DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Bruce Lu
Director – Regulatory Affairs
Xcel Pharmaceuticals
6363 Greenwich Drive
Suite 100
San Diego, CA 92122

RE: NDA #20-148 Migranal® (dihydroergotamine mesylate, USP) Nasal Spray
NDA #05-929 D.H.E. 45® (dihydroergotamine mesylate, USP) Injection
MACMIS #11337

Dear Mr. Lu:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified a detail aid for Migranal® (dihydroergotamine mesylate, USP) Nasal Spray (MIG000IA0802) and an accompanying insert for D.H.E. 45® (dihydroergotamine mesylate, USP) Injection (MIG000IA0802), submitted under cover of Form FDA 2253 by Xcel Pharmaceuticals (Xcel), that make claims that are false or misleading under sections 201(n) and 502(a) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 321(n) & 352(a)).

Background

According to the approved product labeling (PI), Migranal is indicated for the acute treatment of migraine headaches with or without aura. It is not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine. D.H.E. 45 is indicated for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes. FDA is not aware of substantial evidence or substantial clinical experience demonstrating that D.H.E. 45 is effective for the treatment of status migrainosis or intractable migraine.

The PI for both products contains a boxed warning that states (in pertinent part):

> Serious and/or life threatening peripheral ischemia has been associated with the coadministration of DIHYDROERGOTAMINE with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of DIHYDROERGAMTAMINE, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated.

The PI for both products also states that the drugs should not be given to patients with uncontrolled hypertension, patients who have used 5-HT_1 agonists, ergotamine-containing or ergot-type medications or methysergide within the last 24 hours, or patients with hemiplegic or basilar migraine.

Ergotamine and drugs in the triptan class (also sometimes referred to as 5-HT-1 receptor agonists) are also indicated for the treatment of migraine, but are not associated with certain risks identified in the PI for Migranal and D.H.E. 45.

Misleading Comparative Claims

Page 1 of the detail aid presents the following bulleted claim:

- "Migranal Nasal Spray works in a similar way to triptans and has a **comparable safety profile**, but with a broader receptor profile"

This represents or suggests that Migranal is comparable in safety to triptans. This is misleading because the comparable safety of Migranal to triptans has not been demonstrated by substantial evidence or substantial clinical experience. The study cited in the detail aid did not compare Migranal to triptans. The claim is also misleading because it implies that Migranal is superior to triptans because of a broad receptor profile when, in fact, the clinical significance of a broad receptor profile is unknown. Finally, this claim is misleading because, as discussed above, Migranal is associated with certain serious risks that are not associated with triptans.

The insert presents the following claim:

- "Dihydroergotamine (DHE) was developed as a safer alternative to ergotamine"

This implies that D.H.E. 45 is safer than ergotamine. This is misleading because the superior safety of dihydroergotamine to ergotamine has not been demonstrated by substantial evidence or substantial clinical experience. The study cited in the insert did not compare dihydroergotamine to ergotamine.

Omission and Minimization of Risk Information

The detail aid and the insert are misleading because they fail to present certain contraindications from their respective PIs. Specifically, the detail aid and the insert fail to include the contraindications that patients with uncontrolled hypertension, patients who have used 5-HT_1 agonists, ergotamine-containing or ergot-type medications, or methysergide within the last 24 hours, or patients with hemiplegic or basilar migraine should not use Migranal or D.H.E. 45.

Furthermore, the detail aid and the insert are misleading because they minimize the risk information for Migranal and D.H.E. 45. Specifically, effectiveness claims for Migranal and D.H.E. 45, such as "Migranal Nasal Spray – A True Alternative for Migraine Relief" and "D.H.E. 45 – Established Efficacy in Migraine Therapy," are prominently presented in the detail aid and insert by way of large, bolded, and colorful headers. In addition, the four-page detail aid and the two-page insert contain effectiveness claims featuring bulleted information, colorful charts and graphs, and a significant amount of white space. However, all of the risk information for Migranal and D.H.E. 45 is relegated to the second page of the detail aid and the second page of the insert and is presented in a single-spaced paragraph format without additional emphasis. Furthermore, the risk information is presented within the same paragraph that begins with the indication for the drugs. This makes the risk information even more difficult to locate and discern from the effectiveness claims. Therefore, the detail aid and insert are misleading because they minimize the risks associated with Migranal and D.H.E. 45.

