

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202278Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	8/17/2011
From	Eric Bastings, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	202,278
Supplement#	
Applicant	NuPathe, Inc.
Date of Submission	10/29/10
PDUFA Goal Date	08/29/11
Proprietary Name / Established (USAN) names	Zecuity/sumatriptan iontophoretic transdermal system
Dosage forms / Strength	Iontophoretic transdermal patch (6.5mg sumatriptan delivered)
Proposed Indication(s)	Acute treatment of migraine
Recommended:	Complete response

1. Introduction

Nupathe, Inc., submitted 505 (b)(2) NDA 202,278 for Zecuity, a new transdermal dosage form of sumatriptan. Sumatriptan was the first triptan approved for the acute treatment of migraine (in 1992), and is currently available as a tablet, subcutaneous injection (SQ), and nasal spray. A number of generics are also available for the tablet and subcutaneous injection dosage forms. GSK, sponsor of the reference listed drug, has three approved NDAs for sumatriptan: NDA 20,080 (Imitrex Injection), NDA 20,132 (Imitrex Tablets), and NDA 20,626 (Imitrex Nasal Spray). For this 505(b)(2), the sponsor is relying on FDA prior findings of safety and effectiveness for the sumatriptan tablet and SQ injection.

The application was reviewed by the following FDA staff:

Project Manager: Lana Chen, Pharm.D.

CMC: Caroline Strasinger, Ph.D.; David Claffey, Ph.D.

CDRH: Geeta Pamidimukkala.

Biopharmaceutics: Tapash K. Ghosh, Ph. D.

Non Clinical: Charlie Thompson, Ph.D.

Clinical Pharmacology: Jagan Parepally, Ph.D.

Microbiology: Stephen E. Langille, Ph.D.,

Clinical Safety and Efficacy: Nushin Todd, MD.

Statistics: Jingyu (Julia) Luan, Ph.D.

DRISK (labeling): Robin Duer, MBA, BSN, RN

DRISK (REMS): Carolyn L. Yancey, M.D.

DSI: Antoine El-Hage, Ph.D, and Tejashr Purohit-Sheth, M.D.

2. Background

As discussed in the various review documents, Zecuity is a drug/device combination product, designed to administer sumatriptan through an iontophoretic process. The product consists of two parts: a dual drug reservoir that contains 86 mg of sumatriptan succinate in one pad and a salt solution in the other pad, and an electrode patch, consisting of two electrodes (a ^{(b) (4)} anode and a ^{(b) (4)} cathode) connected to a programmed circuit. Before using the product, patients are to remove the top foils protecting the drug reservoir and the electrodes, and to apply the electrodes over the drug reservoir, which is intended to transfer the drug/saline filled pads over the electrodes. The patch can then be applied to the upper arm or the thigh, and a button has to be pressed to initiate drug delivery. The patch is to automatically deactivate after four hours.

As discussed by Dr. Todd, the development program for Zecuity was discussed with the sponsor at a pre-IND meeting in October 2006. At that meeting, the division accepted that a single positive efficacy study would be sufficient to support the efficacy of the new product, as the efficacy of other formulations of sumatriptan for the acute treatment of migraine is well established. Human dermal safety testing was also discussed.

A pre-NDA meeting was held in November 2009. At that meeting, the size of the safety database was discussed. Instead of the typical FDA-required database of at least 300 subjects who treated, on average, at least 2 migraine attacks per month for six months and 100 subjects who treated, on average, at least two migraine attacks per month for one year, the sponsor proposed a database of at least 300 subjects who treated, on average, 3 migraine attacks for six months and 50 subjects who treated, on average, 3 migraine attacks for 12 months. FDA accepted the proposal.

3. CMC/Device

General product quality considerations

Dr. Caroline Strasinger and Dr. David Claffey conducted the CMC review. From a CMC perspective, they recommend a complete response action, because, in their opinion, the sponsor has not provided sufficient information to assure the identity, strength, purity, and quality of the product. The CMC review team believes that the fundamental design of this product is not acceptable, and that the sponsor has not provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent quality of the drug substance and drug product. These issues are described in detail in the CMC review document, to which I refer the reader.

The CMC issues were communicated to the sponsor in a 5/19/2011 CMC review discipline letter, of which the content is reproduced in the CMC review (page 75-78), and also appended to this memorandum (appendix 1). The sponsor responded to the CMC review discipline letter in a 6/10/2011 submission to the NDA. The CMC team reviewed that response, and issued a 7/15/2011 discipline letter summarizing the outstanding issues. In that second letter, the CMC team noted that the sponsor addressed some of the concerns identified in the 5/19/2011 letter, but that there was a number of outstanding unresolved concerns (listed in appendix 2). Briefly, the CMC team remains concerned about the following key issues:

- Lack of uniformity in the distribution of drug formulation on the non-woven pad
- Lack of drug formulation containment and risk of unintentional exposure
- Lack of proper disposal procedures during and post use
- Patient usability (CMC notes that the sponsor submitted new data from a usability study, but that these may not be reviewed during this cycle).

Regarding the product usability, one could argue that the sponsor demonstrated the efficacy of the product in the pivotal efficacy trial, and that therefore these patients were presumably able to use the product. However, patients in the trial were instructed on how to use the product, which may have mitigated some of the issues described in the CMC review. In post-marketing conditions of use, there is no doubt that the quality of instruction will be variable, absent a mandatory training of patients and of prescribers. Such a mandatory training may partially address some of the usability concerns, but would not respond to the concerns related to the lack of drug formulation containment and the environmental risk. Also, some adverse reactions (e.g., burns, discoloration) reported in clinical studies may also be related to usability

issues (see below for further discussion under "Safety"), and occurred despite patients being instructed on how to use the product.

CDRH

Geeta Pamidimukkala, Biomedical Engineer, conducted the CDRH review. Ms. Pamidimukkala identified the following deficiencies, to be communicated to the sponsor:

Labeling (to be discussed in the next cycle)

- The provided labeling information included in Section 1.14 does not include the carton labeling. Please submit the primary carton/pouch labels for review.
- The Patient labeling section includes the following statement; "(b) (4)"
Please add a statement explaining that if the light turns off before 4 hours, the full 6.5 mg sumatriptan dose may not have been delivered.
- The Patient Labeling section under the "How should I use Zecuity" heading states "(b) (4)"
This statement can be interpreted to mean users can apply 2 active patches simultaneously. Please revise this statement to make clear that users may apply a second patch following shut down of the first patch.
- Please add the following contraindication: for patients with known sensitivity or adverse reaction to application of electrical current.
- Please add the following to the Warnings/Precautions sections of your labeling: "patch can be worn during normal activity, however excessive motion may cause poor contact between skin and electrodes. This may result in uneven distribution of current increasing the risk of skin irritation." Additionally, please add a statement instructing users to remove the patch if they experience a burning sensation during use.

Stability/Shelf Life

You evaluated the performance of the clinical and commercially packaged system after 9 months and 6 months storage, respectively, to support an expiration date of "(b) (4)" months. Please address the following:

a) NuPathe Stability Protocol for Zecuity Documents for Device Stability, Lot MBR-75-NP101-007-0012 and Lot MBR-75-NP101-017-0001 (Document Nos: Prot-CM-NP101-007 and Prot-CM-NP101-008, respectively) state the protocol was amended to "(b) (4)"

b) You included a document in section 3.2.P.8.2 of the original submission titled "Post-approval Stability Protocol and Stability Commitment." This document states that you intend to "(b) (4)"

(b) (4)
Please provide a rationale for why these evaluations will not be conducted.

c) Please provide the pass/fail criteria for the (b) (4)

d) Please clarify to what extent your shelf life validation evaluated the potential for corrosion (or other break down) of the power supply.

Biocompatibility

You provided the test reports from the completed cytotoxicity, irritation, and dermal sensitization evaluations to demonstrate biocompatibility of patient contacting device components. The test article in each report is described as the "E-Patch (with (b) (4) removed); testing (b) (4), pad transfer ring, overtape with adhesive, foam barrier with adhesive." Please state if the evaluated test articles are identical to the final device materials intended for commercial distribution. Please be advised that biocompatibility should be established for the device you intend to market.

Software/Firmware

You list and describe the following modes in the software description section of your submission (section 8.2 of 3.2.R.4): sleep mode, self test, test mode, active mode, self test fail mode, (b) (4) mode. There are discrepancies in the naming convention and description of each mode within the software related documents you provided in attachments 17-48. Please address the following:

(b) (4)

Please state what is the expected result if the “On” button is depressed at any point once the device is no longer in Sleep mode.

The Hazard Analysis you provided in attachment 17 of the original submission identified hazards associated with firmware or hardware failure. Please address the following:

- a) This is an incomplete analysis as you did not evaluate potential hazards associated with use of the device in other categories (e.g., electrical, operational, environmental, mechanical). Please update your hazard analysis to include all potential hazards that result from device use. Alternatively, you may provide a rationale for why you have omitted identification and evaluation of other hazards from your analysis.
- b) Bums and blistering are commonly reported adverse events for iontophoretic drug delivery patches; however you did not identify this hazard in the Hazard Analysis. Please update the hazard analysis to include this risk and all potential causes, along with appropriate mitigating actions.
- c) You provided several samples of the system for review. The drug and salt patches have a very similar appearance and it is possible for users to inadvertently switch the anode and cathode patches. Please address the potential for such an occurrence and discuss the potential hazards to the patient. Please update the Hazard Analysis accordingly.
- d) The Software Safety Report in attachment 17 states the analysis was performed on software Version (b) (4). Please clarify if all risk controls identified in the Hazard List table have been implemented in the software Version (b) (4) (the version that is intended for commercial distribution).

