CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022497Orig1s000

SUMMARY REVIEW

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: 9 November 2011

FROM: Mitchell V. Mathis, M.D.
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Division of Psychiatry Products, HFD-130

TO: File NDA 22-497 Bupropion HCL 450 mg ER tablets for MDD, Intelgenx Corp.

SUBJECT: Approval Recommendation

Background

This 505(b)(2) application is for an extended-release, once daily formulation of bupropion hydrochloride for the treatment of major depressive disorder (MDD). This sponsor has produced a single strength: 450 mg. The maximum dose of the RLD (Wellbutrin XL) is 450 mg once daily, but the RLD is available only in two lower strengths: 150 mg and 300 mg. Therefore, this formulation represents a convenient formulation for patients who take the highest recommended dose of Wellbutrin XL. The basis for this application is CMC information submitted to support this new formulation, and bioequivalence data to link this new formulation to the approved product. The original application included a BA/BE study, a food effect study, and an *in vitro* alcohol interaction study. The IND to support this application is (b) (4) We had several meetings with the sponsor including a pre-IND meeting in January 2007 and an EOP2 meeting in January 2008. This sponsor was issued a CR Letter on 3 Feb 2010 due to critical CMC deficiencies (including an unidentified manufacturing facility for the drug product) and an OCP concern of an up to 25% increase in Cmax with food, which is a problem with bupropion secondary to a dose-related increase in seizures.

The sponsor responded to the CR action with a reformulation of the product (increasing the tablet coating thickness). The resubmission was largely a repeat of the original program and consisted of a second BE study which demonstrated bioequivalence, and a repeat food effect study which demonstrated no increase in Cmax with food.

Summary of Conclusions and Recommendations from Review Teams

CMC

The CMC reviewer, Pei-I Chu, Ph.D., has recommended approval. The drug product manufacturing and testing sites have been found to be acceptable by the Office of Compliance, and they have issued an overall recommendation of acceptable for this NDA.

Pharm/Tox

There are no pharmacology-toxicology deficiencies.

OCP

The OCP review was conducted by Bei Yu, Ph.D. In their response to this submission, the sponsor conducted two new *in vivo* studies with a reformulated product, one BE study (fasting, single dose) and one food effect study—the first food effect study was the main reason for the earlier CR Letter because Cmax was increased by 25%, which is a problem for this drug due to Cmax-related seizures that are dose-related, and this product represents the largest approved dose. The product was reformulated to increase the tablet coating thickness, and the reformulated product then demonstrated bioequivalence to the approved product and the reformulation resolved the difference in Cmax when taken with food.

BE Study: This product was compared to Wellbutrin XL 150 mg tablets x 3 to achieve the same dose and bioequivalence was demonstrated for the parent (bupropion) and the three active metabolites for Cmax and AUC.

Food Effect Study: With the new formulation, food prolonged drug absorption, but did not affect Cmax (we believe seizure risk is related to maximum concentration). A single dose of the new product was compared to Wellbutrin XL 150 mg x 3 tablets (total 450 mg). While food did not affect Cmax of bupropion; systemic exposure (AUC) to bupropion was increased by 25% when the new product was taken with food, but PK simulation of steady state plasma concentration-time profiles based on the single dose study indicate that at steady state, the exposure to bupropion following a 450 mg tablet of the new product under fed conditions is within the concentration window of bupropion given as Wellbutrin XL 150 mg x 3 tablets under fasted conditions. Therefore, the effect of food with the new formulation is not clinically significant.

There was an alcohol interaction study conducted as part of the initial submission, with results that indicated a potentially clinically relevant increase dissolution effect at the highest concentration of alcohol (22% dissolution at 2 hours in 40% alcohol, not a physiologic reality), but the reformulation increased the coating thickness of the tablet, which OCP felt would only decrease dissolution in alcohol, so the team determined that there was no need for another alcohol interaction study with the new formulation.

Clinical

This application was reviewed by Jen Sellers, M.D. There were no important adverse events noted in the comparative bioavailability studies of bupropion ER 450 mg crossed over with 3 Wellbutrin XL 150 mg tablets. There were no deaths, no dropouts due to adverse reactions, and no serious adverse events in the studies. Mild to moderate adverse reactions already noted in approved labeling were seen in the studies (abdominal pain, diarrhea, headache), as expected.

DMEPA

Tradename “Forfivo XL” was approved.

DSI

Findings from Sripal Mada, Ph.D.: clinical data acceptable for review.

Labeling

Draft labeling was negotiated with the sponsor and we have reached agreement. SEALD was involved with the review. This formulation is the highest approved strength of bupropion extended-release tablets, and so labeling necessarily reflects that this high dose cannot be the starting dose and that other formulations must be used in titration prior to using this product. Adverse reactions have been assembled from clinical studies of the previously approved formulations of bupropion. The label notes that pediatric efficacy and safety have not been established for this product, and that this highest dose is not recommended in patients with renal or hepatic impairment.

Conclusions and Recommendations

The sponsor has submitted adequate information to demonstrate bioequivalence to the approved product, the food effect issue has been resolved with reformulation of the product, the inspections have all been completed and are satisfactory, and so I recommend that the Director approve this application. There are no post-marketing requirements or commitments that have been identified. A full pediatric waiver for this highest dose approved in adults has been supported by the Pediatric Review Committee (PeRC).

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/s/

MITCHELL V Mathis
11/09/2011
DDD Memo