



NDA 021343/S-019  
NDA 021379/S-015  
NDA 021488/S-016  
NDA 021731/S-012

**SUPPLEMENT APPROVAL**

sanofi-aventis U.S. LLC  
Attention: Gregory Urbancik  
Director, U.S. Regulatory Affairs Marketed Products  
55 Corporate Drive  
Bridgewater, NJ 08807

Dear Mr. Urbancik:

Please refer to your Supplemental New Drug Applications (sNDA) dated November 11, 2010, received on November 12, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following GnRH agonists:

Application	Supplement	Drug Name
NDA 021343	S-019	Eligard® (leuprolide acetate) for Injectable Suspension, 7.5 mg
NDA 021379	S-015	Eligard® (leuprolide acetate) for Injectable Suspension, 22.5 mg
NDA 021488	S-016	Eligard® (leuprolide acetate) for Injectable Suspension, 30 mg
NDA 021731	S-012	Eligard® (leuprolide acetate) for Injectable Suspension, 45 mg

We acknowledge receipt of your amendment dated December 22, 2010, and January 14, 2011.

We also refer to our letter dated October 20, 2010, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for GnRH agonists. This information pertains to the risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, and stroke).

These supplemental new drug applications provide for revisions to the labeling for Eligard (leuprolide acetate) products listed above. The agreed upon changes to the language included in our October 20, 2010, letter are as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~).

Under the HIGHLIGHTS – WARNINGS AND PRECAUTIONS:

**Hyperglycemia and diabetes:** Hyperglycemia and an increased risk of developing diabetes have been reported ~~with~~ in men receiving GnRH analogs. Monitor blood glucose level and manage according to current clinical practice. (5.3 ✕)

**Cardiovascular diseases:** Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported. Monitor for cardiovascular disease and manage according to current clinical practice (5.4 ¶)

Under WARNINGS AND PRECAUTIONS section of the full prescribing information (or in the PRECAUTIONS section for non-PLR format):

5.3 ¶: Hyperglycemia and an increased risk of developing diabetes have been reported in men (b) (4) receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes.

5.4 ¶: Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements and any annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

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MedWatch Program  
Office of Special Health Issues  
Food and Drug Administration  
10903 New Hampshire Ave  
Building 32, Mail Stop 5353  
Silver Spring, MD 20993

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Susan Jenney, Regulatory Project Manager, at (301) 796-0062.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.  
Director  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center of Drug Evaluation and Research

ENCLOSURE: Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AMNA IBRAHIM  
01/14/2011  
For Dr Robert Justice