CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-764/S-011
20-241/S-017

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY

NDA number:	20-241
Sequence number/date/type of submission:	Jun 5th 2002/labelling supplement
Information to sponsor:	Yes (x) No ()
Sponsor and/or agent:	GlaxoSmithKline RTP, NC 27709
Reviewer name:	Aisar Atrakchi, Ph.D.
Division name:	Neuropharmacological Drug Products
HFD #:	120
Review completion date:	March 31, 2003

Drug:

Trade name:	Lamictal® tablets
Generic name (list alphabetically):	lamotrigine
Relevant INDs/NDAs/DMFs:	N20764 chewable dispersible tabs
Drug class:	Exact mechanism unknown; *in vitro* studies showed that it inhibits voltage sensitive sodium channels
Indication:	Bipolar Disorder/Anticonvulsant

This is a labeling supplement that included revisions to the pharmacology/mechanism of action section of the label. The following pharmacology study is reviewed and comments on revisions are discussed:

"Lamotrigine inhibits 5-HT uptake *in vitro* and modulates the p-chloroamphetamine-induced 5-HT behavioral syndrome in rats/conducted by Glaxo Wellcome

Objective and Methods:

This study was done to assess the potential effect of lamotrigine on the reuptake of biogenic amines *in vitro* and the drug's effects on p-chloroamphetamine-induced 5HT behavioral syndrome *in vivo* . Blockade of this latter syndrome is an acceptable marker for inhibition of 5HT uptake *in vivo*. Rat synaptosomes and human platelets were prepared according to standard methods. Adult male Lister hooded rat brains were removed and synaptosomes were prepared from the cerebral cortex (5HT and noradrenaline uptake), and striatum (dopamine uptake). For the uptake studies, radioactivity from ^{3}H-5HT, ^{3}H-noradrenaline, or ^{3}H-dopamine was quantified using liquid scintillation counting. The 5HT behavioral syndrome was induced in the rats by i.p. injection of 10mg/kg of p-chloroamphetamine and 0.5hr later, animals were assessed for presence or absence of the standard signs of 5HT behavioral syndrome: tremors, forepaw treading, head weaving, and hind-limb abduction at 10min intervals for 1hr. Lamotrigine was administered at 20mg/kg i.p. and the positive control fluoxetine at 3 & 10mg/kg i.p. at 30, 30, and 90min before p-chloroamphetamine administration.

Results:

Lamotrigine showed a very weak but concentration-dependent inhibition of 5HT uptake in both synaptosomes (IC_{50} 481uM) and human platelets (IC_{50} 266uM)(figures from sponsor). Fluoxetine effectively inhibited uptake with IC_{50} values of 18 and 7nM in synaptosomes and platelets respectively).

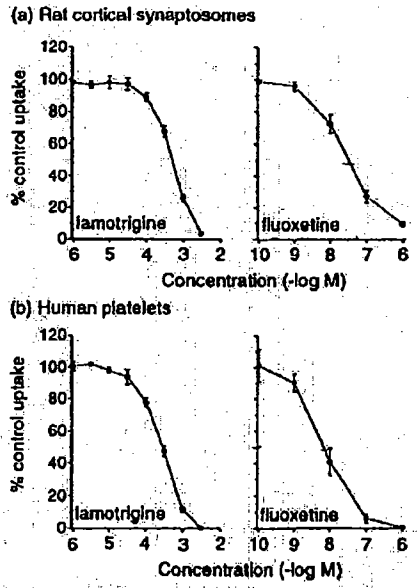

Fig. 1. Lamotrigine inhibits 5-HT uptake in rat and human tissues *in vitro*. Concentration-inhibition curves for lamotrigine and fluoxetine on 5-HT uptake in (a) rat cortical synaptosomes and (b) human platelets.

Lamotrigine significantly blocked the scores for forepaw treading and head weaving whereas, fluoxetine at 3 or 10mg/kg significantly reduced all 4 parameters of the syndrome (figures from sponsor).

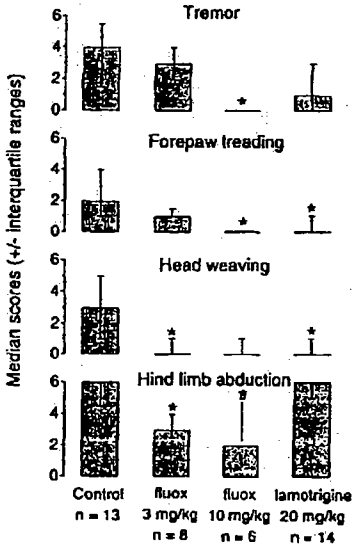

Fig. 3. Effects of lamotrigine and fluoxetine (floux) on the tremor, forepaw treading, head weaving, and hind limb abduction components of the p-chloroamphetamine-induced 5-HT behavioural syndrome in rats. * = $p < 0.05$.

Lamotrigine also was a very weak inhibitor of noradrenaline and DA uptake in the rat synaptosomes with IC_{50} values of 213 and 453uM respectively compared to positive controls of nomifensine at IC_{50} of 34nM and GBR12909 at IC_{50} of 3.3uM (the latter is a DA transport blocker).

Lamotrigine was also tested against standard anticonvulsants as well as Li on 5HT uptake. Among the anticonvulsants tested, only carbamazepine at 1mM blocked uptake by 70% in both human platelets and rat synaptosomes. In contrast, valproate, phenytoin, gabapentin, and Li showed little or no activity at 1mM.