You have completed all of the validation and verification activities on firmware version (b) (4) however the E-patch will be commercially released with version (b) (4) and a full validation of this version was never completed. You provided a memo in attachment 48 which states that the differences between the two versions are not expected to impact performance and that version (b) (4) passed the “(b) (4)” test and the “(b) (4)” test. Please provide the test report (method, results, discussion) for these completed tests and provide a rationale for why these two tests alone are sufficient. Alternatively, please complete a full validation and verification of the firmware version you intend to use in the commercial product.

Testing

In section 2 of 3.2.R.4 of the original submission, you declare conformity to several standards, including IEC 60601-2-2 (2006); Medical Electrical Equipment Part 2-2: Particular requirements for the safety of high frequency surgical equipment. It is not apparent how this standard is applicable to your device as your device does not generate or deliver high frequency current. Please explain the extent to which your device conforms to this standard.

Facilities review/inspection

Acceptable.

4. Nonclinical Pharmacology/Toxicology

Dr. Thompson recommends a complete response action. Dr. Thompson identified the following deficiencies:

1. The acute dermal toxicity study data are not interpretable because the drug/device combination tested was not identical to the proposed marketed product in drug formulation or device power source.
2. The 9-month repeated-dose toxicity study in miniature swine was inadequate by design, as there was no control group included, and that there was an insufficient number of animals studied. Also, animals were dosed only once per week for 4 hours, and the dosing site was unclear. Only 4 animals received full, 36-patch treatment over 9 months. The iontophoretic device current flow/control was undefined, and the stability of test article for full study duration was not confirmed.
3. The submission contains no nonclinical data to address whether sumatriptan administered via transdermal iontophoresis results in a metabolite profile comparable to that of the RLDs. Dr Thompson defers to the clinical team regarding the availability of human data to address that issue.
4. The sponsor has not provided adequate justification for waiving the requirement for conducting a dermal carcinogenicity study with the proposed clinical drug product formulation.

Dr. Thompson recommends that the following be requested from the sponsor to address these deficiencies:

1. The acute dermal toxicity study in miniature swine (or other appropriate species) should be repeated with the actual to-be-marketed clinical drug product/device combination.
2. The chronic (9-month) toxicity study in non-rodent (miniature swine or other appropriate species, all of a single strain) should be repeated utilizing a study design that is consistent with relevant Agency guidance (i.e., Guidance for Industry and Review Staff: Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route, CDER 2008). Specifically, the study design should incorporate adequate numbers of animals for meaningful interpretation at each sacrifice (minimally, 4/sex/dose group) and should include appropriate control groups (vehicle/untreated). Multiple dose levels should be included to allow assessment of the dose responsiveness of any toxicity observed, up to a dose documented to be either a maximum tolerated or maximum feasible dose (MTD/MFD). The dosing regimen should consist minimally of 3 patch applications per week per animal on the same application site. Inclusion of at most one interim sacrifice into the study design may be appropriate. Toxicokinetic analyses should be included in the study design.
3. Unless a repeated and sufficiently robust chronic dermal toxicity study in non-rodent (see second bullet above) results in absolutely no evidence of any neoplastic and/or pre-neoplastic responses, the sponsor will need to provide appropriate justification for why a dermal painting carcinogenicity study is not relevant and not feasible.

Lois Freed, Ph.D, supervisory pharmacologist, concurs with Dr. Thompson's conclusion that the sponsor has not provided adequate nonclinical data to support approval of Zecuity, based on the lack of (1) an adequate chronic dermal toxicity study and (2) either a dermal carcinogenicity study in one species or sufficient justification for why such a study would not be feasible or informative. Dr. Freed emphasizes that it has been suggested that the results of

the chronic dermal toxicity study be taken into account when assessing the need for a carcinogenicity study. However, Dr. Freed notes that the 9-month dermal toxicity in minipig was inadequate by design (e.g., no control group), and did not adequately cover the intended clinical dosing regimen. Therefore, there is no adequate assessment of the local effects of chronic administration and the results of the sponsor's minipig study cannot be taken into consideration when assessing whether or not a dermal carcinogenicity study is needed. She also agrees that the sponsor's reasons for why a dermal carcinogenicity study is not feasible were not compelling.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

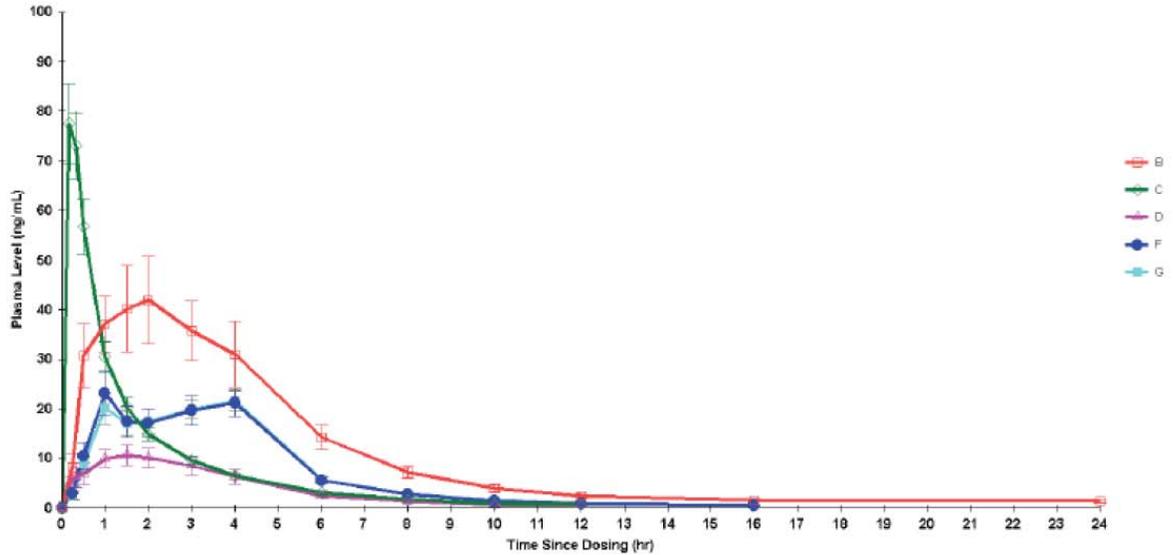
Dr. Parepally conducted the Clinical Pharmacology review. Table 1, adapted from Dr. Parepally's review, shows the principal PK studies conducted in Zecuity development program:

Table 1: PK studies in Zecuity development program

	Objective	Design
NP101-005 (n=25)	Compare the PK of Zecuity with currently approved formulations of Imitrex	Open-label, randomized, , single-dose, crossover study vs. sumatriptan sc injection, oral tablet, and nasal spray
NP101-013 (n=63)	Assess the BE of the Zecuity patch used in Study Zecuity-007 and that intended for commercial use, compared to oral Imitrex	Open-label, randomized, single-dose, crossover study vs sumatriptan oral tablet
NP101-012 (n=33)	Assess the BA of Zecuity applied to two different sites; and assess the PK of Zecuity in elderly subjects	Group I: Open-label, randomized, single-dose, 3-way crossover study vs. sumatriptan sc injection in subjects 18-45 Group II: Open-label, single-dose study in subjects >65

Dr. Parepally notes that the Zecuity C_{max} and AUC values are between those of the 20 mg sumatriptan nasal spray and 100 mg sumatriptan oral tablets (see **Figure 1**). Zecuity C_{max} is about 30% of that of the SQ formulation, while Zecuity AUC_{0-inf} is similar to that of the SQ formulation.

Figure 1: Comparative PKs between Zecuity (called NP101 in this graph) and other formulations of sumatriptan (Treatment F has the same total dose of sumatriptan as the Zecuity product proposed for marketing)



- Treatment B (n=23): 100 mg sumatriptan oral tablet
- Treatment C (n=23): 6 mg sumatriptan subcutaneous injection
- Treatment D (n=23): 20 mg sumatriptan nasal spray
- Treatment F (n=17): NP101 patch F (NP101 patch contains 3g of formulation)
- Treatment G (n=17): NP101 patch G (NP101 patch contains 2.6g of formulation)

Dr Parepally described PK differences between White and non-White patients (see Table 2), but he considers that the study from which these PK data were derived was too small to draw any conclusion. That finding however suggests that the product’s efficacy may be reduced in non-White patients, and as described below, there was no drug benefit on pain freedom demonstrated in the pivotal efficacy study in non-White patients.

Table 2: Racial PK differences

	Non-whites	Whites	Ratio non-white/white
AUC 0-inf (hr*ng/mL)	98	124	0.78
Cmax (ng/mL)	19	26	0.74

Although the Zecuity Cmax in non-White subjects is higher than Cmax with the Imitrex nasal spray (which may potentially be used to support Zecuity efficacy in non-White subjects), the sponsor has not provided patent certification or a statement with respect to each patent listed in FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” for Imitrex Nasal Spray, so that reliance on the prior finding of efficacy for Imitrex Nasal Spray is not possible for a 505(b)(2) application.

In addition, as discussed in Dr. Parepally's review addendum, the clinical portion of Study NP101-013 is not acceptable for review because of a failure to randomly select and retain reserve samples for the test and reference products used in this study, as required by 21 CFR 320.38 (Retention of bioavailability samples). Due to the absence of reserve samples, authenticity of the test and reference products used in Study NP101-013 cannot be assured. Therefore, OCP recommends that the results obtained from pivotal BE Study NP101-013 are not acceptable, and that the study should be repeated.

Biopharmaceutics

Tapash K. Ghosh, Ph. D., conducted the Biopharmaceutics review. Dr. Ghosh notes that FDA requested the sponsor to develop a discriminating *in vitro* method with the ability to evaluate drug permeation as a quality control tool to detect lot to lot variability (reject bad performance product), and requested that the NDA submission provide the final report for the *in vitro* permeation test including all data collected during development and validation of the test.

