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*APPLICATION NUMBER:*

**22-108**

# PHARMACOLOGY REVIEW(S)

# PHARMACOLOGY/TOXICOLOGY MEMO TO THE FILE

NDA 22-108.
Submissions: N-000, original submission, letter-dated 9/27/2006, stamp-dated 9/28/2006; N-000, major amendment/multidisciplinary, letter-dated 10/23/2007, stamp-dated 10/23/2007; N-000, BZ, minor amendment/multidisciplincay, letter-dated March 17, 2008.

Drug: bupropion hydrobromide, as extended-release oral tablets.
Sponsor: Biovail Laboratories International SRL.
Indication: treatment of major depressive disorder.

Reviewer: Linda H. Fossom, Ph.D., Pharmacologist.
HFD-130, Division of Psychiatry Products.

**RE: Impurity issues for this bupropion HBr formulation, which was submitted under 505(b)(2).**

**Background:** The Sponsor has submitted the current NDA under 505(b)(2), citing GlaxoSmithKline's Wellbutrin XL (for bupropion HCl) as the reference listed drug product that is the basis for this submission.

**The first review cycle:** As noted in Dr. Rosloff's memo (dated 7/13/07), because this NDA was submitted under 505(b)(2), the non-clinical studies that were submitted under the current NDA comparing bupropion as the hydrobromide salt, which is the form used in the current NDA, with the hydrochloride salt, which was used in the reference listed drug product were considered adequate; no further non-clinical studies would be required to support this NDA. Also, as noted in that memo, the current Sponsor provided studies comparing the 2 salts (HBr and HCl) for 1) convulsant potential, 2) general toxicity in a 28-day study in rats, and 3) an Ames test (both salts were negative; this should be included in labeling).

However, during the original review of this NDA, it became apparent that there were 2 impurity issues that might require further Pharmacology/Toxicology assessment; these issues have been discussed in detail by Dr. Lyudmila Soldatova in her 1st Chemistry Review of the original submission of this NDA (as finalized 7/6/2007). *Firstly* (as noted in CMC deficiency #4), there was a potentially genotoxic impurity , for which the specification had been set in the drug substance. Although this is the same specification listed for the reference listed drug in the USP, it would result in daily exposure of up to mg for that impurity at the maximum recommended human dose of 522 mg per day (equivalent to 450 mg of bupropion HCl); this is well above the threshold currently

b(4)

allowed for genotoxic impurities. *Secondly* (as noted in CMC deficiency #11), the specification for another impurity (without any structural alerts) , had been set , which is considerably higher than the specification of for this impurity listed for the reference listed drug in the USP. b(4)

**The second review cycle:** The Sponsor has addressed both impurity issues that had Pharmacology/Toxicology impact. *Firstly*, they have lowered the specification for the potentially genotoxic impurity from the previous specification of ppm in the drug substance (see Dr. Soldatova's 2nd review, dated 2/29/08). This will result in of the impurity administered clinically at the highest recommended human daily dose of 522 mg (which is equivalent to 450 mg of bupropion HCl); this is considered near enough (within rounding error) to the limit of currently accepted for a genotoxic impurity. *Secondly*, the Sponsor (in a submission to this NDA, letter-dated March 17, 2008; also see Dr. Soldatova's 3rd review dated 4/4/08) has agreed to lower the specification for which is the specification for this impurity listed in the USP for the reference listed drug. b(4)

**Conclusions/Recommendations:** The impurity issues that might have had impact for Pharmacology/Toxicology have been resolved during this review cycle. From a Pharmacology/Toxicology perspective, this NDA may be APPROVED.

Linda H. Fossom, Ph.D., Pharmacologist *{see appended electronic signature page}*
Barry Rosloff, Ph.D., Supervisor *{see appended electronic signature page}*

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/s/
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Linda Fossom
4/7/2008 03:59:19 PM
PHARMACOLOGIST

Barry Rosloff
4/8/2008 12:50:34 PM
PHARMACOLOGIST

9/13/7

Barry N. Rosloff, Ph.D.
7/13/07

**NDA 22-108---PHARMACOLOGY MEMO**

This is a 505b2 application for bupropion HBr for the treatment of MDD. (The currently marketed product is the HCl salt). The sponsor performed (1) a study comparing the convulsant potential of the 2 salts in mice (in which it was shown that the HBr salt was somewhat less convulsive than the HCl salt, although one would want to see this replicated before concluding a true difference), (2) a 28 day toxicity study comparing the 2 salts in rats (no differences seen, although the study was not adequate in that the HD of 300 mg/kg produced no clinical signs or bodyweight effects; both salts caused hepatocyte hypertrophy which has been previously seen with bupropion), and (3) an Ames test (both salts were negative; results put in labeling).

This NDA is approvable.

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/s/

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Barry Rosloff
7/13/2007 11:59:38 AM
PHARMACOLOGIST