

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-287**

**APPROVAL LETTER**



NDA 22-287

**NDA APPROVAL**

Takeda Global Research and Development Center, Inc  
Attention: Nancianne Knipfer, Ph.D., RAC  
Manager, Regulatory Affairs Strategy  
One Takeda Parkway  
Deerfield, IL 60015

Dear Dr. Knipfer:

Please refer to your new drug application (NDA) dated December 28, 2007, received December 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kapidex (dexlansoprazole) Delayed Release Capsules 30, 60, (b) (4) mg.

We acknowledge receipt of your submissions dated February 5, 18, 19, 2008; March 7 and 26, 2008; April 28 and 29, 2008; May 22 and 30, 2008; June 24, 26, 30, 2008; July 11 and 15, 2008; August 21 and 26, 2008; September 9, 10, 26, 2008; October 20 and 21, 2008; November 7, 14, 21, 2008; December 10, 17, 23, 2008 and January 12, 13, 14, 22, 23, 27, 28, 2009.

This new drug application provides for the use of Kapidex (dexlansoprazole) Delayed Release Capsules 30 mg for maintaining healing of erosive esophagitis, and for treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD). This new drug application also provides for the use of Kapidex (dexlansoprazole) Delayed Release Capsules 60 mg for healing of all grades of erosive esophagitis.

As discussed in the November 5, 2008 teleconference, we are not approving the (b) (4) dose of Kapidex (dexlansoprazole) Delayed Release Capsules.

We have completed our review of this application, as amended. It is approved for the 30 and 60 mg doses, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than one month for the following indications: healing and maintenance of healing of all grades of erosive esophagitis (EE) and treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD) because the necessary studies are impossible or highly impractical.

We are waiving the pediatric study requirement for ages 1-11 months for the following indications: healing and maintenance of healing of all grades of erosive esophagitis (EE) because necessary studies are impossible or highly impractical. The number of pediatric patients with erosive esophagitis in this age group would be limited.

We are deferring submission of your pediatric studies for ages 1 year to 17 years for healing and maintenance of healing of all grades of erosive esophagitis (EE) and for 1 month to 17 years for treating heartburn associated with non-erosive gastroesophageal disease (GERD) because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1. Deferred pediatric study under PREA for healing and maintenance of healing of all grades of erosive esophagitis (EE) in pediatric patients 1 year to 11 years.

Final report submission: October 31, 2013

2. Deferred pediatric study under PREA for healing and maintenance of healing of all grades of erosive esophagitis (EE) in pediatric patients 12 years to 17 years.

Final report submission: March 31, 2013

3. Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 month to 11 months.

Final report submission: July 31, 2016

4. Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 year to 11 years.

Final report submission: October 31, 2013

5. Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 years to 17 years.

Final report submission: March 31, 2013

Submit final study reports to your NDA 22-287. Use the following designator to prominently label all submissions:

**Required Pediatric Assessments**

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk for bone fractures in patients who have prolonged use and/or higher doses of Kapidex (dexlansoprazole) Delayed Release Capsules.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing clinical trial:

6. A clinical trial to evaluate the effect of Kapidex (dexlansoprazole) Delayed Release Capsules on bone homeostasis. The primary endpoint will be biomarkers of bone formation and bone resorption. Treatments will include: placebo, dexlansoprazole and esomeprazole.

The timetable you submitted on January 12, 2009, states that you will conduct this trial according to the following timetable:

Final protocol Submission:	August 31, 2009
Trial Start Date:	October 31, 2009
Final Report Submission:	December 31, 2011

Submit the protocol to your IND 69,927, with a cross-reference letter to this NDA 22-287. Submit all final reports to your NDA 22-287. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to

report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-287."

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the January 13, 2009 submitted carton and immediate container labels, with the exception of the Hospital Unit Dose Blister Labels for 30 mg and 60 mg doses, of which we accept the January 23, 2009 submission as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-287**". Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see [www.fda.gov/cder/ddmac](http://www.fda.gov/cder/ddmac).

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

If you 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 an electronic copy of the letter to both this NDA and to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B05  
5600 Fishers Lane  
Rockville, MD 20857

### **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 Anna Simon, Regulatory Project Manager, at (301) 796-3509.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure: Package Insert