Dr. Ghosh notes that the method is still undergoing validation and optimization at the time of his review. He describes the following parameters as unresolved:

- Can the sampling area be reproducibly moved without disturbing the integrity of the system?
- Can the electronics be precisely controlled especially in changing the (b) (4) (b) (4) ?
- How is the total amount of drug delivered calculated?
- Is the system able to detect and precisely prevent passive transport of the drug?

Dr. Ghosh notes that a Product Quality and Manufacturing Memo for *in-vitro* release testing site of Zecuity has been generated. Dr Ghosh conducted a preliminary review of the proposed validation method, but he will defer a full review until the sponsor has completed the validation of the *in-vitro* release method and proposes a release and stability *in-vitro* specification. Dr. Ghosh has identified the following preliminary issues/questions for communication to the sponsor:

- Explain when approximately (b) (4) mg of sumatriptan is targeted to be delivered to the patient *in-vivo* over 4 hours of application, why your last *in-vitro* release specification proposes a $Q = (b) (4)$ mg after 4 hour.
- Submit *in-vitro* release data/profiles generated using your final release method from clinical/biobatches for the Agency to review. More than one point specification is recommended for this product, especially at the juncture of changing the (b) (4) from (b) (4).
- The sponsor's proposed specification with a range of $Q \pm (b) (4)\%$ is not acceptable without an established IVIVC and/or supportive bioequivalence data.
- The Agency usually recommends a range of $Q \pm (b) (4)\%$. Please provide a justification for your choice of Q values.
- Explain how the sampling area can be reproducibly moved without disturbing the integrity of the system.

- Explain how the electronics can be precisely controlled especially in changing the (b) (4)
- Explain how the total amount of drug delivered is calculated.
- Explain how the system is able to detect and precisely prevent passive transport of the drug.

6. Microbiology

Stephen E. Langille, Ph.D., conducted the microbiology review. Dr. Langille notes that the sponsor failed to provide proof of antimicrobial effectiveness or microbial control of the finished product. Dr. Langille discusses that the sponsor claims that (b) (4) testing was conducted according to USP <51> but did not provide the results of the testing for either the salt pad or the sumatriptan pad. In section 5.2.3.1.1 of section P.2.5 of the application, the sponsor stated that a USP <51> (b) (4) test conducted on the salt pads failed. The sponsor provided an insufficient explanation as to the cause of the failure but concluded that methylparaben (the proposed preservative) is an adequate preservative and that (b) (4) testing will be replaced with a methylparaben content assay “as recommended by the FDA”.

Dr. Langille discusses further that although the sponsor claimed that FDA indicated that USP <51> (b) (4) testing should be replaced by a preservative content test, FDA’s meeting minutes indicate that the decision to drop (b) (4) testing on stability samples was left up to the sponsor [and therefore would be a review issue]. Dr. Langille notes that testing for preservative content is an acceptable alternative to (b) (4) testing if (b) (4) has been demonstrated at the minimal acceptable preservative content, which is not yet the case for Zecuity.

Dr. Langille lists the following comments/questions to be communicated to the sponsor:

Please provide the following product quality microbiology information:

1. English translations of the raw data lab reports for antimicrobial effectiveness testing on the salt pads.
2. Evidence that the minimum specified amount of (b) (4) is capable of preserving the salt patch over the shelf life of the product.
3. An explanation for the out of specification results for preservative content in salt patch stability batches 7063718, 7063728, and 7063738 when stored at (b) (4) % humidity.
4. An explanation as to why antimicrobial (b) (4) testing failed on salt patch stability lot MBR-75- NP101-017-0001 and why antimicrobial (b) (4) testing was not conducted on salt patch stability lot MBR-75- NP101-007-0012. Please note that preservative identity and content testing may be used as an alternative to (b) (4) testing only if the minimum acceptable concentration of preservative, as listed in the product specification and stability protocol, is shown to be effective in a USP <51> or equivalent antimicrobial effectiveness test.
5. (b) (4) storage time limits for the salt and sumatriptan solutions.
6. Verification of the USP <61>/<62> method for microbial limits testing on the sumatriptan and salt patches.

7. Clinical/Statistical- Efficacy

The sponsor conducted a single pivotal efficacy study (NP101-007), which is acceptable, as sumatriptan is already approved for the same indication under other routes of administration. The sponsor is also relying on prior findings of safety and efficacy of the sumatriptan tablet and subcutaneous injection under the 505(b)(2) provisions. As discussed above, the C_{max} of Zecuity is below that of the Imitrex tablet and subcutaneous injection, so that efficacy can't be extrapolated on a pharmacokinetic basis only.

Jingyu (Julia) Luan, Ph.D., conducted the statistical review. Dr. Luan notes that Study NP101-007 was a randomized, parallel group, double-blind, placebo-controlled, multicenter study, in which 530 subjects were randomized in a 1:1 ratio (stratified by race) to Zecuity or to a placebo patch. The study was conducted in 38 centers in United States. At the randomization Visit, subjects were instructed how to apply the iontophoretic transdermal patch. Upon experiencing a qualifying migraine headache, subjects were to apply the patch for four hours and to record their responses to diary questions at 0.5, 1, 2, 3, 4, 6, 12, and 24 hours (or beyond, if their skin assessment results dictated) post-patch activation.

As described by Dr. Luan, the primary endpoint was the proportion of subjects who were headache pain free at two hours. The three key secondary endpoints were the proportion of subjects who were photophobia free, phonophobia free, and nausea free at two hours after patch activation. All efficacy analyses were based on logistic regression models. The primary analysis was conducted on the intent-to-treat population (ITT, defined as all subjects who applied the patch, activated it, and had at least one post baseline assessment for pain). The study also included a per-protocol population, defined as all ITT subjects who did not have any major protocol violations during the study. For the primary endpoint (proportion of subjects who were headache pain free at two hours), the model included treatment group as a main effect and randomization stratum (race) as a factor. In addition to these two factors, the model for analysis of secondary endpoints included the baseline value of the symptom as a covariate. For the headache pain severity score and the nausea, photophobia, and phonophobia scores at the two-hour post patch activation time point, missing values were imputed using a last observation carried forward (LOCF) method, and two sets of sensitivity analyses were carried out to assess the impact of the imputation methodology, one based on a baseline carried forward (BCF) method and one based on observed cases (OC) only.

Dr. Luan discusses that out of 530 randomized patients, 469 applied the study patch and were included in the safety analysis population. Of these, 454 patients were part of the ITT population, and 446 of the per-protocol population. The study population had a mean age of 41 years, was 85% female, and 81% white, which is typical for that indication. Of the 19% of non-white patients, 15% were black, 2% Asian, and 2% American Indian or pacific islander. About 75% of patients were prior users of sumatriptan (mostly the tablet). As discussed by Dr. Luan, the prevalence of photophobia and phonophobia at time of treatment was similar between the treatment groups, but there was a higher prevalence of nausea in the placebo group (52%) vs. the active group (43%).

Dr. Luan reports that there was a significantly greater proportion of subjects who were headache pain free at two hours post-treatment in the Zecuity treatment group than in the placebo treatment group (see Table 3: Key efficacy results in Study NP101-007). For the three key secondary endpoints (nausea-free, photophobia-free and phonophobia-free), Zecuity was significantly better than placebo.

Table 3: Key efficacy results in Study NP101-007

Endpoint at 2-hour	Zecuity	Placebo	p value
Pain-free	18%	9%	0.0092
Nausea-free	84%	63%	<0.0001
Photophobia-free	51%	36%	0.0002
Phonophobia-free	55%	39%	0.0028

The 2-hour pain-relief rates (defined as mild or no pain) were 53% for Zecuity and 29% for placebo. By historical comparison, the 2-hour pain-relief rate are on the low end of results seen in triptan clinical studies, in which 2-hour pain relief rates usually are above 60% (which was the case for other sumatriptan formulations, e.g., the tablet and the nasal spray). It must also be noted that the sustained pain-relief rate (defined as no or mild pain at all time points from 2 through 24 hours and no rescue medication used from baseline through 24 hours post-dose) was not significantly higher for Zecuity than for placebo (even though it was numerically higher, 34% vs. 21%).

An important subgroup analysis is that of the non-White population, as Clinical Pharmacology studies suggested a lower C_{max} in that group. The results indicate that in non-White subjects, Zecuity was no better than placebo for the primary endpoint: 12.5% vs. 11.4%, p=0.87 (according to the sponsor analysis). Even though that subgroup was relatively small (19% of the study population), the results question the efficacy of the product in non-White subjects, as two lines of evidence (PK and subgroup efficacy analysis) point in that direction. The sponsor should be required to address these findings.

8. Safety

Safety database

During the Zecuity development program, the division requested data on at least 300 subjects who treated, on average, at least 2 migraine attacks per month for six months, and 100 subjects who treated, on average, at least two migraine attacks per month for one year. The sponsor proposed providing data on 300 subjects who treated an average of [at least] 3 migraine attacks for six months and 50 subjects who treated an average of [at least] 3 migraine attacks for 12 months. The Agency found these proposed numbers acceptable.

The NDA, as of the 120-day safety update, included data on 338 patients who have completed 6 months of study (average: 2.3 attacks per month), and 163 patients who have completed one year of study (average: 2.47 attacks per month). As discussed by Dr. Todd, 165 patients treated >2 migraine attacks per month, on average, for 6 months, and 100 patients treated >2 migraine

attacks per month, on average, for 12 months. There were 74 patients who treated >3 attacks per month, on average, for 6 months, and 42 patients who treated >3 attacks per month, on average, for a year. The sponsor also reported that 280 patients used at least 12 patches during the study (regardless of the duration of treatment).

