



May 14, 2007

VIA FEDERAL EXPRESS

Division of Dockets Management (HFA-305)
 Food and Drug Administration
 Room 1061
 5630 Fishers Lane
 Rockville, MD 20852

RE: Comments of Mylan Pharmaceuticals Inc. on Docket No. 2006P-0405:
 Action on Regulation of Generic Levetiracetam Tablets, and New Product
 Approvals for Levetiracetam Tablets

Dear Sir or Madam:

Mylan Pharmaceuticals Inc. ("Mylan"), submits these comments in response to the above-referenced Citizen Petition filed by Ergos Fabrice, Pharm.D., Ph.D. ("Dr. Fabrice" or "Petitioner"), President of UCB Inc. ("UCB"), on October 3, 2006 (the "Petition").

Mylan has an interest in the Petition, because Mylan currently markets anti-epileptic drug products and because Mylan has submitted an abbreviated new drug application ("ANDA") for generic Levetiracetam Tablets ("levetiracetam"). The Petitioner has recommended to the Food and Drug Administration ("FDA" or "Agency") to put certain restrictions on anti-epileptic drugs, of which levetiracetam would be considered.

Dr. Fabrice has requested the following actions: 1) that all antiepileptic drugs contain specific warning information, as follows: "Physicians and pharmacists should exercise extreme caution when switching from patients who are seizure free or whose seizures are well controlled on a given antiepileptic drug. In general, switches in patients who are well controlled have achieved stability on a given antiepileptic drug should be undertaken only when medically necessary and with full disclosure to the treating physician and the patient."; 2) that a discussion of antiepileptic drugs be added to Section 1.8 of the Orange Book wherein "Description of Special Situations" should highlight risks associated with substitution of antiepileptic drugs and recommend against switches of antiepileptic drugs in patients who are seizure free or whose seizures are well controlled, and 3) that FDA's bioequivalency lower criteria limit for 90% confidence intervals be raised from 80% to 90%.

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Although UCB's petition purports to relate to a broad class of anti-epileptic drugs, it is worth noting that UCB's leading drug product, Keppra® (levetiracetam) faces an imminent potential loss of exclusivity as the result of pending generic patent challenges brought by Mylan and other generic applicants who submitted "Paragraph IV" certifications to the Orange-Book listed patents for Keppra®. Indeed, the 30 month stay applicable to Mylan's Levetiracetam ANDA will expire on or about May 30, 2007, and Mylan's ANDA would be eligible for final approval at that time. UCB's citizen petition is a late-stage attempt to confound and forestall entry of generic Levetiracetam Tablets into the marketplace.

Mylan is sympathetic to the patient population with respect to maintaining safety and efficacy associated with use of antiepileptic drugs, which is a matter of record, for example as relates to Mylan's approved extended phenytoin sodium products. And, as will be demonstrated, UCB's requests lack both substance and scientific merit with respect to levetiracetam. Therefore, it is requested that the petition submitted by Dr. Fabrice at a minimum be considered inapplicable to levetiracetam tablets and, even if the petition is not immediately denied (as it should be), the Agency should not allow this petition to delay the approval status of ANDAs for Levetiracetam drug products.

Levetiracetam (Keppra®) is a second generation antiepileptic agent that is highly water soluble (104.0 g/ 100 mL)¹. In addition, levetiracetam possesses linear pharmacokinetics (over a dose range of 500 to 5000 mg, which is within the recommended daily dose range), has low intra- and inter-subject variability, and is not considered a narrow therapeutic index drug.^{2,3} With a maximum recommended daily dose of 3000 mg, levetiracetam readily dissolves into solution when administered with a standard glass of water. The oral bioavailability of levetiracetam is 100%, with the tablets being bioequivalent to an oral solution in both rate and extent of absorption.⁴

In fact, levetiracetam tablets may be considered as a Biopharmaceutics Classification System (BCS) Class I oral dosage form by the FDA.⁵ A BCS Class I oral dosage form must be in an immediate-release dosage form and have high solubility (highest dose strength should be soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5) and should be highly permeable (extent of absorption is 90% or more of an administered dose based on mass balance or in comparison to an intravenous reference dose).⁶ In addition, the immediate-release drug product must be rapidly dissolving with no less than 85% of the labeled amount of the drug substance dissolved in thirty minutes using USP Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in 900 mL or less in three different media.⁷

¹ Keppra® Package Insert. Revised September 15, 2006.

² Ibid

³ Summary Basis for Approval for Keppra® FDA Application 21-035. Approved 11/30/1999.

⁴ Keppra® Package Insert. Revised September 15, 2006.

⁵ FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Issued August 2000

⁶ Ibid.

