



John C. Kim, RPh, JD
Senior Director, Regulatory Affairs
Ferring Pharmaceuticals Inc.
4 Gatehall Drive
3rd Floor
Parsippany, NJ 07054

RE: NDA #22201
Firmagon[®] (degarelix for injection) for subcutaneous administration
MA # 19

Dear Mr. Kim,

As part of its monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the Food and Drug Administration (FDA) has reviewed the sales aid titled "Electronic Sales Aid, Short Version (iPad MVA)" (FIRM-2911) (sales aid) for Firmagon[®] (degarelix for injection) for subcutaneous administration (Firmagon) submitted by Ferring Pharmaceuticals, Inc. (Ferring) under cover of Form FDA-2253. This sales aid is misleading because it recommends or suggests uses for Firmagon for which the drug has not been evaluated by the FDA and overstates the efficacy of Firmagon. As a result, this sales aid misbrands the drug in violation of the Federal Food, Drug and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a) & (f)(1), and implementing regulations. 21 CFR 201.100(c)(1) & 201.128. Cf. 21 CFR 202.1(e)(6)(i). These violations are concerning from a public health perspective because they encourage the use of Firmagon in circumstances other than those for which the drug has been shown to be safe and effective and suggest Firmagon is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Background¹

Below are the indications and summary of the most serious and most common risks associated with the use of Firmagon. According to the FDA-approved Firmagon product labeling (PI):

Firmagon is a GnRH receptor antagonist indicated for treatment of patients with advanced prostate cancer.

¹ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

Firmagon is associated with a number of serious risks, as detailed in the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the PI. These risks include fetal harm, prolongation of the QT interval, and suppression of the pituitary gonadal system. Caution is advised to monitor prostate specific antigen (PSA); if increased, serum testosterone should be measured.

The most common adverse reactions observed with Firmagon include injection site reactions (e.g. pain, erythema, swelling, or induration), hot flashes, increased weight, fatigue, and increases in serum levels of transaminases and gamma-glutamyltransferase.

Unapproved New Use

The sales aid is false or misleading because it suggests new “intended uses” for Firmagon- namely, as neoadjuvant therapy prior to radiation and as treatment in patients with a rising PSA.

The sales aid includes the statements:

“USE FIRMAGON FIRST” (page one)

“USE FIRMAGON[®] (degarelix for injection) FIRST IN 3 PATIENT TYPES” (pages two and three)

The claim on page three is followed by a description of several hypothetical patients, including “Joe”, who is “[p]lanning to start hormone therapy prior to receiving radiation therapy in the coming months, and wants a rapid reduction in testosterone levels,” and “Gregory”, who is “[c]onsidering hormone therapy due to rising PSA levels, even after curative attempt.” This sales aid is misleading because it suggests new “intended uses” for Firmagon- namely, as neoadjuvant therapy (i.e., prior to surgery or radiation) and as treatment for patients with a rising PSA. According to the INDICATIONS AND USAGE section of the Firmagon PI, Firmagon is indicated for treatment of **advanced** prostate cancer. Firmagon is not indicated for neoadjuvant use (e.g. prior to radiation therapy) or to treat rising PSA. Furthermore, the pivotal study that led to the FDA approval of Firmagon specifically excluded recruiting both those patients indicated for neoadjuvant hormonal therapy and those receiving neoadjuvant hormonal therapies.² We recognize that Firmagon’s indication for prostate cancer is a general one; however, the drug is not approved and has not been evaluated by FDA as neoadjuvant therapy or to treat rising PSA. FDA is not aware of any substantial evidence to support the safety or efficacy of Firmagon in the neoadjuvant setting before local treatment, such as radiation, or for the treatment of rising PSA.