Table 4: Long term safety database (copied from table 3 of 120-day updated clinical safety summary)

Parameter	Original NDA ^a (N=662)	120-Day Update ^b (N=662)
Number (%) of subjects who used at least:		
6 patches	406 (61.3)	409 (61.8)
9 patches	311 (47.0)	329 (49.7)
12 patches	254 (38.4)	280 (42.3)
24 patches	91 (13.7)	137 (20.7)
36 patches	27 (4.1)	54 (8.2)

Overall, the safety database includes the number of patients agreed upon for patients exposed for one year, and treating at least 2 attacks per month (i.e., at least 100 patients). The database (n=42) was also close to the FDA agreement for the number of patients who treated at least 3 attacks per month (i.e, at least 50 patients). Regarding 6 months exposure, the 338 patients who completed that treatment duration treated an average of 2.3 attacks per month, but only 165 patients treated >2 attacks per month, on average. It must be emphasized that FDA requirement was based on an average number of attacks at the patient level, i.e., to be counted, a patient had to treat at least 2 attacks per month, on average. The sponsor appeared aware of that requirement, as a question asked by the sponsor at the pre-NDA meeting was as follows: *“NuPathe proposes submitting 300 patients who have treated with an average of three [Zecuity] patches per month for six months and 50 patients who have treated with an average of three [Zecuity] patches per month for 12 months”*. That requirement is also consistent with the approach taken for other migraine products NDAs. Following that approach, the 6-month safety database is insufficient, and data on about 135 additional patients treating an average of at least 2 attacks per month for 6 months should be required, in order to have sufficient power to adequately characterize the frequency of significant but relatively infrequent adverse events. No additional one-year exposure data is however needed, in my opinion.

Deaths and Serious Adverse Events

There were no death or serious adverse event attributed to Zecuity during the development program.

Adverse dropouts

Controlled efficacy study

A total of 2.1 % of patients on Zecuity discontinued the controlled efficacy study because of an adverse event (pain or skin reaction), and 1.3% because the patch failed. The proportions were similar for the placebo patch. For this product, interpretation of placebo group data is unusual in that patients in that group could experience possible adverse reactions related to the patch itself, so that the difference between the active and placebo group is only representative

of the effects of sumatriptan. This product is a drug/device combination, and the side effects related to the device component are expected in both treatment groups.

Long term open-label study

There was a very high rate of discontinuation in the long-term safety study (55%). As noted by Dr. Todd, the most common reason for discontinuation was “withdrawal of consent”, in 20% of patients across treatment groups. Unfortunately, the reason for the “withdrawal of consent” was not described, and it is well known that adverse events often lead patients to withdraw their consent. This deserves further investigation, by asking the sponsor to describe adverse events reported in patients who “withdrew consent”. Another 13% of patient withdrew for adverse events, mostly local reactions.

Adverse events

Controlled efficacy study

As described by Dr. Todd, 50% of patients on active drug, and 44% of patients in the placebo group experienced an adverse event. Again, the placebo-group had a patch applied to the skin, and had electrical current delivered, which likely explains the high event rate in that group.

The adverse events were largely related to the application site, with 26% of patients treated with Zecuity reporting an application site reaction (i.e. paresthesia, dryness, discoloration, bruising, warmth, or “reaction”), and 23% experiencing pain sufficiently severe to be reported as an adverse event. The incidence of application sites reactions was similar in the placebo group (27%), but the rate of application site pain adverse reactions was lower (15%).

Long term safety studies

By the time of the 120-day safety update, 48% (381/796) of subjects in the long term trials experienced at least one treatment-emergent adverse event, again mostly related to application sites conditions, most commonly pain and pruritus (see Table 5).

Table 5: Application site adverse events in long term safety studies (adapted from Labeling Summary 2, Appendix B of the 120-day safety update)

Application side adverse event	Frequency
Pain	22%
Pruritus	15%
“Reaction” (generic term)	6%
Paresthesia	5%
Hypersensitivity	4%
Dryness	4%

It is noteworthy that bruising and vesicles were reported in 2.4% of patients. Also, application site burns were reported in 5 patients (0.6%), including 3 cases (0.4%) reported as severe, and two cases (0.3%) as moderate. An application site scar was also reported in one patient as an adverse reaction. The incidence of these events may even be higher, as some reactions were coded under the generic terms “site reaction” (5.7%) and “adverse drug reaction” (1.1%). Severe burns at that frequency are not an acceptable side effect for an acute treatment of

migraine, in particular in a situation where there is no demonstrated benefit over other formulations of the same product.

Application site discoloration was reported in 4.3% of patients, but the sponsor provided insufficient information to assess the time course and reversibility of the discoloration. This deserves to be fully addressed, as permanent discoloration does not constitute an acceptable adverse reaction for this indication. Importantly, the summary of clinical safety cross-referenced (in section 2.1.5.1.4) the narratives of several cases of patients who experienced permanent skin lesions. For example, patient 117-1197 was noted to have a “a slightly raised keloid of 2x1 cm at the application site and some discoloration of the skin in that area” 4.5 months after application of the patch. Another patient (134-2221) was reported as having “skin discoloration at patch site” eighty days post-patch application. That patient had two consultations with a dermatologist and one with a plastic surgeon to discuss cosmetic repair for the discoloration. Patient 125-1275 was noted to have “minimal residual mark in area of previous noted blister”. The sponsor described these events in a section titled “Improper Application”. I disagree with the argument that these lesions can be attributed to “improper application” of the patch (i.e., suggesting the patient and not the product is the cause for the adverse event), as patients in clinical studies were instructed by the Investigational Site Personnel on how to apply the patch. In that setting, the potential for a use of the product different from what was intended appears to be more attributable to product design issues than to patient misuse. I believe that clinical trials conditions represent a “best case scenario”, and that the potential for skin lesions may be even greater under post-marketing conditions of use. Unless the sponsor provides evidence that cases of administration site adverse event (e.g., burn, scar, discoloration or abnormal pigmentation) ultimately resolved, I believe that the risk of significant skin lesion (in particular with permanent sequelae) is not justified by the benefits of the product.

Skin self-examination findings

Beside adverse events reporting, subjects were required to complete a skin self-examination evaluation upon removal of the patch, and again at 6, 12, and 24 hours post patch removal, using a 5-point assessment scale (0 = no redness; 1 = minimal skin redness; 2 = moderate skin redness with sharp borders; 3 = intense skin redness with or without swelling; and 4 = intense skin redness with blisters or broken skin). Subjects skin-examination were also evaluated by a medical monitor within 24 hours if subjects documented a score of 3 or 4, or developed worsening skin assessment score after a period of improvement. After completing the study, all subjects had their records reviewed for allergic contact dermatitis (ACD) by a medical safety review team. The cases identified by the safety review team as ACD as well as those reported in the database as ACD during the trial were assessed by a dermatology expert. The dermatology findings were also reviewed by Dr. Snezana Trajkovic, from the FDA dermatology division.

Controlled efficacy study

Dr. Trajkovic’s believes that Zecuity “has significant irritation potential and is sensitizing”. Dr. Trajkovic reviewed the skin self assessment data of the controlled efficacy study, and

observes that upon patch removal (4 hours post patch activation), 88% (199/226) of Zecuity-treated patients reported having an erythema score of ≥ 1 . By 24 hours, almost 70% of the Zecuity treatment group and 30% of the placebo group had erythema scores of ≥ 1 . The mean time to resolution of erythema for Zecuity treatment group was 10 days, vs. 6 days in the placebo group.

Long term safety study

Skin assessment findings were similar in the long term safety studies, with erythema score of ≥ 1 upon patch removal after 83% of applications, and ≥ 1 at 24 hours after 47% of applications. A summary of subject skin assessment by time point is presented in Table 6. As described by Dr. Todd, possible or probable allergic contact dermatitis (ACD) occurred in 7.9% of patients in the long term safety study. Intense redness was observed in 2.7% of patients 24 hours after treatment, with blisters or broken skin in 0.5% of patients. That number may be an underestimation, as the sponsor's dermatology expert only evaluated cases filtered by the sponsor's "safety team".

Table 6: Summary of Skin Assessment by Time Point after Patch Activation in the Long Term Safety Trials (copied from table 30 of Dr. Todd's review).

Skin Assessment Scores	Time Point Post Patch Application (N=662)			
	4 Hours	6 Hours	12 Hours	24 Hours
Number of patches scored	7378	7457	7340	7259
Distribution, n (%) ^a				
No redness	1284 (17.4)	1862 (25.0)	2601 (35.4)	3883 (53.5)
Minimal redness	2139 (29.0)	2169 (29.1)	2210 (30.1)	1521 (21.0)
Moderate redness	3510 (47.6)	3067 (41.1)	2269 (30.9)	1658 (22.8)
Intense redness with or without swelling	415 (5.6)	333 (4.5)	232 (3.2)	158 (2.2)
Intense redness with blisters or broken skin	30 (0.4)	26 (0.3)	28 (0.4)	39 (0.5)
Missing ^b	10	9	10	12
Mean (SD)	1.4 (0.85)	1.3 (0.90)	1.0 (0.91)	0.8 (0.92)
Median	2.0	1.0	1.0	0.0
Minimum, Maximum	0, 4	0, 4	0, 4	0, 4

^a The denominator is the total number of patches with a score at the respective time point.

^b Missing is not included in the denominator.

Resolution of erythema ranged from 0.2 days to 164 days (mean of 3 days).

