DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Ludwig Hantson
Head of Pharma North America and CEO
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

RE: NDA 21-014/21-285
Trileptal® (oxcarbazepine) Tablets and Oral Suspension
MACMIS ID #15867

WARNING LETTER

Dear Mr. Hantson:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a Partial Seizure Lenticular Magnet (TPL-OT-0167-A) (magnet) for Trileptal® (oxcarbazepine) Tablets and Oral Suspension (Trileptal) submitted by Novartis Pharmaceuticals Corporation (Novartis) under cover of Form FDA-2253. The magnet is violative because it omits the full indication for Trileptal and omits information about the risks associated with its use. Thus, the magnet misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) and 321(n) and FDA implementing regulations. These violations are concerning from a public health perspective because they may encourage the use of Trileptal in circumstances other than those for which the drug has been shown to be safe and effective and suggest that Trileptal is safer and more effective than has been demonstrated.

Background

The INDICATIONS AND USAGE section of the approved product labeling (PI) for Trileptal[1] states:

> Trileptal® (oxcarbazepine) is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and as monotherapy in the treatment of partial seizures in children aged 4 years and above with epilepsy, and as adjunctive therapy in children aged 2 years and above with epilepsy.

[1] The PI disseminated with the promotional piece, and referred to within this letter, was dated October 2005. The most recent version of the PI was revised and approved on August 31, 2007.

Trileptal is also associated with numerous risks. The PI contains warnings for hyponatremia, past history of sensitivity to carbamazepine, serious dermatological reactions, and withdrawal of antiepileptic drug therapy. The PI also contains precautions for cognitive/neuropsychiatric events, multiorgan hypersensitivity, drug interactions, and use in patients with renal impairment. In general, the most commonly observed (≥5%) adverse experiences seen in association with Trileptal and substantially more frequent than in placebo-treated patients were: dizziness; somnolence; diplopia; fatigue; nausea; vomiting; ataxia; abnormal vision; abdominal pain; tremor; dyspepsia; and abnormal gait.

Omission of Indication and Risk Information

The magnet has a lenticular design; the image and claims on the front of the magnet alternate, depending on the angle of the viewer, between two presentations: (a) the claim "For every patient with a generalized seizure..." along with an image of one woman and the Trileptal logo; or (b) the claim "For every patient with a generalized seizure....there are 4 with partial seizures" along with an image of four people and the Trileptal logo. Regardless of the viewer's angle, the claim, "For every patient with a generalized seizure," along with the Trileptal logo at the bottom of the magnet, is always visible. The magnet presents these effectiveness claims for Trileptal but fails to adequately communicate its indication and risk information associated with its use. Indication and risk information for Trileptal is printed on the back of the magnet; however, as a practical matter, this information is not communicated to the viewer. The magnet is designed to adhere to magnetic surfaces and, therefore, once the magnet is displayed, content on the back of the magnet is not visible. Presenting indication and risk information in this manner is not sufficient to ensure that the claims on the magnet are truthful and non-misleading. *Cf.* 21 CFR 202.1(e)(3)(i). As a result, the piece misleadingly suggests that Trileptal is safer and more effective than has been demonstrated by substantial evidence or substantial clinical evidence.

In addition, without the full indication presented on the front of the magnet, the mention of generalized seizures, especially in the view where only generalized seizures is visible, implies that Trileptal is approved for use in the treatment of generalized seizures, when it is, in fact, only approved for use in the treatment of partial seizures, a subcategory of seizures that is distinct from generalized seizures (e.g., primary generalized, generalized tonic-clonic, myoclonic). We understand that this information on generalized seizures serves, in part, to convey background disease-state information in the context of this presentation, but it also misleadingly implies that Trileptal is indicated for seizure types other than partial seizures and, thus may encourage the use of Trileptal in circumstances other than those for which the drug has been shown to be safe and effective.

Conclusion and Requested Action

For the reasons discussed above, the magnet misbrands Trileptal in violation of the Act, 21 U.S.C. 352(a) & 321(n).

DDMAC requests that Novartis immediately cease the dissemination of violative promotional materials for Trileptal such as those described above. Please submit a written response to

this letter on or before May 16, 2008, stating whether you intend to comply with this request, listing all violative promotional materials for Trileptal such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at (301) 847-8444. Please refer to MACMIS ID #15867 in addition to the NDA numbers in all future correspondence relating to this matter. DDMAC reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Trileptal comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Kristin Davis
5/1/2008 05:26:21 PM
Signed on behalf of Thomas Abrams