DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-278

NDA APPROVAL

NuPathe, Inc.
Attention: Sanjay Sehgal, Ph.D.
227 Washington Street, Suite 200
Conshohocken, PA 19428

Dear Dr. Sehgal:

Please refer to your New Drug Application (NDA) dated and received October 29, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zecuity (sumatriptan) iontophoretic transdermal system.

We acknowledge receipt of your amendments dated the following:

July 16, 2012	November 16, 2012	December 14, 2012	January 7, 2013
August 17, 2012	November 20, 2012 (2)	December 17, 2012	January 14, 2013 (3)
September 7, 2012	November 26, 2012	December 28, 2012	January 15, 2013
October 16, 2012	November 26, 2012	January 3, 2013	January 16, 2013 (2)
October 25, 2012	December 13, 2012	January 4, 2013	January 17, 2013

The July 16, 2012, submission constituted a complete response to our August 29, 2011, action letter.

This new drug application provides for the use of Zecuity (sumatriptan) iontophoretic transdermal system for the acute treatment of migraine headache.

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 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 carton and immediate-container labels submitted on January 16, 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 202-278**." Approval of this submission by FDA is not required before the labeling is used.

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

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Lana Chen, RPh
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room4353
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

ADVISORY COMMITTEE

Your application for Zecuity (sumatriptan) iontophoretic transdermal system was not referred to an FDA advisory committee because this drug is not the first in its class.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth through 5 years of age because necessary studies are impossible or highly impracticable. This is because the number of patients less than 6 years of age with migraine is too small.

We are deferring submission of your pediatric studies for ages 6 through 17 years, 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.

2000-1: Adolescent Pharmacokinetic Study
Open label, single dose pharmacokinetic study of Zecuity (sumatriptan) iontophoretic transdermal system in adolescents 12 to 17 years of age with a history of migraine, which compares the results with appropriate adult historical control data. The number of adolescent migraine patients in this study must be sufficient to adequately characterize the single dose pharmacokinetics of adolescents compared to adults. There must be similar number of patients in the 12 to 14 years and 15 to 17 years age groups. There must be a reasonable distribution of both sexes in this age bracket.

The timetable you submitted on January 14, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2013
Study Completion:	May 2014
Final Report Submission:	July 2014

2000-2: Adolescent Efficacy Study
Randomized, double-blind, placebo-controlled, parallel group study to evaluate the effectiveness and safety of a single Zecuity (sumatriptan) iontophoretic transdermal system compared to a

single placebo iontophoretic transdermal system in adolescents 12 to 17 years of age with a history of acute migraine. An enrichment design must be used to reduce the placebo effect. The primary efficacy endpoint must be pain freedom at 2 hours. The study must be powered to detect an effect size similar to that seen in the adult population. There must be similar number of patients in the 12 to 14 years and 15 to 17 years age groups. The protocol must allow the use of appropriate rescue medication after a suitable post-dosing interval.

The timetable you submitted on January 14, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission: August 2014
Study Completion: September 2015
Final Report Submission: December 2015

2000-3: Adolescent Long-Term Safety Study
Open label, 12-month study to evaluate the long-term safety of Zecuity in adolescents 12 to 17 years of age with a history of migraine. Safety assessments must include adverse events, subject and investigator skin irritation evaluations, and monitoring of vital signs. The study must evaluate a sufficient number of adolescent migraine patients to be able to characterize the long-term safety of Zecuity when used to treat multiple migraine attacks over one year. Each patient must treat, on average, at least one migraine attack per month for six to twelve months. At a minimum, 200 patients, using an effective dose, must be exposed for six months, and 75 patients, using an effective dose, must be exposed for one year. There must be similar number of patients in the 12 to 14 years and 15 to 17 years age groups.

The timetable you submitted on January 14, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission: August 2014
Study Completion: September 2016
Final Report Submission: December 2016

Submit the clinical protocols to your IND, with a cross-reference letter to this NDA. The clinical protocol for the Adolescent Efficacy Study should be submitted for Special Protocol Assessment.

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.

Pediatric studies in children ages 6 years to 11 years will be determined by the Agency after data has been reviewed from the required safety and efficacy studies in adolescent patients between ages 12 years to 17 years.

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 identify an unexpected serious risk of the carcinogenic potential of Zecuity (sumatriptan) iontophoretic transdermal system.

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 this serious risk.

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

2000-4 An *in vivo* repeat-dose dermal painting study (with toxicokinetic [TK] analysis) of sumatriptan succinate conducted in an appropriate mouse model, and using various penetration enhancers.

The timetable you submitted on January 14, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	April 2013
Study Completion:	September 2013
Final Report Submission:	November 2013

2000-5 A dermal (painting) carcinogenicity study of sumatriptan succinate in mice.

The timetable you submitted on January 14, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	April 2014
Study Completion:	June 2016
Final Report Submission:	December 2016

Submit draft protocols for these postmarketing requirements at least 60 days prior to the final protocol submission date to allow for review and agreement on the protocols.

Submit the protocols to your IND 74,877, 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.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). We request that any case of skin burn and any case of scar at the site of administration be submitted as a 15-day report. We also request that assessment of

adverse events related to skin burn, intense erythema with blister(s) or broken skin, and allergic contact dermatitis be compiled in PSURs.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling

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

/s/

ERIC P BASTINGS
01/17/2013