Skin irritation study

The sponsor also conducted a specific skin irritation study (NP101-104). This was a randomized, placebo-controlled, repeat patch test study that compared the Zecuity patch to a placebo patch. Up to 30 subjects were to apply one Zecuity patch and one placebo patch each day to each upper arm. Once the patches were applied, they were activated for 4 hours. The patches automatically turned off after 4 hours, and were left in place for 23 hours. The

application (to the same exact anatomical site) and activation of the Zecuity and placebo patches was to be done daily for a maximum of 21 days. The 5-point skin irritation scale described above was used to assess patients. Patch adherence was also assessed, using a 0-4 scale (0= \geq 90% adhered; 4=patch detached). Among the first 10 patients cohort, one patient had patch adherence of \geq 75% to <90% for the placebo patch on Day 1, and two subjects had \geq 50% to <75% adherence for placebo patch on Day 1. The study reports did not describe adherence scores on subsequent days. This represents 10% of application sites (2/20) with adherence <75%.

All subjects in the first cohort of 10 patients were discontinued due to adverse events of application site irritation (skin irritation score = 4). By Day 5 (after four days of patch application), four subjects had a skin irritation assessment score of 4 (intense erythema with edema and blistering/erosions) for at least one skin assessment site. By Day 6, three additional subjects had a score of 4; and by Day 7, the three remaining subjects had a skin irritation score of 4 for at least one skin assessment site. Erythema was completely resolved for six subjects at Day 21, for three additional subjects at Day 28, and for one subject at Day 38. That study confirms the strong irritation and sensitization potential of Zecuity. Other adverse events for the subject's Zecuity-treated arm in the skin irritation study included application site discoloration (3 subjects), application site reaction (3 subjects), application site bruising (one subject), application site hyperesthesia (one subject), and application site pain (one subject).

Maximum safe frequency of administration

The sponsor proposed a labeling statement that (b) (4) and that (b) (4). There is insufficient information to support application of a second patch after 2 hours, or to support use of more than 2 patches a month. Given the irritation potential of the product, the sponsor should be required to present adequate and acceptable safety information for patients using the product under the conditions proposed to be described in labeling, e.g., using a second patch after 2 hours, or using up to the maximum recommended frequency of use.

The sponsor has provided ample evidence that this product has significant irritation potential and is sensitizing, so that it is important to know how soon the product can be reapplied at the same site. The sponsor provided no information about the minimal amount to time between two applications of the product at the same site necessary to avoid increased skin reactions. The sponsor proposed language in labeling stating that "Zecuity should not be applied to a previous application site until the site remains erythema free for 72 hours", but has provided no information to support that contention. As discussed above, the number of patients who used the product more than 3 times a month in the long term safety study was small, and the sensitization study provides evidence that application of a new patch within a day of application at the same site may lead to more severe skin reactions, as all patients had skin assessment scores of 0 after the first application of the patch, but 5 patients had a score of 2 after application one day later, and one patient had a score of 3 one day later. That study provided no information on the safety of reapplying a patch after 72 hours of resolution of

erythema. Safety data supporting use of the product 72 hours after resolution of erythema should be provided.

The sponsor voluntarily proposed REMS that includes a Medication Guide (b) (4). In addition to these proposed REMS elements, the sponsor submitted two proposed (b) (4). It does not appear that the proposed REMS would (b) (4).

On February 28, 2011, the Food and Drug Administration published a Federal Register notice concerning the availability of a draft FDA guidance entitled "Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)." In addition to discussing the FDA's policy on Medication Guide distribution, this draft guidance addresses the following two topics related to Medication Guides: the FDA's current thinking regarding when Medication Guides will be required as a component in a REMS program as well as procedures for sponsors to follow to request removal of a Medication Guide from a REMS. In light of this draft Guidance, the review team made an initial assessment that it was not necessary for the Medication Guide to be part of a REMS to ensure that the benefits of Zecuity outweigh its risks. The sponsor was informed during the review cycle of that assessment, and was also told that "the review team believes, however, that the Medication Guide is still necessary for patients' safe and effective use of Zecuity. The Medication Guide under review is being considered as part of labeling; if the NDA is approved, the Medication Guide would become a part of the approved labeling". This was communicated to the sponsor in a May 19, 2011 email. The initial assessment of the need for a REMS was made at a time when the safety review was still ongoing, and some of the significant safety findings (e.g., burns, long-term discoloration) had not yet been identified. I believe that the need for a REMS should be reconsidered once the additional safety information required from the sponsor in the Complete Response is reviewed. Other REMS elements may also be considered.

9. Advisory Committee Meeting

No advisory meeting was held for this application during the review cycle.

10. Pediatrics

The following pediatric plan (described in Appendix 3) was accepted by PeRC:

- Full waiver for patients age 0 months to (b) (4) years, because studies are impossible in that age group. Migraine in this age group differs in several important respects from migraine in older children and adults. Attacks are more likely to be of shorter duration, to involve more gastrointestinal symptoms and fewer headaches, and to be resolved

more frequently with sleep. Additionally, the number of patients with migraines in this age group is very small. These characteristics, combined with the difficulty or impossibility of communicating with children in this age group about their symptoms, would make the necessary studies impossible or highly impractical.

- Deferral for patients age 6 to 17 years, as adults studies are ready for approval. 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.

11. Other Relevant Regulatory Issues

DMEPA

DMEPA found the initial proposed proprietary name, Zelrix, to be unacceptable, because “Zelrix” is orthographically and phonetically similar to and shares similar product characteristics with the marketed products Salvax and Tobrex, and with the once marketed and now discontinued product, Lidex.

The sponsor proposed an alternate name, Zecuity, which was accepted by DMEPA.

Office of Scientific Investigations

Antoine El-Hage, Ph.D., conducted the OSI review of the pivotal efficacy study (NP101-007). Dr. El-Hage notes that DSI inspected the site of Dr. David Kudrow, from Santa Monica, CA. This site was targeted for inspection due to enrollment of a relatively large number of subjects (2nd largest), and because the percentage of headache pain free patients for treatment group in that site was larger than in other sites. The study appears to have been conducted adequately at the Kudrow’s site, and the data generated by this site were found acceptable to support the pending application.

Charles R. Bonapace, Pharm.D., and (b) (4), Pharm.D, from the Bioequivalence Branch of OSI, conducted audits of the clinical and analytical portions of the pivotal bioequivalence trial (NP101-013). The clinical portion of the study was conducted at Prism Research, LLC, St. Paul, MN. The analytical portion of the study was conducted at (b) (4). OSI recommends that the analytical data generated at (b) (4) be accepted for review. However, OSI cannot assure the identity of the test and reference drug products used to dose subjects in this study at Prism Research, because Prism Research failed to retain reserve samples for the test or the reference products.

505(b)(2) eligibility

For this 505(b)(2) application, the sponsor relied on previous findings of safety and effectiveness of Imitrex oral tablets (NDA 20,132) and Imitrex Subcutaneous Injection (NDA

20,080)¹, which was found acceptable by the Agency. The sponsor did not rely on the Imitrex Nasal Spray NDA.

DRISK

DRISK deferred their review to the next cycle, considering the unresolved issues with the product.

12. Labeling

Because of the multiple deficiencies with this product, the labeling review is deferred until the next review cycle.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend a complete response action. There are multiple major deficiencies that must be resolved before approval can be considered. These most important issues are listed below:

CMC and Device (CDRH)

- Lack of uniformity in the distribution of drug formulation on the non-woven pad
- Lack of drug formulation containment and risk of unintentional exposure
- Lack of proper disposal procedures during and post use
- Usability of the product is in question
- Device hazard analysis

Microbiology

- Inadequate proof of antimicrobial effectiveness or microbial control of the finished product

Non Clinical

- Inadequate chronic dermal toxicity study
- Lack of a dermal carcinogenicity study in one species or sufficient justification for why such a study would not be feasible or informative.

¹ This was confirmed in an August 16, 2011 email. There was initially some confusion about which specific listed drug was relied upon, as on the application's 356h, the drug(s) relied upon is identified by name/sponsor (Imitrex (sumatriptan succinate)/GSK) and not by any application number(s). The applicant's cover letter mentions the following sumatriptan approved NDAs, but does not specifically cite reliance on any of them: NDA 20-132 (oral tablets), NDA 20-080 (sq injection), NDA 20-626 (nasal spray), and NDA 22-239 (needleless sq injection). The August 16, 2011 email clarified that issue.

Biopharmaceutics

- Lack of a discriminating in vitro method with the ability to evaluate drug permeation as a quality control tool to detect lot to lot variability (reject bad performance product).

Clinical Pharmacology

- Inadequate clinical pharmacology study comparing the bioavailability of the product intended for commercial use with the product used in the pivotal efficacy study, because the identity of the test and of the reference drug products used to dose subjects in this study can not be verified.

Clinical

- Serious concerns about the potential for the product to cause severe burns, and permanent skin lesions (e.g., discoloration)
- Inadequate information about the time course and resolution of application site discoloration
- Serious concerns about the irritation and sensitization potential of the product
- Inadequate analysis/description of skin adverse reactions (e.g., described as aspecific “site reactions” or “adverse drug reactions”) and insufficient information on the final outcome of skin adverse reactions (e.g. skin discoloration, burns)
- Insufficient information about the minimal time between 2 applications of the patch at the same site, and maximum frequency of use of the product
- Insufficient information on reasons for treatment discontinuations in the long term safety studies
- Insufficient number of patients exposed for 6 months, and treating an average of at least 2 migraine attacks per month
- Inadequate information to support efficacy of the product in non-White patients

Risk Benefit Assessment

I have serious concerns about the safety of the product, as serious skin toxicity (e.g. burns, skin discoloration, scar) has been observed in clinical studies, despite the fact that patients who participated to these studies were instructed on how to use the product. There appears to be fundamental flaws in the design of the product, which may be responsible for some of the adverse reactions observed in clinical trials. There are also a number of unanswered questions (see above) about the safety of the product.

