DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

May 26, 1998

TRANSMITTED VIA FACSIMILE

Richard U. De Schutter
Chairman, President and CEO
G.D. Searle & Co.
5200 Old Orchard Road
Skokie, IL 60077

Re: NDA No. 20-868
Flagyl ER (metronidazole extended release tablets)
MACMIS No. 6547

WARNING LETTER

Dear Mr. De Schutter:

This Warning Letter addresses G.D. Searle & Co. ("Searle's") dissemination of a journal advertisement for Flagyl ER (metronidazole extended release tablets). This advertisement was published in *Drug Topics* on May 4, 1998. The Division of Drug Marketing, Advertising, and Communications ("DDMAC") has reviewed this advertisement as part of its monitoring and surveillance program. DDMAC has concluded that Searle's advertisement is misleading and lacking in fair balance in violation of the Federal Food, Drug, and Cosmetic Act (the "Act"), 21 U. S. C. §§ 352(n) and 321(n), and applicable regulations. By its dissemination of this advertisement, Searle is misbranding Flagyl ER.

The prescription drug regulations at 21 C.F.R. § 202.1(e)(7)(viii) provide that an advertisement "may be false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act" if it fails to present the information relating to side effects and contraindications of the advertised drugs with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. The regulation requires that all techniques likely to achieve emphasis be considered including, but not limited to, factors such as typography, layout, contrast, headlines, paragraphing, and white space. DDMAC concludes from its review of Searle's advertisement that Searle failed to provide adequate prominence to such disclosures.

In the advertisement published in the May, 1998, edition of *Drug Topics*, Searle presents information that appears to be some of the risk information associated with the use of Flagyl ER and the generic name.[1] However, because the information is presented in black print on a very dark charcoal grey background, the lack of contrast makes the information illegible.

The prescription drug advertising regulations also provide that an advertisement is false, lacking in fair balance or otherwise misleading if it contains a representation or suggestion, not approved in the labeling, that a drug is more effective or safer than has been demonstrated by substantial evidence or substantial clinical experience (21 C.F.R. § 202.1(e)(6)(i)). In this instance, we cannot determine the validity of Searle's disclosures because of the illegible presentation.

Failure to Submit Post-marketing Reports

Finally, although this advertisement was disseminated in early May, we have not received a copy of this advertisement. Such submissions are required at the time of its first use under the post-marketing reporting requirements. (21 C.F.R. 314.81(b)(3)(i)).

Conclusions and Requested Actions

Searle should advise FDA of other placements of this advertisement and provide original published copies of each placement. In addition, Searle should propose an action plan to disseminate accurate and complete information to the audience that received the misleading message. Searle's action plan should include:

A. *Immediately ceasing the dissemination of all advertisements and labeling* materials that fail to clearly and prominently disclose balancing information; and

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

The action plan should be submitted to DDMAC for approval and should be implemented as soon as possible after such approval.

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[1] The prescription drug regulations at 21 C.F.R. § 202.1(b)(1) requires that an advertisement for a prescription drug present the generic name of the product in conjunction with the brand name. In this instance, the brand name is prominently presented in bright blue on the dark background. The generic name is illegible.

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

We note that this is the second Warning Letter to Searle in six months concerning the dissemination of risk information about its products. These events raise serious concerns about Searle's compliance with the regulations about prescription drug advertising. Accordingly, we invite you to meet with us in the near future to discuss our concerns about Searle's repeated failure to provide fair balance in the promotion of its products and possible remedies to correct the misleading information disseminated in this advertising campaign.

Searle's response should be received no later than June 11, 1998. If Searle has any questions or comments, please contact Dr. Jo Ann Spearmon, 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 Searle that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID 6547.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

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