CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205718Orig1s000

Trade Name: Akynzeo

Generic Name: Netupitant and Palonosetron

Sponsor: Helsinn Healthcare SA.

Approval Date: October 10, 2014

Indications: AKYNZEO is a fixed combination of netupitant, a substance P/neurokinin 1 (NK1) receptor antagonist, and palonosetron, a serotonin-3 (5-HT3) receptor antagonist indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Oral palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

HELSINN EXHIBIT 2005
Azurity Pharmaceuticals, Inc. v. Helsinn Healthcare S.A.
IPR2025-00949

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205718

NDA APPROVAL

Helsinn Healthcare SA
c/o August Consulting, Inc.
Attention: Craig Lehmann, PharmD.
Authorized Representative
515 S. Capital of Texas Hwy., Suite #150
Austin, TX 78746

Dear Dr. Lehmann:

Please refer to your New Drug Application (NDA) dated and received September 27, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Akynzeo (netupitant and palonosetron) capsules.

We acknowledge receipt of your amendments dated October 9, 2013; October 31, 2013; November 8, 2013; November 14, 2013; November 21, 2013; December 16, 2013; December 20, 2013; January 9, 2014; January 17, 2014, January 23, 2014; February 4, 2014; February 5, 2014; February 14, 2014; February 20, 2014; March 24, 2014; March 26, 2014, March 27, 2014; March 28 2014; March 31, 2014; April 4, 2014; April 22, 2014; April 25, 2014; April 30, 2014; May 5, 2014; May 12, 2014; May 14, 2014; May 16, 2014; May 21; 2014; May 22, 2014; May 27, 2014; June 5, 2014; June 17, 2014; June 18, 2014; June 30, 2014; July 3, 2014; July 7, 2014; July 15, 2014; July 16, 2014; July 29, 2014; August 5, 2014; August 8, 2014; August 18, 2014; August 21, 2014; August 28, 2014; September 10, 2014; September 15, 2014; September 16, 2014; September 17, 2014; September 23, 2014; September 25, 2014; and September 26, 2014.

This new drug application provides for the use of Akynzeo (netupitant and palonosetron), a fixed combination for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

We have completed our review of this application, as amended. 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, text for the patient package insert). 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 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 205718**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Akynzeo was not referred to an FDA advisory committee because it is not the first in its class and the application did not raise significant public health questions on the role of Akynzeo in the diagnosis, cure, mitigation, treatment, or prevention of a disease. Outside expertise was not necessary; and 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 deferring submission of your pediatric studies until April 30, 2022, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under 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. These required studies are listed below.

2769-1 An 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with netupitant alone.

Final Protocol Submission:	05/30/2015
Study Completion:	12/30/2015
Final Report Submission:	03/30/2016

2769-2 A PK/PD dose finding study of netupitant to characterize the netupitant PK/PD relationship for complete response in the delayed phase following oral administration of a single dose of netupitant given concomitantly (in separate formulations) with an oral single administration of palonosetron in pediatric cancer patients ages 0 to17 years undergoing treatment with emetogenic chemotherapy, including highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

Final Protocol Submission:	11/01/2015
Study Completion:	04/30/2018
Final Report Submission:	09/30/2018

2769-3 An adequate, well-controlled, double-blind, randomized study to evaluate the safety and efficacy of a dose of the netupitant/palonosetron fixed combination compared to standard therapy in pediatric cancer patients ages 0 to 17 years undergoing treatment with emetogenic chemotherapy, including highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

Final Protocol Submission:	04/30/2019
Study Completion:	12/31/2021
Final Report Submission:	04/30/2022

Submit the protocols to your IND 073493, 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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2769-4 *In vivo* drug interaction study to evaluate the duration of inhibitory effects of Akynzeo (netupitant and palonosetron) on CYP3A4 enzyme activity beyond 4 days after Akynzeo (netupitant and palonosetron) administration.

The timetable you submitted on July 29, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2015
Study Completion:	01/2016
Final Report Submission:	06/2016

2769-5 *In vitro* study to evaluate the potential of netupitant to act as a substrate for P-gp transporter in a bi-directional transport assay system.

The timetable you submitted on July 29, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission:	10/2014

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. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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.

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 APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval 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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center of Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

JULIE G BEITZ
10/10/2014