The efficacy of the product has been established in white patients, but efficacy in non-white patients is in question, as sumatriptan exposure was lower in that subgroup, and there was essentially no drug/control difference in the 2-hour pain-free rate.

This product does not provide any clear benefit over existing formulations of sumatriptan. By historical comparison, pain relief does not appear better with this product than with the approved oral, subcutaneous, or intranasal formulation. A possible argument to justify a consideration of this product for approval is that transdermal administration is not influenced by the gastric stasis that may occur during migraine, and that in that sense the product

addresses an unmet medical need. I do not believe that this argument would be valid, for several reasons. First, 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. Second, patients with prominent nausea already have several non-oral alternatives: a nasal spray, and a subcutaneous formulation to self-administer with an autoinjector, or with a needleless device. This product may theoretically be justified for patients who have prominent nausea or vomiting, and can not tolerate a nasal spray, or one of the subcutaneous formulations. Arguably, that subgroup of patients represents a very small fraction of the migraine population. Given the cutaneous toxicity observed in clinical trials, it is also unclear that tolerability would be better than with an other non-oral formulation. Finally, it is not established that a tablet would not be effective in these patients (with the caveat that ingesting a tablet may be uncomfortable in patients with prominent nausea), and the availability of orally disintegrating tablet formulations for other triptans further shed doubts that a significant unmet medical need does exist. In this situation, I do not foresee that a demonstration of this product addressing an unmet medical need is a viable route to overcome the safety concerns.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

The sponsor proposed a REMS consisting of a Medication Guide (b) (4). I preliminarily agreed with the team that it was not necessary for the Medication Guide to be part of a REMS to ensure that the benefits of Zecuity (sumatriptan iontophoretic transdermal system) outweigh its risks. However, I will reevaluate the need for a REMS in the next review cycle. Elements other than a Medication Guide may also be considered at that time. However, it does not appear that the REMS proposed by the sponsor (b) (4).

Recommendation for other Postmarketing Requirements and Commitments

Postmarketing commitments and requirements will be considered in the next cycle.

Appendix 1: CMC discipline letter of May 16, 2011

APPEARS THIS WAY ON ORIGINAL



NDA 202278

INFORMATION REQUEST

NuPathe Inc.
Attention: Michele A. Roy, RN, MS
Director of Regulatory Affairs
227 Washington Street, Suite 200
Conshohocken, PA 19428

Dear Ms. Roy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zelrix (sumatriptan) iontophoretic transdermal system.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide the following information or a reference to its location in the application:

Chemistry, Manufacturing and Controls

The fundamental design of NP101 is not acceptable. Specifications cannot be established per 21.CFR.314.50 to adequately assure identity, strength, quality, purity, potency and bioavailability of the product. A lack of uniformity of drug formulation distribution, and issues with drug formulation containment, safe disposal procedures, and patient usability raise concerns about the safety and efficacy of the product:

1. Lack of uniformity in the distribution of drug formulation on the non-woven pad

It is visually apparent that the amount of drug on the drug containing pad is not evenly distributed. Furthermore, variable amounts of drug remain on the reservoir side after pad transfer. This lack of uniformity may result in variable amounts of drug transferred from the packaging to the patient, which has potential safety and efficacy implications.

2. Lack of drug formulation containment and risk of unintentional exposure

The drug formulation is not contained once the aluminum foil top is removed from the reservoir. The lack of proper containment increases the safety risk of unintentional exposure to patient, health care provider and general public during assembly, application and wear of the system.

3. Lack of proper disposal procedures during and post use

Drug formulation remaining on the foil packaging material after the system is assembled and the large amount of drug remaining in the system after use pose a safety and potential environmental risk due to exposure to the drug if the packaging and used system are not disposed properly.

4. Patient usability questionable

Inadvertent exposure to the formulated drug substance and improper pad placement for the assembled system pose safety risks. Assembly of the system is complicated and multiple attempts to apply the two pads to the transfer rings increase the opportunity for drug formulation exposure.

Given the complexity of the proposed product a comprehensive quality risk management is highly recommended. Refer to the Guidance for Industry: Q9 Quality Risk Management for further information.

In addition to the comments above, ONDQA has identified the following issues that should be addressed for all proposed systems (Additional issues may be identified in the future upon further review):

General Comments

1. Provide adequate information or submit an appropriate letter of authorization allowing reference to a Drug Master File (DMF) for the following:
 - Non-woven pad
 - Transdermal backing (overtape) of the electrode card
 - Release liner of the electrode patch
 - Transfer ring
 - (b) (4) foam laminate
 - Protective blue slip sheet
2. Clarify if the protective slip sheet is an anti-static treated liner.
3. Include information justifying the size of the patch in section 3.2.P.2 Pharmaceutical Development.
4. Accurately describe the intended dose for NP101. It appears that the system is intended to deliver 6.5 mg of sumatriptan base and the strength is described as 6.5 mg of sumatriptan; however, some descriptions in the NDA state that “approximately (b) (4) mg of sumatriptan is delivered.”
5. Identify the non-woven pad as part of the drug product and not part of the container closure system.

Residual Drug

In reference to the information you provided in response to the 74-Day letter regarding residual drug, we have the following comments:

6. The use of the term (b) (4) should be justified by statistical methods.
7. Provide the volume of the drug formulation and the surface area tested used in the in vitro development studies.

8. Minimize the drug formulation remaining in the reservoir after the system is used and the pads are removed.

Manufacturing Process

9. Assure that (b) (4) and alter the manufacturing flow chart to reflect this.
10. Provide justification for the (b) (4) hold time of the drug formulation.
11. Establish an IPC for (b) (4) per USP <905> of the bulk drug and salt formulations prior to (b) (4).

E-Patch

12. Provide source, brand, amount added, and impurities of the (b) (4) added to the adhesive.
13. Provide a description of the manufacturing process and in process-controls for the electrode card. Include details of the adhesive application process, and overtape, transfer ring, and (b) (4) foam (b) (4) procedures.
14. Establish acceptance limits in the adhesive laminate prior to use in the manufacturing of the E-Patch for the following adhesive impurities, (b) (4).
15. Determine extractables and leachables of the overtape and (b) (4) foam.
16. Establish an intermediate release specification for the adhesive materials in the electrode card manufacturing which includes a test for adhesion, peel from release liner, shear and tack.

Specification

17. Assure that the sample size for each specification test is of statistical significance.
18. Establish a test method and acceptance criterion for crystals and visible particles for the sumatriptan containing and salt containing pads.
19. (b) (4) is not an adequate identification test. Establish an appropriate Identification Test, including a congruent identification test that provides fingerprints for the drug and salt pads.
20. Establish a specification and include acceptance criteria for salt content for the salt pad.
21. Establish a specification and include acceptance criteria for appearance of the electrode card.
 - Include an observation for (b) (4) of the adhesives.
 - Include appearance of each electrode and lack of surface flaws, such as scratches.
22. Include in specification for Orientation of Components an observation for the presence of the slip-sheet.
23. Establish a specification and acceptance criteria for impurities in the salt pad. Alternatively, provide justification for not testing for impurities in the salt pad.
24. Clarify whether (b) (4) is performed on the bulk formulations or the individual patches. USP <905> does not specifically address transdermal systems; therefore, a description of the proposed procedure.

Analytical Methods

25. Modify the sample preparation method for Assay, Uniformity of Dosage Units, Related Substances, and Methylparaben Content, to include only drug formulation of the non-woven pad representing the amount of drug that is physically transferred to the patient. Do not include the drug remaining on the foil top or other portions of the system.

Stability

26. Confirm that all stability data provided utilizes the proposed commercial upper foil (b) (4) of the container closure.
27. Establish a test and acceptance criteria for in vitro release on stability.
28. Perform crystal growth studies.
29. Provide stability data or justification for lack of photostability and freeze-thaw studies.
30. Assess the influence of package orientation on stability as it relates to packaging and storage orientation (laying flat, inverted, on edge, etc).
31. Assess the influence of stacking the individual drug product pouches within a single commercial carton and multiple cartons on each other.
32. Provide acceptance criteria for adhesion, tack, shear, and liner release. Acceptance criteria should be data driven. Adhesion and liner release should have both upper and lower limits.
33. Provide information regarding the investigation in the (b) (4)
34. For lot 7063718 clarify or discuss the following statements in section 3.2.P.8.1.7:
 - “The manufacturing date of the sumatriptan (b) (4) was (b) (4) and the reservoir cards were put on stability (b) (4).” This would indicate that the hold time for the sumatriptan formulation is (b) (4).
 - Explain what is meant by “(b) (4).”

Container Closure

35. Assess extractables and leachables for all packaging components.

Labeling of the Drug Product

36. Provide labeling of the transdermal system.
 - Labeling should include the drug product name, total amount of drug, and expected transdermal flux on the backing membrane of the E-Patch.
 - Inks chosen for printing should not interact with any patch components and assessed for potential leachables and extractables.
37. Provide better identification of the components of the drug product.
 - The drug pad and the salt pad should be clearly labeled and the corresponding electrodes labeled to match. This assures that if the E-Patch or the Reservoir Card detach from the (b) (4) prior to assembly, the proper pads will be matched to the proper electrodes.

Regarding use-related and medication error risks

We recommend that you conduct a comprehensive risk analysis identifying the use-related and medication error risks with the iontophoretic transdermal system. The purpose of a human factors study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users.

We ask that you explicitly demonstrate that all of the use-related risks for this combination product have been successfully mitigated. We expect that the human factors testing that you perform will be aligned with the Human Factors / Usability Testing recommendations, as explained in our Guidance, *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*.

