CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022497Orig1s000

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY MEMO TO THE FILE

NDA 22-497
Submission: SDN 24 (resubmission), submitted 5/4/11, received on 5/13/11
Drug name: FORFIVO XL Tablets (Buproprion HCl extended release tablets as 450mg strength)
Sponsor: IntelGenx Corp
Indication: Major Depressive Disorder
Reviewer: Shiny V. Mathew, Ph.D., Pharmacologist.
HFD-130, Division of Psychiatry Products

RE: New single strength (450mg) formulation of Buproprion HCl extended release tablets; submitted under 505 (b)(2).

Background: FORFIVO XL is an extended release formulation of 450 mg buproprion hydrochloride for the treatment of MDD. The exact mechanism of action of buproprion has not been elucidated although it has weak affinity to dopamine and norepinephrine transporters. Buproprion HCl is currently marketed as Wellbutrin®, Wellbutrin® XL and Wellbutrin® SR which have been approved for MDD and Zyban® for smoking cessation. The currently approved dosage strengths for Wellbutrin® are 150mg and 300mg with a maximum recommended human dosage of 450mg for MDD. This NDA for FORFIVO XL tablets is a 505 (b)(2) application with Wellbutrin® XL as the reference listed drug. FORFIVO XL was previously/originally submitted (sponsored by Cary Pharmaceuticals) and was not approved due to deficiencies found by CMC and OCP (for more details, see the complete response letter dated 2/3/2010). There were no Pharmacology/Toxicology issues impacting drug approval at that time.

The current submission: This submission is a complete response to the deficiencies found with the original NDA. IntelGenx is the current Sponsor of this NDA and maintains that the deficiencies noted in the previous complete response letter have been fully addressed. The Sponsor maintains that by allowing patients to take only one 450mg tablet rather than three 150mg tablets or one 150mg and one 300mg tablet, the risk of dosing errors and consequent risk of inadvertent overdose should be decreased. They also suggest an improvement in overall compliance and therefore efficacy.

There are no Pharmacology/Toxicology issues with this NDA.

Conclusion: There are no Pharmacology/Toxicology issues that would prevent the approval of this NDA.

Signatures:

Shiny V. Mathew, Ph.D., Pharmacologist *{see appended electronic signature page}*
Linda H. Fossom, Ph.D., Team Leader *{see appended electronic signature page}*

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/s/

SHINY V MATHEW
11/08/2011

LINDA H FOSSOM
11/08/2011

PHARMACOLOGY/TOXICOLOGY MEMO TO THE FILE

NDA 22-497.
Submissions: N-000, original submission, letter-dated 3/31/2009, received 4/6/2009.

Drug: bupropion hydrochloride, as extended-release 450-mg oral tablets [Forfivo XL].
Sponsor: Cary Pharmaceuticals, Inc.
Indication: treatment of major depressive disorder.

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

The Sponsor has submitted the current NDA under 505(b)(2), citing GlaxoSmithKline's Wellbutrin XL (bupropion HCl) as the reference listed drug (RLD). It should be noted that Wellbutrin XL has been approved for use as 150- and 300-mg XL tablets for the treatment of major depressive disorder (and the treatment of seasonal affective disorder); however, the current NDA is for use of a new extended-release formulation for a single, new strength of 450-mg, which is the maximum recommended human dose for this drug.

The non-clinical studies that supported the approval of the RLD are considered adequate to support the current NDA. Additionally, the CMC issues that might have had Pharmacology/Toxicology impact have been resolved (see CMC review by Pei-I Chu, Ph.D., dated 1/28/2010). However, it should be noted that there are OCP and CMC issues that prevented the approval of this NDA (see CR letter that issued 2/3/2010) and the potential impact of these issues for Pharmacology/Toxicology is not clear at this time.

Conclusions/Recommendations: From a Pharmacology/Toxicology perspective, there are currently no issues that would prevent the approval of this NDA.

Linda H. Fossom, Ph.D., Pharmacologist, Team Leader *{see appended electronic signature page}*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22497	ORIG-1	CARY PHARMACEUTICALS INC	BUP-450 (BUPROPION HCL)450MG ER ORAL TAB

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/s/

LINDA H FOSSOM
02/05/2010