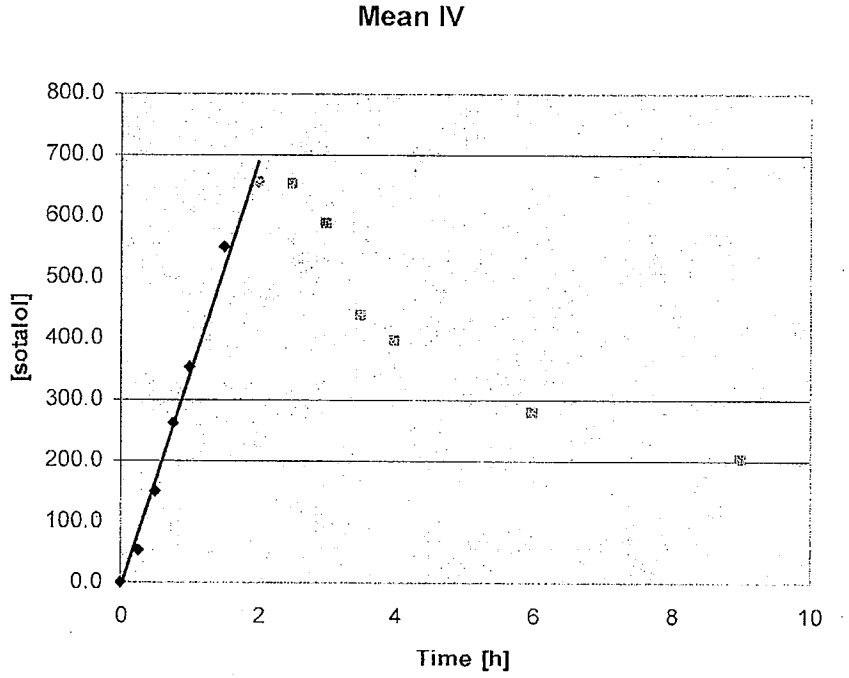
There is a consult to DMEPA for a tradename review dated 29 August 2008, but there is no formal response. I do, however, have e-mails from Sean Bradley (14 May 2009) and Carol Holquist (15 May 2009) indicating that "DMEPA has concerns that the proposed name 'So-Aqueous' could be misleading because [redacted] b(4)

[redacted] b(4)

In a draft of this memo, and in several follow-up e-mails with Carol Holquist, I have expressed the reservations I have with their position on the tradename. Final responsibility resides with DMEPA.

The clinical pharmacologists, Dr. Mehta, and I are all in complete agreement that the IV portion of the one comparative bioavailability study was flawed. This study was

intended to compare the pharmacokinetics for an 80 mg oral Betapace dose and a 75 mg timed infusion of So-Aqueous. The solution to be infused was supposed to be 75 mg in 75 mL. Thus, 5 mL of So-Aqueous 15 mg/mL were to be added to 70 mL of diluent. The 75 mL were to be infused over 2.5 hours. However, one still has to fill the infusion set tubing, and this volume will not be infused by the pump when the bag empties. Thus subjects received about 13 mL (13 mg) less than expected, and the infusion ended about 30 minutes early. This premature termination is seen in the mean plasma concentrations of sotalol shown below:



This is also consistent with (and was discovered because of) the AUC with IV being about 30% lower than with the 80 mg oral dose.

Dr. Mehta cites the variability in Cmax and AUC in the IV data higher than in the oral data (including some extreme outliers) as further evidence that this portion of the study was not well done.

The possibility of sotalol binding to plastic in the bag or tubing has been excluded.

Dr. Mehta cites the RLD's label for PK of oral sotalol: Tmax = 2.5 to 4 hours, absolute bioavailability >90%, and terminal half-life of about 12 hours. These observations are also consistent with the sponsor's study of Betapace.

Dr. Mehta's and the clinical pharmacologists' conclusion is that two conditions need to be satisfied prior to the approval of So-Aqueous. They 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 ——— (Dr. Tornoe's simulations suggest that the infusion should be a little longer than this.) Given the lack of any 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 that DSI consider an inspection, but this does not need to be conducted prior to approval.

b(4)

The team did not review labeling. At the one labeling meeting held 18 May 2009, the clinical pharmacologists suggested not describing the sponsor's PK study in labeling. I agree.

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/s/

Norman Stockbridge
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MEDICAL OFFICER