Overstatement of Efficacy

Promotional materials are misleading if they contain representations that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience, or if they contain favorable data or conclusions in a way that suggest clinical significance when in fact no such clinical significance has been demonstrated. The sales aid presents several claims that overstate the efficacy of Firmagon. Page six of the sales aid makes the following claims regarding the reduction of PSA levels (emphasis original):

“Firmagon reduces PSA levels by more than 60% in just 2 weeks.”²

Provides rapid and sustained reduction in PSA^{2, [3]}

- In 2 weeks, Firmagon reduced PSA levels by 64%²
- Patients treated with LHRH agonists experienced an 18% overall reduction in 2 weeks”²

These claims are presented in conjunction with a bar graph, titled “Rapid PSA reduction” that compares the reduction in PSA levels at day 14 and 28 after initiation of therapy with either Firmagon or leuprolide. The graph shows that patients taking Firmagon had a 64% reduction in PSA levels at 14 days and an 85% reduction in PSA levels at 28 days, while patients taking leuprolide had a reduction of 18% and 68%, respectively, at these two time points. This presentation misleadingly suggests that the velocity of PSA reduction is clinically meaningful for patients with advanced prostate cancer when this has not been demonstrated by substantial evidence or substantial clinical experience. We note the statement, “These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied; no evidence has shown that the rapidity of PSA decline is related to a clinical benefit,” appears below the graph on page six; however, this statement does not mitigate the misleading impression conveyed by the claims included in the sales aid.

Page seven of the sales aid makes the following claims regarding PSA recurrence after treatment with Firmagon at one year:

“Firmagon demonstrated a 34% greater reduction in the risk of PSA recurrence at 1 year vs an LHRH agonist.^[4]”

“Firmagon patients were less likely to experience a PSA recurrence in 1 year.^[4]”

² Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12-month comparable, randomized, open-label, parallel group phase III study in patients with prostate cancer. *BJU Int.*2008;102:1531-1538.

³ FIRMAGON [package insert]. Parsippany, NJ: Ferring Pharmaceuticals, Inc.: 2009.

⁴ Tombal B, Miller K, Boccon-Gibod L, et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. *Eur Urol.* 2010;57:836-842.

These statements are accompanied by a Kaplan-Meier graph that shows the “probability of freedom from PSA recurrence” over the course of a year for patients taking Firmagon or leuprolide. These claims misleadingly suggest that the reduction in risk of PSA recurrence is clinically meaningful or associated with improved disease control or survival when this has not been demonstrated by substantial evidence or substantial clinical experience. We also note that the primary endpoint for the pivotal study was achieving and maintaining testosterone suppression to castration levels (≤ 50 mg/dL) during 12 months (day 28 to day 364) of treatment; PSA levels were monitored as a secondary endpoint. The reference cited to support these claims is an exploratory subgroup analysis of the pivotal study that does not constitute substantial evidence to support efficacy claims such as these.^[4]

Conclusion and Requested Action

For the reasons discussed above, this sales aid misbrands Firmagon because it recommends or suggests uses for Firmagon for which the drug has not been evaluated by the FDA and implies it is more effective than has been demonstrated by substantial evidence or substantial clinical experience in violation of the FD&C Act, 21 U.S.C. 352(a) & (f)(1), and implementing regulations. CFR 201.100(c)(1) & 201.128. Cf. 21 CFR 202.1(e)(6)(i).

OPDP requests that Ferring immediately cease the dissemination of violative promotional materials for Firmagon such as those described above. Please submit a written response to this letter on or before April 13, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Firmagon that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned by facsimile at (301) 847-8444, or at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Promotion (DPP) and the Division of Direct-to-Consumer Promotion (DDTCP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA # in addition to the NDA number in all future correspondence relating to this particular matter. DPP 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 Firmagon comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Marybeth Toscano, PharmD
Regulatory Review Officer
Division of Professional Promotion
Office of Prescription Drug Promotion

Karen Rulli, Ph.D.
Team Leader
Division of Professional Promotion
Office of Prescription Drug Promotion

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/s/

MARYBETH TOSCANO
03/30/2012

KAREN R RULLI
03/30/2012