Unsubstantiated Efficacy Claims

The front cover of the detail aid presents the following headline in large, bold print:

- "When Migraine Therapy Reaches an Impasse"

Page 2 of the detail aid presents the following bolded headline and bulleted claims:

- "When Triptan Therapy Fails…"
- "Triptans – Not for Everyone
- "Triptans only exert agonist effects on 5-HT_1 receptors, with the greatest affinity on 5-HT_{1B} and 5-HT_{1D}"
- "Current therapies do not always provide complete headache relief"
- "In clinical practice, approximately 30% of patients do not get satisfactory results from oral sumatriptan"

The detail aid thus suggests that Migranal is superior to triptans because it will provide migraine relief when other migraine therapies, such as triptans, fail. The studies cited in the detail aid were not designed to examine whether Migranal is superior to the triptans and are, therefore, not sufficient to support the above claims. FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Migranal is superior to triptans. The detail aid is, therefore, misleading.

Broadening of Indication

The insert contains the following bulleted claims:

- "DHE has been established as a standard treatment for status migrainosis or intractable migraine"
- "DHE has provided up to 90% relief in these patients"
- "IV for management of refractory, intractable migraine"

D.H.E. 45 is not indicated for the treatment of status migrainosis or intractable migraine, and FDA is not aware of substantial evidence or substantial clinical experience demonstrating that D.H.E. 45 is effective for the treatment of these conditions. The insert is, therefore, misleading.

Finally, the inclusion of the insert within the detail aid for Migranal, along with failure to make a distinction for "DHE" in most claims (especially those regarding the use of dihydroergotamine for intractable migraine) in the insert is misleading because it implies that Migranal shares these characteristics of D.H.E. 45. FDA is not aware of any substantial evidence or substantial clinical experience demonstrating that Migranal has these characteristics.

Conclusion and Requested Action

Your detail aid and accompanying insert are misleading because they minimize and omit important risk information and include claims for which FDA is not aware of substantial evidence or substantial clinical experience. The detail aid and accompanying insert therefore misbrand Migranal and D.H.E. 45 under section 502(a) of the Act, 21 U.S.C. 352(a).

To address these violations, we request that you immediately cease the dissemination of this detail aid and insert and all promotional materials that contain the same or similar messages. Please respond in writing to us within ten business days of the date on this letter. Your response should include a statement of your intent to comply with the above request, a list of all promotional materials with the same or similar messages, and your methods for discontinuing their use. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile 301-594-6771. Only written communications are considered official.

If you choose to disseminate revised promotional materials, DDMAC is willing to assist you in assuring that your revised materials are in compliance with applicable provisions of the Act and of FDA regulations by reviewing the revisions prior to their use in promotion. There are different ways of revising your materials to address the issues identified in this letter. Xcel could, for example, correct the issue with the unsubstantiated claims by substantiating them, either with substantial evidence or substantial clinical experience. Alternatively, Xcel could choose to omit the claims from promotion entirely. To address the minimization of risk information issue, Xcel could separate the risk information from the information on the indication, and present risk information using the techniques employed to present the claims of effectiveness and benefits, such as the use of bolded headers, white space, and bullet points.

In all future correspondence regarding this matter, please refer to MACMIS #11337 in addition to the NDA numbers.

Sincerely,

{See appended electronic signature page}

Sonny Saini, Pharm.D.
Regulatory Review Officer
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/

Sonny Saini

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