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APPLICATION NUMBER:

202278Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD
Subject	Summary Review for Regulatory Action
NDA/BLA # **Supplement #**	202-278
Applicant Name	NuPathe Inc.
Date of Submission	July 17, 2012
PDUFA Goal Date	January 17, 2013
Proprietary Name / **Established (USAN) Name**	Zelrix/Sumatriptan Succinate
Dosage Forms / Strength	Iontophoretic Transdermal Patch
Proposed Indication(s)	Acute Treatment of Migraine
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Nushin Todd, MD
Pharmacology Toxicology Review	Charles Thompson, Ph.D.
CMC Review/OBP Review	Caroline Strasinger, Ph.D.
Product Quality Microbiology Review	Stephen E. Langille, Ph.D.
Clinical Pharmacology Review	Michael Bewernitz, Ph.D.
CDRH/Human Factors Review	QuynhNhu Nguyen, Biomedical Engineer
CDRH/ODE Review	Katherine Kim, Biomedical Engineer
OSE/DMEPA	Julie Neshiewat, PharmD
OSI	Jyoti Patle, Ph.D.; Sam Haidar, Ph.D., R.Ph.
ONDQA Biopharmaceutics	Tapash Ghosh
CDRH/Compliance	Elijah M. Weisberg

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
ODE=Office of Device Evaluation

1. Introduction

Nupathe submitted a complete response to FDA's August 29, 2011, action letter. That action letter informed the sponsor that their application could not be approved because of a number of product quality, microbiology, clinical pharmacology, nonclinical, and clinical issues. I discussed these deficiencies in an August 17, 2011, cross-disciplinary review, to which the reader is referred.

2. Background

The August 29, 2011, FDA action letter identified 71 CMC/device issues, which for the most part were related to concerns about the fundamental design of the Zecuity Iontophoretic Transdermal System (TDS). These concerns were further discussed with the sponsor at a November 9, 2011, post-action meeting. Specifically, the CMC team summarized the issues as follows: "A lack of containment of the drug formulation once the aluminum foil top is removed poses a safety risk during assembly of the system, use of the system, and disposal of the system. It is visually evident that storage orientation affects the physical location of the formulation within the cold formed wells. The potential for leakage of the gel drug formulation during assembly and wear is high because of the lack of formulation and imbibed pad containment. The lack of containment increases the potential for variable amounts of drug transferred to the patient and also prevents adequate method development, including but not limited to assay and methylparaben content, which is essential to ensure the quality of the product. Additionally, the potential for inadvertent exposure, improper assembly including proper pad transfer, and several other safety issues cannot be mitigated unless the iontophoretic system utilizes contained drug and salt formulation reservoirs". As a result of the flaws with the original Zecuity TDS design, several patients experienced burns and scars the at application site. Because of these issues, FDA recommended a redesign of the product.

The sponsor followed FDA advice, and redesigned the product. The revised product is equipped with a pad detection system. This includes a pre-programmed microprocessor that conducts a series of diagnostic tests to verify pad placement, skin resistance, and device functionality prior to drug delivery. These modifications are intended to ensure that if a Zecuity TDS is misassembled or a medication pad is absent, the Zecuity TDS will not turn on. The sponsor also conducted a usability study with the new system.

3. CMC/Device

I concur with the conclusions reached by Dr. Caroline Strasinger, chemistry reviewer, Dr. Steven Languille, product quality microbiology reviewer, and by Katherine Kim, device

reviewer, regarding the acceptability of the manufacturing of the Zecuity Iontophoretic System. The sponsor adequately addressed all 71 CMC/device issues identified in the CR letter.

Usability of the redesigned product (as evaluated in the new usability study [NP101-027]), was found acceptable by QuynhNhu Nguyen, Biomedical Engineer, CDRH, and by Dr. Julie Neshiewat, OSE. Manufacturing site inspections were acceptable. There are no outstanding CMC or device issues.

4. Nonclinical Pharmacology/Toxicology

Dr. Charles Thompson recommends a "not approvable" action, because he considers that the nonclinical issues identified in the CR letter were not adequately addressed. These issues were related to an inadequate chronic dermal toxicity study, and an inadequate justification for allowing a waiver for the dermal carcinogenicity study. As discussed in the CR letter, the chronic dermal toxicity study was important to inform whether the dermal carcinogenicity study should be conducted. The issue was further discussed at the end-of-review meeting, at which FDA re-emphasized that the sponsor will need to demonstrate that a meaningful study cannot be conducted using sumatriptan painted onto the skin, e.g., using a formulation designed to enhance dermal absorption, in order to support a waiver. In this submission, the sponsor maintains that the chronic dermal toxicity study was adequate, and that sufficient data has been provided to support the infeasibility of conducting a dermal carcinogenicity study.

