

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
022271Orig1s000

Trade Name: Nesina

Generic Name: alogliptin

Sponsor: Takeda Pharmaceuticals U.S.A., Inc.

Approval Date: 1/25/2013

Indications: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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APPLICATION NUMBER:

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APPROVAL LETTER



NDA 022271

NDA APPROVAL

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Cosner:

Please refer to your New Drug Application (NDA) dated and received December 27, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nesina (alogliptin) tablets, 6.25 mg, 12.5 mg, and 25 mg.

We acknowledge receipt of your amendments dated February 20 and 22, March 21, April 1 and 24, May 7, 9, 16, and 30, June 26, July 22 and 31, August 5, 11, 25, and 29, September 5, October 3, 16, 17, and 29, November 10, 13, and 18, and December 17 and 18, 2008, and January 19 and 21, March 4, 10, 16, and 25, April 9, May 6, 20, and 28, August 31, and October 28, 2009, and January 21, February 11, March 15, April 13, May 7, June 21, and July 21, 2010, and May 25, July 13 and 25, August 25, September 14, October 5, 6, and 11, November 7, 17, and 22, and December 2, 7, and 20, 2011, and January 20 (2), 23, and 24 (2), February 1, 9, 13, 14, and 22 (2), March 6, 8, 13, 22, 23, 26, 27, 28, and 30, April 4, 5, 19, 27, and 30, May 30, July 12 and 26, August 1 (2), 2, 6, 14, and 27, September 13 and 25, October 5, 10, 11, and 23, November 1, 7, 9, 15, 16, 27, and 30, and December 18, 2012, and January 7 (2), 9 (2), 11, and 17, 2013. We also acknowledge receipt of your emails dated January 24 and 25, 2013 that included the agreed-upon labeling.

The submission dated July 26, 2012, constituted a complete response to our action letter dated April 25, 2012.

This new drug application provides for the use of Nesina (alogliptin) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application. It is 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 the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels submitted on **January 17, 2013**, 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 *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. 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 022271.**” 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.

EXPIRY DATING PERIOD

A 30-month expiry dating period is granted for Nesina (alogliptin) 6.25 mg tablets and a 36-month expiry dating period is granted for Nesina 12.5 mg and 25 mg tablets when stored at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F).

ADVISORY COMMITTEE

Your application for Nesina was not referred to an FDA advisory committee because this drug is not the first in its class and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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 indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 through 9 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

We are deferring submission of your pediatric study for ages 10 to 17 years for this application 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 FDCA 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 FDCA. The required studies are listed below.

- 2007-1:** A clinical pharmacology study in pediatric patients with type 2 diabetes to evaluate the pharmacokinetics of alogliptin and to determine the dose(s) for the subsequent Phase 3 studies that will be conducted under the Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of alogliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive). At least 25% of randomized subjects will be 10-13 years of age.

Study Completion: December 31, 2013
Final Report Submission: June 30, 2014

- 2007-2:** A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin when added on to metformin in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age, and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

Final Protocol Submission: July 31, 2015
Study Completion: July 31, 2019
Final Report Submission: January 31, 2020

2007-3: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin in pediatric patients ages 10 through 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age, and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

Final Protocol Submission: July 31, 2015
Study Completion: November 30, 2020
Final Report Submission: May 31, 2021

Submit the protocols to your IND 069707, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes 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.

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 signals of serious risks of hepatotoxicity, acute pancreatitis, hypersensitivity reactions, cardiovascular events, serious hypoglycemia, and renal impairment in patients treated with Nesina (alogliptin).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2007-4: An assessment and analysis of spontaneous reports of serious hepatic abnormalities, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson Syndrome) in patients treated with Nesina (alogliptin). Specialized follow-up should be obtained on these cases to collect additional information on the events. This enhanced pharmacovigilance should continue for a period of 5 years from the date of approval for reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and

10 years from the date of approval for reports of serious hepatic abnormalities and severe hypersensitivity reactions.

The timetable you submitted on January 21, 2013, states that you will conduct this study according to the following schedule:

| | |
|-----------------------------|--------------------|
| Final Protocol Submission: | October 31, 2013 |
| Interim Report Submissions: | March 31, 2014 |
| | March 31, 2015 |
| | March 31, 2016 |
| | March 31, 2017 |
| | March 31, 2018 |
| | March 31, 2019 |
| | March 31, 2020 |
| | March 31, 2021 |
| | March 31, 2022 |
| Study Completion: | January 31, 2023 |
| Final Report Submission: | September 30, 2023 |

Finally, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus, and available data have not definitively excluded the potential for this serious risk with Nesina (alogliptin). We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with antidiabetic medications, including Nesina (alogliptin). Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2007-5: A randomized, double-blind, placebo-controlled trial evaluating the effect of Nesina (alogliptin) on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. The primary objective of the trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with Nesina (alogliptin) to that observed in the control group is less than 1.3. The long-term effects of Nesina (alogliptin) on hepatotoxicity, hypersensitivity reactions (including severe cutaneous reactions), serious hypoglycemia, pancreatitis, and renal safety will also be evaluated. The trial must include at least 200 Nesina (alogliptin)-treated patients with moderate renal impairment and 100 Nesina (alogliptin)-treated patients with severe renal impairment

The timetable you submitted on January 21, 2013, states that you will conduct this trial according to the following schedule:

| | |
|--------------------------|--------------------|
| Trial Completion: | December 31, 2013 |
| Final Report Submission: | September 30, 2014 |

Submit the protocol to your IND 069707, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, 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.

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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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, 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 Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

Prescribing Information
Medication Guide
Carton and Container Labels

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH

01/25/2013

I am approving the single-entity alogliptin first, before approving the combination products containing alogliptin.