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

Sincerely,

{See appended electronic signature page}

Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

TERRANCE W OCHELTREE
05/16/2011

NDA 202,278 Cross Discipline Team Leader Review

Appendix 2: CMC discipline review letter of July 15, 2011



NDA 202278

**DISCIPLINE REVIEW LETTER
CHEMISTRY, MANUFACTURING, AND CONTROLS**

NuPathe Inc.
Attention: Michele A. Roy, RN, MS
Director of Regulatory Affairs
227 Washington Street, Suite 200
Conshohocken, PA 19428

Dear Ms. Roy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zelrix (sumatriptan) iontophoretic transdermal system.

We acknowledge your June 10, 2011 response to our May 16, 2011 Information Request Letter. FDA remains unconvinced that the lack of formulation containment, the drug formulation (b) (4) and large quantity of residual drug after use do not pose a safety risk to the patient, health care provider, children, or pets. Below is the CMC Response to the document received June 10, 2011 for each of the Information Request Letter's 4 Overall Comments and 37 General Comments.

OVERALL COMMENTS

FDA Overall Comment #1

1. Lack of uniformity in the distribution of drug formulation on the non-woven pad

FDA Response: The release and stability presented do not adequately justify the apparent lack of uniformity as it does not account for the lack of drug containment, effect of storage orientation (intended and unintended) and effect of age of the reservoir cards.

FDA Overall Comment #2

2. Lack of drug formulation containment and risk of unintentional exposure

FDA Response: The lack of drug containment is not adequately justified. The passive delivery of sumatriptan succinate through abraded, irritated, sensitized, or other skin abnormality is not adequately addressed. The risk of unintentional exposure to patient, health care provider and general public during assembly, application and wear remain with the use of an uncontained system. Additionally, the potential of drug and salt formulation migration due to lack of containment during assembly, application and wear could result in adhesive failure or reduced delivery.

FDA Overall Comment #3

3. Lack of proper disposal procedures during and post use

FDA Response: Bitter taste does not necessarily deter children or pets from ingesting. As such, bitter taste, is not significant justification for disposal issues associated with the large quantity of formulation remaining after use. Additionally, toxicities in pets, children, and sensitized individuals are currently unknown.

Although NP101 qualifies for a categorical exclusion, Lithium-manganese dioxide battery disposal at individual locations may have specific regulations (i.e. state and county regulations), therefore a statement similar to "Dispose of in accordance with state and local regulations" should be added to labeling to direct the consumer towards proper local disposal requirements.

FDA Overall Comment #4

4. Patient usability questionable

FDA Response: Refer to FDA Response to Overall Comment #2 regarding passive delivery concerns. Acceptability of the new data from the usability study of IND 74,877 is a review issue. Additional information submitted to the NDA after June 10, 2011 may or may not be reviewed in this review cycle depending on available resources.

GENERAL COMMENTS

FDA General Comment #1

1. Provide adequate information or submit an appropriate letter of authorization allowing reference to a Drug Master File (DMF) for the following:

- **Non-woven pad**
- **Transdermal backing (overtape) of the electrode card**
- **Release liner of the electrode patch**
- **Transfer ring**
- **(b) (4) foam laminate**
- **Protective blue slip sheet**

FDA Response: FDA acknowledges the information provided; however, table information, additional DMFs and component information may or may not be reviewed in this review cycle depending on available resources.

FDA General Comment #2

2. Clarify if the protective slip sheet is an anti-static treated liner.

FDA Response: FDA acknowledges the information provided; however anti-static and ESD properties may or may not be reviewed by the CDRH reviewer during this review cycle.

FDA General Comment #3

3. Include information justifying the size of the patch in section 3.2.P.2 Pharmaceutical Development.

FDA Response: The response is adequate. The justification of size is adequate for this design.

FDA General Comment #4

4. Accurately describe the intended dose for NP101. It appears that the system is intended to deliver 6.5 mg of sumatriptan base and the strength is described as 6.5 mg of sumatriptan; however, some descriptions in the NDA state that “approximately (b) (4) mg of sumatriptan is delivered.”

FDA Response: The response is adequate.

FDA General Comment #5

5. Identify the non-woven pad as part of the drug product and not part of the container closure system.

FDA Response: The response is adequate.

FDA General Comment #6

6. The use of the term “(b) (4)” should be justified by statistical methods.

FDA Response: It is understood that the in vitro study described did not provide nor was designed to provide a statistically significant analysis. However, the Agency remains unconvinced that the NP101 and its subsequent drug formulation have been optimized for sound product quality and safety. Refer to FDA Overall Comments above for more information.

FDA General Comment #7

7. Provide the volume of the drug formulation and the surface area tested used in the in vitro development studies.

FDA Response: The response is adequate.

FDA General Comment #8

8. Minimize the drug formulation remaining in the reservoir after the system is used and the pads are removed.

FDA Response: The methodology presented is adequate and the need for (b) (4) g of gel formulation in the drug reservoir is understood to reduce erythema and maintain skin contact when associated with the current design of the NP101. However, the fundamental design of the system, the (b) (4) and the lack of formulation containment remain a review issue.

Manufacturing Process

FDA General Comment #9

9. Assure that (b) (4) and alter the manufacturing flow chart to reflect this.

FDA Response: The response is adequate.

FDA General Comment #10

10. Provide justification for the (b) (4) hold time of the drug formulation.

FDA Response: FDA acknowledges the information provided; however provide analytical data to support the hold period. Acceptability of a hold time remains a review issue until process validation is complete.

FDA General Comment #11

11. Establish an IPC for (b) (4) per USP <905> of the bulk drug and salt formulations prior to (b) (4).

FDA Response: The response is adequate. The addition of (b) (4) and the test for (b) (4) testing on the final product is adequate.

E-Patch

FDA General Comment #12

12. Provide source, brand, amount added, and (b) (4) added to the adhesive.

FDA Response: The response is adequate.

FDA General Comment #13

13. Provide a description of the manufacturing process and in process-controls for the electrode card. Include details of the adhesive application process, and overtape, transfer ring, and (b) (4) foam (b) (4) procedures.

FDA Response: The response is adequate.

FDA General Comment #14

14. Establish acceptance limits in the adhesive (b) (4) prior to use in the manufacturing of the E-Patch for the following adhesive impurities, (b) (4)

FDA Response: FDA acknowledges the information provided; however, assessment of the levels of (b) (4) provided in Tables 6 and 7 will be done in conjunction with the assessment of (b) (4).

Additional information submitted to the NDA after June 10, 2011 may or may not be reviewed in this review cycle depending on available resources.

FDA General Comment #15

15. Determine extractables and leachables of the overtape and (b) (4) foam.

FDA Response: FDA acknowledges the commitment; however, additional information submitted to the NDA after June 10, 2011 may or may not be reviewed in this review cycle depending on available resources.

FDA General Comment #16

16. Establish an intermediate release specification for the adhesive materials in the electrode card manufacturing which includes a test for adhesion, peel from release liner, shear and tack.

FDA Response: FDA acknowledges the commitment to establish intermediate specifications for adhesion, peel, shear and tack; however, additional information submitted to the NDA after June 10, 2011 may or may not be reviewed in this review cycle depending on available resources.

Specification

FDA General Comment #17

17. Assure that the sample size for each specification test is of statistical significance.

FDA Response: The response is not adequate. The sample size for all specification testing must reflect statistical significance.

FDA General Comment #18

18. Establish a test method and acceptance criterion for crystals and visible particles for the sumatriptan containing and salt containing pads.

FDA Response: The response is adequate.

FDA General Comment #19

19. (b) (4) is not an adequate identification test. Establish an appropriate Identification Test, including a congruent identification test that provides fingerprints for the drug and salt pads.

FDA Response: The response is not adequate. (b) (4) is not an adequate secondary test for identification. Provide a secondary identification test (in addition to HPLC) that provides fingerprints for the drug and salt pads. Refer to ICH Q6a for more information.

FDA General Comment #20

20. Establish a specification and include acceptance criteria for salt content for the salt pad.

FDA Response: The response is adequate.

FDA General Comment #21

21. Establish a specification and include acceptance criteria for appearance of the electrode card.

- **Include an observation for (b) (4) of the adhesives.**
- **Include appearance of each electrode and lack of surface flaws, such as scratches.**

FDA Response: FDA acknowledges the commitment to establish a test for (b) (4); however, acceptability of the acceptance criteria remains a review issue. Additional information to be submitted in July 2011 may or may not be reviewed in this review cycle depending on available resources.

FDA General Comment #22

22. Include in specification for Orientation of Components an observation for the presence of the slip-sheet.

FDA Response: The response is adequate.

FDA General Comment #23

23. Establish a specification and acceptance criteria for impurities in the salt pad. Alternatively, provide justification for not testing for impurities in the salt pad.

FDA Response: The justification is adequate. No specifications for impurities in the salt pad are required.

FDA General Comment #24

24. Clarify whether (b) (4) is performed on the bulk formulations or the individual patches. USP <905> does not specifically address transdermal systems; therefore, provide a description of the proposed procedure.

FDA Response: The response is adequate with regard to the use of USP <905> dosage form "others" method; however, refer to the FDA response to General Comment #25 for a discussion regarding assay test method 04-456-03-0-00621-cv.

Analytical Methods

FDA General Comment #25

25. Modify the sample preparation method for Assay, Uniformity of Dosage Units, Related Substances, and Methylparaben Content, to include only drug formulation of the non-woven pad representing the amount of drug that is physically transferred to the patient. Do not include the drug remaining on the foil top or other portions of the system.