The sponsor's arguments were reviewed by Dr. Thompson, and by Dr. Lois Freed, supervisory pharmacologist. Dr. Thompson concludes that no new information has been submitted to address the nonclinical issues, and that these issues remain unresolved. Dr. Freed agrees, and proposed that conducting an appropriate feasibility study in rodent (mouse) and then (if supported by the feasibility study) a dermal carcinogenicity study could be an acceptable path to address the issues, in which case the 9-month study does not need to be repeated.

The timing of the required additional nonclinical data then becomes in question, and in particular, whether there is a clinical benefit that would justify allowing marketing of the product before the nonclinical studies described above are conducted. There is no definite evidence that this product addresses an unmet medical need. The efficacy of Imitrex tablets was established in a typical migraine population, i.e., there was a substantial proportion of patients with nausea at the time of treatment in Imitrex tablet clinical trials. Patients with prominent nausea already have several non-oral alternatives, including a nasal spray, and a subcutaneous formulation for self-administration with an autoinjector, or with a needleless device. Nevertheless, the product may offer benefit for patients who have prominent nausea or vomiting and who cannot tolerate or are unwilling to use the marketed formulations of sumatriptan. Arguably, that subgroup of patients represents a very small fraction of the migraine population, but also a very disabled subgroup. Considering the vast experience with other formulations of sumatriptan, and the absence of a signal for carcinogenicity with the other routes of administration, I find it acceptable to have the sponsor conduct the following nonclinical studies as postmarketing requirements:

- An in vivo repeat-dose dermal painting study (with TK analysis) of sumatriptan succinate in an appropriate mouse model, and using various permeation enhancers.
- A dermal (painting) carcinogenicity study of sumatriptan succinate in mouse.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by Dr. Michael Bewernitz, clinical pharmacology-biopharmaceutics reviewer, that there are no outstanding clinical pharmacology issues that preclude approval. As discussed by Dr. Bewernitz, the sponsor adequately documented the bioequivalence of the to-be-marketed system (equipped with the pad detection system) with the systems used in clinical studies (original and modified).

6. Clinical/Statistical-Efficacy

Substantial evidence of efficacy was established in the original submission for the overall migraine population. Efficacy in non-white patients, however, appeared questionable from the results of the pivotal efficacy study. The sponsor provided additional analyses which, as discussed by Dr. Todd, do not provide a very convincing argument of efficacy in non-white patients, with the caveat that the study was not powered to establish efficacy in that subgroup. However, pharmacokinetic data support bioequivalence of the product in white and non-white patients. On that basis, it is reasonable to conclude that the product is expected to have similar efficacy in white and non-white patients.

7. Safety

The fundamental safety issue with the original Zecuity TDS that prevented approval was a risk of burns and scars, as evidenced by multiple occurrences in the long term safety study. There were also a number of other local tolerability issues that also needed clarification.

As discussed above, the sponsor redesigned the Zecuity TDS, by adding a pad detection system that prevents device activation if the Zecuity TDS is misassembled or a medication pad is absent. The sponsor provided adequate engineering evidence to support that the pad detection system will operate as expected, and the review team agreed that this is sufficient to address the burn/scarring issue. I agree, but given the lack of clinical experience with the redesigned product, the sponsor will be required to report all post-marketing cases of burns and scarring as 15-day safety reports.

In her review, Dr. Todd discussed how the sponsor addressed the other clinical safety issues identified in the CR letter. I agree with her assessment and recommendations regarding these issues.

8. Advisory Committee Meeting

This product is not a new molecular entity, and was not referred to an advisory committee meeting.

9. Pediatrics

As discussed in my August 17, 2011, cross-disciplinary review, pediatric studies will be required under PREA in patients age 6-17 years.

10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues. The application was cleared on a 505(b)(2) perspective.

11. Labeling

The proposed tradename, Zecuity, was found acceptable by DMEPA. There are no unresolved labeling issues.

12. Decision/Action/Risk Benefit Assessment

As discussed by the review team, the sponsor has adequately addressed all issues identified in the CR letter, with the exception of nonclinical issues related to the evaluation of local carcinogenicity. As discussed above, the necessary nonclinical studies will be conducted as post-marketing requirements. Zecuity has local tolerability issues, and this will likely limit its use mostly to migraine patients who are disabled by nausea and unable or unwilling to use other formulations of sumatriptan or of other triptans.

An approval letter will be sent to the sponsor. The approval letter will include a requirement for expedited reporting of all post-marketing cases of burn and/or scar after Zecuity use. The action letter will include the following Postmarketing Requirements:

1. Adolescent Pharmacokinetic Study.
2. Adolescent Efficacy Study.
3. Adolescent Long-Term Safety Study.

4. In vivo Repeat-dose Dermal Painting study.
5. Dermal (painting) carcinogenicity study (which will only be conducted if the dermal painting study does not support that the carcinogenicity study is not feasible).

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/s/

ERIC P BASTINGS
01/17/2013