DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

John Leach
Associate Director
Organon Inc.
375 Mount Pleasant Avenue
West Orange, NJ 07052

RE: NDA 20-582
Follistim® (follitropin beta for injection)
MACMIS #11099

Dear Mr. Leach:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified a promotional detail aid (FOL-3001), for Follistim (follitropin beta for injection), submitted under cover of Form FDA 2253 by Organon Inc. (Organon), that is in violation of section 502(a) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a). This detail aid is misleading because it minimizes the risks associated with Follistim and makes unsubstantiated superiority claims for the drug. Our specific objections follow below.

Background

According to the FDA-approved labeling (PI), Follistim is indicated for (1) the development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program and (2) the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. The PI includes the following risk information in the Warnings section:

- "Follistim is a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) with or without pulmonary or vascular complications and multiple births."
- "OHSS is a medical entity distinct from uncomplicated ovarian enlargement and may progress rapidly to become a serious medical event."
- "Reports of multiple births have been associated with Follistim treatment. The patient and her partner should be advised of the potential risk of multiple births before starting treatment."

The Warnings section of the PI also states that "Follistim should be used only by physicians who are experienced in infertility treatment."

The PI also addresses the effectiveness of Follistim compared to Metrodin (uFSH). In clinical trials, there was no clinically significant difference in treatment duration days (11.0 days versus 11.6 days) when Follistim was compared with Metrodin.

Organon has received specific guidance from DDMAC on the need to present risk information with sufficient prominence. On June 26, 1998, DDMAC sent Organon an untitled letter regarding a promotional brochure for Follistim. In that letter, we stated that we found the brochure to be lacking in fair balance because the risk information was presented in small print on the back page of the brochure. On October 16, 1997, we sent advisory comments to Organon on launch materials for Follistim. In that letter, too, we stated that, in our view, a proposed sales aid would be lacking in fair balance because of a lack of prominence and readability in the presentation of risk information. We said, further, that a proposed journal ad would be lacking in fair balance unless the risk information was given prominence and readability reasonably comparable to the efficacy information.

Minimization of Risk Information

Your detail aid is misleading because it minimizes the serious risks associated with the use of Follistim that are described in Warnings section of the PI. All of the risk information appearing in the detail aid is relegated to the last of the six pages and is presented in a single-spaced, paragraph format without additional emphasis. In contrast, effectiveness claims such as "recFSH: substantial benefits over uFSH," "Clinical studies clearly demonstrate high effectiveness and efficiency of human recFSH in ART" and "Recombinant FSH Follistim – Life source for today's ART successes" are presented as large, colorful, bolded headers and other claims of effectiveness and benefits are presented throughout the detail aid with colorful charts, bolded headers, bullet points, and a significant amount of white space. The risk information from the PI is summarized in a single, small font paragraph without any header or other presentation elements that emphasize to the reader that it is important safety information.

Misleading Comparative Claims

The detail aid is also misleading because it contains superiority claims that, to our knowledge, are not supported by substantial evidence or substantial clinical experience. FDA is not aware of any data to support the following claims appearing in the detail aid:

- "Larger number of embryos for cryopreservation may reduce costs and treatment risks for subsequent cycles, when necessary"
- "Smaller dose and fewer treatment days [i.e. for Follistim] require less monitoring, allowing patients to save money."
- "Demonstrated efficiency and higher potency of recombinant FSH reduces total treatment costs of patients"

As noted above, in clinical trials, there was no clinically significant difference in treatment duration days between Follistim and Metrodin. Hoomans et al.[1], referenced in the detail aid, concluded that "treatment length was similar in the two groups, 9.9 days in the recFSH group [Puregon] as compared

[1] Hoomans EHM, Andersen AN, Loft A, Leerentveld RA, van Kamp AA, Zech H. A prospective, randomized clinical trial comparing 150 IU recombinant follicale stimulating hormone (Puregon) and 225 IU highly purified urinary follicle stimulating hormone (Metrodin-HP) in a fixed-dose regimen in women undergoing ovarian stimulation. *Hum Reprod.* 1999;14:2442-2447.

to 9.6 days in the uFSH-HP [Metrodin-HP] group." We are not aware of substantial evidence or substantial clinical experience demonstrating that Follistim provides a treatment duration that is superior to that provided by Metrodin.

Conclusion and Requested Actions

Your detail aid is misleading because it minimizes important risk information and contains unsubstantiated superiority claims. The detail aid, therefore, misbrands Follistim under section 502(a) of the Act, 21 U.S.C. 352(a). We request that Organon immediately cease the dissemination of this violative detail aid and all other 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 violative promotional materials with the same or similar messages, and your methods for discontinuing their use.

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. Organon could, for example, correct the issue with the superiority claims by substantiating them, either with substantial evidence or substantial clinical experience. Alternatively, Organon could choose to omit the claims from promotion entirely. To address the risk information issue, Organon could revise its materials to ensure that they present risk information using the techniques employed to present the claims of effectiveness and benefits, such as the use of larger font, bullet points, and bolded headers. For a detail aid of this length, you should also include risk information on more than just the last page.

If you have any questions, please contact me by facsimile at (301) 594-6771, or at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 8B-45; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS #11099 and NDA 20-582.

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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