⁷ Ibid

Levetiracetam appears to meet these strict criteria. As previously stated, levetiracetam is highly water soluble (1.04g/mL).⁸ Levetiracetam has been demonstrated to have a high permeability via a mass balance study where urine excretion accounted for 95% of the administered dose.⁹ The innovator's immediate-release tablets demonstrate greater than 85% release within 30 minutes in three different pH media¹⁰, as is suggested for Mylan's tablets; therefore, these products appear to conform to BCS 1 classification. Thus, bioequivalency studies are in effect not required.¹¹ Further, the FDA noted in their summary basis of approval of UCB's product, that not only do levetiracetam tablets belong to the category of BCS 1, but that the drug should not be considered as a narrow therapeutic drug class due to the low order of toxicity and relatively high therapeutic index.¹²

However, even though levetiracetam tablets meet these criteria, Mylan elected to conduct bioequivalence studies under fasting and fed conditions in healthy volunteers according to FDA's proven bioequivalence standards. Table 1 demonstrates Mylan's levetiracetam tablets are clearly bioequivalent to UCB's Keppra[®] under fasting conditions, while Table 2 demonstrates bioequivalence under fed conditions.

Table 1: Levetiracetam pharmacokinetic parameters in twenty-six healthy subjects following a single oral 750 mg (1 x 750 mg) dose of levetiracetam tablets under fasting conditions

Parameter	LSMEANS Ratio (Test/Ref)	90% Confidence Interval
AUCL* ($\mu\text{g} \times \text{hr/mL}$)	0.98	95% – 100%
AUCI* ($\mu\text{g} \times \text{hr/mL}$)	0.97	95% – 99%
Cmax* ($\mu\text{g/mL}$)	0.95	89% – 103%

* Used natural log transformed parameter

Table 2: Levetiracetam pharmacokinetic parameters in thirty healthy subjects following a single oral 750 mg (1 x 750 mg) dose of levetiracetam tablets under fed conditions

Parameter	LSMEANS Ratio (Test/Ref)	90% Confidence Interval
AUCL* ($\mu\text{g} \times \text{hr/mL}$)	0.98	96% – 101%
AUCI* ($\mu\text{g} \times \text{hr/mL}$)	0.99	97% – 100%
Cmax* ($\mu\text{g/mL}$)	0.95	89% – 100%

* Used natural log transformed parameter

⁸ Keppra[®] Package Insert. Revised September 15, 2006.

⁹ Summary Basis for Approval for Keppra[®] FDA Application 21-035. Approved 11/30/1999.

¹⁰ Ibid.

¹¹ FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Issued August 2000

¹² Summary Basis for Approval for Keppra[®] FDA Application 21-035. Approved 11/30/1999.

As evidenced by the data presented above, Mylan's levetiracetam tablets are bioequivalent to Keppra[®]. Mylan conducted these bioequivalence studies even though levetiracetam tablets may be considered a BCS Class I formulation that does not require such studies.

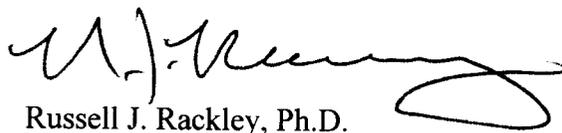
The fact that both levetiracetam formulations are both highly soluble and rapidly dissolving, in effect, removes concerns of any formulation differences. Following ingestion of either formulation, dissolution rapidly occurs such that levetiracetam becomes available for absorption as a solution. Any perceived differences between Mylan and UCB dosage forms are unfounded as the normal process of absorption is analogous to comparing absorption of two similar solutions. UCB's currently approved labeling indicates that their tablet formulation is bioequivalent to a solution, thus confirming lack of uniqueness to their solid oral dosage form. Further, Mylan has confirmed bioequivalency under fasted and fed conditions through actual blood level studies. Based upon the intrinsic physical and chemical characteristics of levetiracetam, the formulation will not affect the dissolution or permeability of the product and physicians, pharmacists, and patients should feel confident in generic substitution of levetiracetam tablets.

It is clear that the discussion provided by Dr. Fabrice is irrelevant to levetiracetam. It is acknowledged that the epileptic patient should be carefully monitored for control of disease and Mylan is sympathetic and committed to providing affordable healthcare to this population. Dr. Fabrice, however, provides no substantive discussion that pertains specifically to levetiracetam tablets. Thus it becomes apparent from the biopharmaceutics-based discussion relative to BCS characterization of levetiracetam, the current petition appears to be a desperate measure of last resort, obviously devised to delay generic approval of levetiracetam tablets.

CONCLUSION

For all of the foregoing reasons, the Citizen Petition should be denied and, at a minimum, it should not delay or affect approval of Mylan's ANDA for levetiracetam tablets as soon as the 30 month Hatch-Waxman stay of approval expires on or about May 30, 2007.

Respectfully submitted,



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Executive Director, PK/DM
Mylan Pharmaceuticals Inc.

Desk Copy: Dr. Egros Fabrice, Pharm.D., Ph.D.
UCB, Inc.