ACCUTANE

Food and Drug Administration
Rockville MD 20857

19

March 5, 1998

TRANSMITTED VIA FACSIMILE

Mr. Patrick J. Zenner
President and CEO
Hoffmann-La Roche, Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

RE: NDA 18-622
Accutane (isotretinoin) Capsules
MACMIS ID 6254

WARNING LETTER

Dear Mr. Zenner:

This Warning letter concerns Hoffmann-La Roche, Inc.'s (Roche) advertising and promotional labeling for Accutane (isotretinoin) Capsules including, but not limited to, journal advertisements and promotional labeling pieces.[1] As part of its routine monitoring of prescription drug promotion, the Division of Drug Marketing, Advertising, and Communications' (DDMAC) has reviewed these materials and has determined that they are false or misleading and promote Accutane for an unapproved use in violation of the Federal Food, Drug, and Cosmetic Act, 21 USC §§ 355(a), 352(a), 352(f), 331(a), and 331(d), and applicable regulations. Moreover, Roche's failure to disclose important risk information in its promotional materials raises significant safety concerns.

Promotion of Unapproved Use, False or Misleading Promotion, and Failure to Disclose Safety Information

Roche's promotional materials state or suggest that Accutane is safe and effective in the treatment of what Roche describes as the "psychosocial trauma" and "emotional

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[1] One journal advertisement appeared in the January 1998 edition of the Journal of the American Academy of Dermatology. The promotional labeling pieces are identified as booklets 18-002-023-013-086, 18-002-023-002-036, and 18-064-023-002-037. These promotional materials are representative of the violative materials disseminated by Roche in its promotion of Accutane.

suffering" associated with acne, including "negative psychosocial effects such as depression and poor self-image." For example:

- One recent journal ad for Accutane states, "Remission can stop the physical scarring-and emotional suffering" and "Effective treatment of severe recalcitrant nodular acne minimizes progressive physical scarring--as well as negative psychosocial effects such as depression and poor self-image."[2] (Emphasis added).

- A booklet suggests that treatment with Accutane will stop the "negative emotional and psychosocial effects include depression and poor self-image."[3] (Emphasis added).

The statements and suggestions in Roche's promotional materials that Accutane therapy will minimize or improve the patient's psychosocial status, including depression, are false or misleading and promote an unapproved use.

We do not doubt that patients with severe nodular acne who are unresponsive to conventional therapy are greatly disturbed by their condition and may even become clinically depressed because of it. Roche, however, has not systematically studied the ability of Accutane to modify or prevent such illnesses as depression and has presented no basis for asserting that Accutane is effective in improving the psychosocial and emotional well-being of such patients. This claim is particularly troublesome in light of information recently presented in a Dear Doctor letter, that Accutane may cause depression, psychosis, and rarely, suicidal ideation, suicide attempts and suicide.

Roche's promotional claims also contradict or minimize the risk information disclosed in the approved product labeling. The "Adverse Reactions" section of the labeling prior to the recent changes, stated:

> Depression has been reported in some patients on Accutane therapy. In some of these patients, this has subsided with discontinuation of therapy and recurred with reinstitution of therapy.

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[2] Journal advertisement appeared in the January 1998 edition of the Journal of the American Academy of Dermatology.

[3] Booklet no. 18-002-023-002-036.

Thus, Roche misleadingly suggests in its promotional materials that Accutane has a positive effect on psychosocial effects, such as depression, in patients with severe recalcitrant nodular acne. At the same time, Roche fails to disclose in its promotional materials that depression may be associated with the use of Accutane.

Conclusion and Requested Actions

The materials and promotional messages Roche disseminated contain false or misleading information about the safety and effectiveness of Accutane and promote the product for an unapproved use. Accordingly, Roche should propose an action plan to disseminate corrective messages about the issues discussed in this letter to all health care providers, institutions, and organizations who received the violative messages over the last 12 months.

We ask that this corrective plan include:

A. Immediately ceasing the dissemination of all materials and claims that state, suggest, or imply that Accutane is safe and effective for psychological or emotional suffering, including depression, in the indicated patient population and that contain false or misleading claims of the type discussed in this letter.

B. A written statement of Roche's intent to comply with "A" above.

C. A complete listing of all advertising and promotional labeling that will remain in use and those that will be discontinued. Also, provide two copies of all promotional materials for Accutane that Roche intends to continue to distribute.

D. Within 15 days of the date of this letter, disseminating a message to all Roche sales representatives and marketing personnel involved in the marketing and sales of Accutane, instructing them to immediately cease dissemination of all promotional materials and messages discussed in this letter and providing each person with a copy of this letter.

E. All new promotional materials should prominently disclose information about the psychiatric disorders described in the Warnings section of the revised labeling in addition to other risk information.

Roche's action plan should be submitted to DDMAC for approval. After such approval, the corrective message should be disseminated as quickly as possible.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of Roche's campaign for Accutane and we may determine that additional remedial measures will be necessary to fully correct the false or misleading messages resulting from Roche's violative conduct.

Roche's response should be received no later than March 18, 1998. If Roche has any questions or comments, please contact Jean Raymond, Dr. Tracy Acker, or Norman A. Drezin, Esq. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Roche that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 6254 and NDA 18-622.

Sincerely,

Minnie Baylor-Henry

Minnie Baylor-Henry, R.Ph., JD
Director
Division of Drug Marketing,
Advertising and Communications