CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-108

SUMMARY REVIEW

4/22/8

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 22, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Bupropion HBr ER tablets for MDD

TO: File NDA 22-108
[Note: This overview should be filed with the sponsor's 10-23-07 complete response to our 7-19-07 non-approvable letter.]

Background

[Note: See my 7-19-07 not-approvable memo for a more detailed history of this application.]

This is a 505(b)(2) application for an extended release (once daily) formulation of bupropion hydrobromide. The sponsor has produced three tablet strengths, i.e., 174 mg and 348 mg to match the two available strengths of Wellbutrin XL (150 mg and 300 mg, respectively), and also a 522 mg strength. The basis for this application is the CMC information to support this new formulation and comparative bioavailability data that the sponsor feels represent an adequate demonstration of therapeutic equivalence for these two formulations. The work in support of this application was done under IND 73,781. Unfortunately, the sponsor never sought advice from us on this program. Thus, their biopharm program was limited to a multiple dose (MD) steady state comparative bioavailability study, a food effect study, and a single dose (SD) dose proportionality study. Importantly, they did not conduct a SD comparative bioavailability study, and this was initially considered a critical deficiency by OCP, necessitating a not approvable action. A non-approvable letter was issued 7-19-07. This letter focused on the failure to conduct a SD comparative bioavailability study and various CMC deficiencies. We subsequently met with the sponsor on 8-14-07 to discuss the not-approvable action, and the sponsor argued that simulations showed that a MD study should be sufficient and a SD study is not needed.

The sponsor provided a response to our NA letter on 10-23-07, and we considered this a complete response.

Summary of Conclusions and Recommendations from Review Teams

CMC

There were a number of CMC deficiencies conveyed in the not-approvable letter, but these have now been addressed. There remained a problem with the expiry that could be granted for the 522 mg strength, however, based on the available stability data and the agreed upon dissolution specifications, we have reached agreement on a 12 months expiry for the 522 mg strength and 24 months expiry for the other 2 strengths.

Pharm/Tox

The ___ impurity issues that remained at the time of the not-approvable letter have been resolved by the sponsor agreeing to lower the specification in both instances. b(4)

OCP

I had mixed feelings about the requirement for a SD study. Although it is true that a SD study is more sensitive, and it is possible that a SD study might fail, it is also true that, for this condition, a MD study may be more relevant. MDD is a chronic illness in which patients need chronic treatment, and furthermore, it would not be expected that patients would immediately worsen upon switching to a formulation that might deliver, on the first dose, an exposure to parent and major metabolite that may be as much as 50% less than the exposures seen with the reference formulation. During steady state, however, the new formulation delivers an acceptable exposure, and this is probably more relevant from a clinical perspective. Indeed, even if the sponsor conducted a SD study that failed, we might well overlook this outcome and approve this formulation in any case, given the MD results. On the other hand, current guidance requires a SD study in this setting, and it would not have been helpful to create this precedent. In addition, clinicians should know about the inadequate exposures that would likely result in the setting of single doses. Thus, I accepted this advice from OCP and we asked for a SD study in the not-approvable letter.

In response to this deficiency stated in the non-approvable letter of not having a SD study, the sponsor submitted a simulation showing that a MD steady state study would give the same 90% confidence interval information as a SD study. Based on this outcome, OCP has now agreed that a SD study is not needed.

As a separate matter, OCP has proposed dissolution specifications for which we have now reached agreement with the sponsor.

Clinical

There were no clinical deficiencies noted in the not-approvable letter.

DMETS

We have now reached agreement with the sponsor on a name for this product and on container labels.

Labeling

We have reached agreement with the sponsor on final labeling.

Other Issues

After some discussion, the sponsor agreed to conduct a pediatric depression program post-approval (for ages 7-17), and we agreed to defer this requirement (and waive such studies for ages less than 7). The sponsor has also agreed to conducting a REMS in order to meet the requirements of FDAAA 2007.

Conclusions and Recommendations

All issues have now been resolved, including agreement on dissolution specifications and labeling, and I will issue an approval letter.

cc:
Orig NDA 22-108
HFD-130/TLaughren/MMathis/RLevin/RGrewal

DOC: Bupropion HBr ER_Laughren_AP Memo.doc

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/s/

Thomas Laughren
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MEDICAL OFFICER