Conclusion:
Lamotrigine showed a very weak but concentration dependent inhibition of 5HT uptake in rat synaptosomes and human platelets. The drug had a 0.004% the potency of fluoxetine based on IC_{50} values in the rat and 0.003% that for the human platelets. The potency was however, comparable to that observed for the Na-channel inhibition with an IC_{50} of 500uM and 100uM at currents held at -90 and -60mV using Chinese hamster ovary cells transfected with human type II Na channels respectively (Xie et al., 1995). Lamotrigine biogenic reuptake inhibition was non-selective for noradrenaline, 5HT, or DA. Among the anticonvulsant tested on 5HT uptake, only carbamazepine was effective in blocking uptake however, this cpd is not an effective drug in controlling acute bipolar depression. Nevertheless, carbamazepine showed comparable potency to lamotrigine in inhibiting uptake, this suggests that other mechanism(s) or factors that may play a role in this effect. The incomplete effect of lamotrigine on p-chloroamphetamine-induced behavioral syndrome which occurred at a dose that was at the upper end of the range tested for seizure blockade in the rat, questions the relevance and contribution of lamotrigine's uptake inhibition of biogenic amines to the psychotropic effects of the drug at therapeutic doses in bipolar patients.

Reviewer Comments on Labelling Revisions:

Based on the results of this study, the change proposed by the sponsor is not acceptable and the following text should replace it:

Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, or serotonin (IC50 >200uM) when tested *in* ——rat synaptosomes and/or human platelets.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Aisar Atrakchi
4/7/03 08:14:03 AM
PHARMACOLOGIST

Barry Rosloff
4/15/03 05:06:33 PM
PHARMACOLOGIST

Memo to File: 20241 S17, 20764 S11
Labeling Consult
March 21, 2003
Dr. Andrew Sostek
Cc. Dr. John Feeney
Dr. Phil Sheridan

NDA Lamictal (Bipolar)

The Neurology group has reviewed the proposed labeling and has the following comments based on discussions between Drs. Feeney, Sheridan and Sostek.

BLACK BOX (Rashes)

The Sponsor has proposed expressing the risk of serious rashes for [redacted]
We disagree with this approach and would propose the following alternative language.
Line 14 Page 1: "...receiving Lamictal as adjunctive therapy for epilepsy and 0.3% (3 per 1000) in adults on adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood disorders, the rate of serious rashes was [redacted] [Note to Sponsor: Please break down the risk of serious rash in these latter trials for patients on initial monotherapy (not conversion to monotherapy) vs. adjunctive therapy."]

Page 7 Hepatic Disease
The language here is the subject of a pending labeling supplement and should not be acted upon now.

Page 15: Adult Population:
The Sponsor has proposed text. As discussed above, we disagree with [redacted]
Please follow the same guidelines as for the BLACK BOX.

Page 15 Acute Multiorgan Failure

As with rash, we would not combine the epilepsy and bipolar populations. We would prefer to revert to the old text and insert additional phrases so that the text will read as follows (Beginning with line 477). Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received LAMICTAL in clinical trials [redacted] No such fatalities have been reported in bipolar patients in clinical trials.

ADVERSE REACTIONS

Page 25 Table 4
We would prefer to leave this as a 2% table given that meeting the [redacted] criteria would require [redacted] patients to experience the event.

Page 28 Table 6
Given that [redacted] of patients represent only [redacted], we concur with changing this to a 5% table.

Page 30 Table 7, We believe this should remain a 2% table.

Page 35 Line 1023. Spelling: cerebellar.

Page 37. Patients with Hepatic Impairment. See discussion above of pending hepatic labeling supplement.

Conversion to monotherapy from the two drug combination Lamictal-Valproate. We refer you to our action letter dated10/10/02 in which we discuss the current difficulties with providing dosing recommendations in this situation for epilepsy patients (see attachment).

Following on the last point, and given the added length and complexity of the label, we believe in the epilepsy section of Dosage and Administration the existing cautionary note about conversion from Lamictal-valproate to Lamictal Monotherapy (line 1088, 1089) may not be fully appreciated by the prescriber. Therefore, we think this message should be reiterated on page 40 between line 1191 and 1192 as follows.

Header-" Conversion from the Combination Lamictal-Valproate to Lamictal Monotherapy in Patients $\geq$ 16 years of age with epilepsy."
"Discontinuing valproate [redacted] shorten the half-life of lamotrigine. However, there is insufficient information to provide dosing guidelines for this conversion. The safety and effectiveness of Lamictal has not been established for the conversion to monotherapy from the two drug combination Lamictal-valproate."

Page 43. We note the Sponsor's proposed Table 15. We see the merits in such a table, although we believe it could be clearer. We note there is no comparable discussion in the epilepsy section. We would ask the Sponsor to propose a section for epilepsy discussing this dosing situation.

Attachment:

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
Food and Drug
Administration
Rockville MD 20857
NDA 20-241/S-016
NDA 20-764/S-009
SmithKline Beecham Corporation
d/b/a GlaxoSmithKline
Attention: Elizabeth A. McConnell, Pharm.D.
Project Director, Regulatory Affairs, Neurology
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709
Dear Dr. McConnell:
Please refer to your supplemental new drug applications dated November 29, 2001, received
December 10, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic
Act for Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets.
We acknowledge receipt of your submissions dated June 27, 2002, July 17, 2002, August 5,
2002, August 26, 2002, August 30, 2002, September 6, 2002, and September 11, 2002.
These supplemental new drug applications propose revisions to the Lamictal (lamotrigine)

4 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Andrew Sostek
3/24/03 12:48:47 PM
PHARMACOLOGIST