FDA Response: The response is not adequate. Although FDA recognizes the amount of residual drug in the packaging appears consistent, FDA still requires that your sample preparation method include only the amount transferred to the patient. Because the drug product is a viscous gel formulation, the analytical results should reflect the sampling of a gel solution; this can be compared to a viscous gel in a tube. Sampling would be required from top, middle and bottom of the tube. By sampling the entire reservoir, you are sampling the entire tube and not showing that all portions of the tube are, and remain of consistent drug concentration. FDA is concerned that throughout shipping and shelf life there maybe drug substance migration and by sampling the entire reservoir this migration would not be detected. Additionally, as described, your current design results in (b) (4), therefore an identification of this overage and a rationale for its use must be provided per ICH Q8. Refer to FDA Overall Comments above for more information.

Stability

FDA General Comment #26

26. Confirm that all stability data provided utilizes the proposed commercial upper foil (b) (4) of the container closure.

FDA Response: The response is adequate.

FDA General Comment #27

27. Establish a test and acceptance criteria for in vitro release on stability.

FDA Response: The response provided is not adequate. General Comment #27 is a request is to include in vitro release testing as part of the stability protocol. Establish a test and acceptance criteria for in vitro release on stability.

FDA General Comment #28

28. Perform crystal growth studies.

FDA Response: FDA acknowledges the commitment to conduct crystal studies; however, additional information submitted to the NDA after June 10, 2011 may or may not be reviewed in this review cycle depending on available resources.

FDA General Comment #29

29. Provide stability data or justification for lack of photostability and freeze-thaw studies.

FDA Response: The response is adequate.

FDA General Comment #30

30. Assess the influence of package orientation on stability as it relates to packaging and storage orientation (laying flat, inverted, on edge, etc).

FDA Response: FDA acknowledges the commitment; however, additional information submitted to the NDA after June 10, 2011 may or may not be reviewed in this review cycle depending on available resources.

FDA General Comment #31

31. Assess the influence of stacking the individual drug product pouches within a single commercial carton and multiple cartons on each other.

FDA Response: The provided shipping study is not adequate, pouch-tightness should be added to the post-test inspection as visual inspection for product leakage can not ensure that the (b) (4) seal remained in tact.

FDA General Comment #32

32. Provide acceptance criteria for adhesion, tack, shear, and liner release. Acceptance criteria should be data driven. Adhesion and liner release should have both upper and lower limits.

FDA Response: FDA acknowledges the information provided; however, additional information submitted to the NDA after June 10, 2011 may or may not be reviewed in this review cycle depending on available resources.

FDA General Comment #33

33. Provide information regarding the investigation in the (b) (4)

FDA Response: The requested information provided regarding the investigation is adequate, however this is not a determination by FDA on whether a corrective action is not required nor if the (b) (4) is acceptable. The acceptability of (b) (4) and any OOS results remain a subject of review and are deferred to the Microbiological Reviewer's final assessment.

Additionally, it was noted that the corrective action currently being considered is to increase the (b) (4) as permitted in USP (b) (4). Neither the manufacturing facility nor NuPathe have taken into account the need to also determine the lowest level at which the (b) (4) is effective as stated in USP (b) (4). To date no testing has been conducted to determine the lowest level at which (b) (4) is effective in the salt (b) (4) or drug containing (b) (4). Include as part of the justification to (b) (4) content a test demonstrating the lowest level at which (b) (4) is effective.

FDA General Comment #34

34. For lot 7063718 clarify or discuss the following statements in section 3.2.P.8.1.7:

- **“The manufacturing date of the sumatriptan (b) (4) was (b) (4) and the reservoir cards were put on stability (b) (4). This would indicate that the hold time for the sumatriptan formulation is (b) (4).”**

- **Explain what is meant by** [REDACTED] (b) (4)
[REDACTED] ”

FDA Response: The response is adequate.

Container Closure

FDA General Comment #35

35. Assess extractables and leachables for all packaging components.

FDA Response: FDA acknowledges the information provided; however, additional information submitted to the NDA after June 10, 2011 may or may not be reviewed in this review cycle depending on available resources.

Labeling of the Drug Product

FDA General Comment #36

36. Provide labeling of the transdermal system.

- **Labeling should include the drug product name, total amount of drug, and expected transdermal flux on the backing membrane of the E-Patch.**
- **Inks chosen for printing should not interact with any patch components and assessed for potential leachables and extractables.**

FDA Response: FDA acknowledges the information provided; however, additional information submitted to the NDA after June 10, 2011 may or may not be reviewed in this review cycle depending on available resources.

FDA General Comment #37

37. Provide better identification of the components of the drug product.

- **The drug pad and the salt pad should be clearly labeled and the corresponding electrodes labeled to match. This assures that if the E-Patch or the Reservoir Card detach from the [REDACTED] (b) (4) prior to assembly, the proper pads will be matched to the proper electrodes.**

FDA Response: FDA acknowledges the information provided; however submit samples of the drug product with the use of the new identification to the attention of the CMC reviewer.

REGARDING USE-RELATED AND MEDICATION ERROR RISKS

We recommend that you conduct a comprehensive risk analysis identifying the use-related and medication error risks with the iontophoretic transdermal system. The purpose of a human factors study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. We ask that you explicitly demonstrate that all of the use-related risks for this combination product have been successfully mitigated. We expect that the human factors testing that you perform will be aligned with the Human Factors / Usability Testing recommendations, as explained in our Guidance, *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*.

FDA Response: FDA acknowledges the response; acceptability of the new data is a review issue. Information submitted to the NDA after June 10, 2011 may or may not be reviewed in this review cycle depending on available resources.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Terrance Ocheltree, Ph.D.
Director
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

TERRANCE W OCHELTRIE
07/15/2011

Appendix 3: Pediatric Development Plan

Types of Studies/Study Design:

Nonclinical Studies:

Study 1: Adolescent Pharmacokinetic Study

Open label, single dose pharmacokinetic study of Zecuity sumatriptan iontophoretic transdermal patch in adolescents 12 to 17 years of age with a history of acute migraines, which compares the results with appropriate adult historical control data.

Clinical Studies:

Study 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 patch compared to a single placebo iontophoretic transdermal patch in adolescents 12 to 17 years of age with a history of acute migraines. The protocol must allow the use of appropriate rescue medication after suitable post-dosing interval.

[Redacted] (b) (4)

Number of patients to be studied or power of study to be achieved:

Study 1 (PK study): A sufficient number of adolescent migraine patients to adequately characterize the single dose pharmacokinetics of adolescents compared to adults. The ages should be uniformly distributed across the age range. There must be a reasonable distribution of both sexes in this age bracket. [Redacted] (b) (4)

Study 2 (efficacy and safety study): A sufficient number of adolescent migraine patients to be able to detect a clinically significant difference between treatment and control on a valid measure of efficacy. There must be similar number of patients in the 12 to 14 and 15 to 17 age groups. The study must be powered to detect an effect size similar to that seen in the adult population.

Study 3 (long-term safety study): 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, approximately 1 or more headaches 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 and 15 to 17 age groups.

Entry criteria:

Study 1 (PK study): Adolescent patients between 12 and 17 years of age, with a diagnosis of migraine

with or without aura, as defined by the International Headache Society (IHS) current classification. IHS defined migraine headaches per month.

Study 2 (efficacy and safety study): Adolescent patients between 12 and 17 years of age, with a diagnosis of migraine with or without aura, as defined by the IHS current classification.

Study 3 (long-term safety study): Adolescent patients between 12 and 17 years of age, with a diagnosis of migraine with or without aura, as defined by the IHS current classification.

Clinical endpoints:

Study 1 (PK study): Plasma concentrations of sumatriptan in adolescents 12-17 years of age when delivered by the transdermal route should be determined. Pharmacokinetic parameters including AUC_{0-last} , $AUC_{0-\infty}$, C_{MAX} , T_{MAX} , and $t_{1/2}$. must be calculated and covariates such as age, body weight, body surface area, gender, and concomitant medications must be studied as appropriate. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available under <http://www.fda.gov/cder/guidance/1970dft.pdf>.

Study 2 (efficacy and safety study): The primary endpoint must be a reasonable measure of acute migraine relief in this population, and must be submitted as part of a special protocol for Agency review and concurrence prior to initiating the study. Additional standard secondary migraine efficacy measures and standard measures of safety (clinical- including signs and symptoms, and laboratory) must be included.

Study 3 (long-term safety study): Appropriately frequent standard measures of safety (clinical including signs and symptoms, and laboratory).

Timing of assessments:

Study 1 (PK study): Blood samples must be obtained at prescribed times for PK analysis including baseline blood draw (at least 12 hours prior to patch activation) and must include time points during treatment with the patch and several hours afterwards.

Study 2 (efficacy and safety study):

Efficacy assessments will be performed at baseline, during and after patch activation. Safety assessments will be performed at screening through 30 days post patch activation. Additionally, for subjects with skin irritation lasting more than 30 days post patch activation, investigators must follow these subjects until resolution of skin irritation.

Study 3 (long-term safety study):

Skin irritation evaluation by the subject will be conducted during and after patch activation. Investigator skin evaluation, vital signs and ECG monitoring must be conducted on scheduled visits.

Statistical information (statistical analyses of the data to be performed):

Study 1 (PK study): Descriptive analysis of the pharmacokinetic parameters and comparison to historic data from adults.

Study 2 (efficacy and safety study): Summary tables will be prepared for study populations, baseline characteristics, primary and secondary efficacy endpoints, and safety endpoints for each treatment groups at each time point. Treatment effects on the primary and secondary efficacy endpoints will be assessed using logistic regression models. Analysis summary tables will provide the number and proportion of responders, adjusted odds ratio and the corresponding 95% confidence intervals, and the nominal p value for the comparison between the Zecuity and placebo groups.

Study 3 (long-term safety study): Statistical analyses will be descriptive with summary statistics.

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/s/

ERIC P BASTINGS
08/26/2011