CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202278Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-278

COMPLETE RESPONSE

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) dated October 29, 2010, received October 29, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zecuity (sumatriptan) iontophoretic transdermal system.

We acknowledge receipt of your amendments dated the following:

October 29, 2010	February 24, 2011	March 18, 2011	May 16, 2011
November 23, 2010	February 25, 2011	March 31, 2011	June 1, 2011
December 17, 2010	March 9, 2011	April 11, 2011	June 10, 2011
February 3, 2011	March 17, 2011	May 3, 2011	

We also acknowledge receipt of your 2011 amendments dated June 15, June 21, June 30, July 1, July 15, July 22, August 3 (2) and August 17, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The list below is inclusive of requests communicated that remain outstanding from the Discipline Review letter dated July 15, 2011 and additional CMC, biopharmaceutics, and CDRH issues identified that were not included in the July 15, 2011 letter.

Outstanding Issues of the July 15, 2011 Discipline Review Letter

Refer to the July 15, 2011 Discipline Review Letter for additional information on each deficiency. The comment number in the document has been provided in parenthesis for reference.

1. (FDA Overall Comment #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. (FDA Overall Comment #2)
Lack of drug formulation containment and risk of unintentional exposure
The drug formulation is not contained once the (b) (4) 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. (FDA Overall Comment #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 of properly.

4. (FDA Overall Comment #4)
Patient usability
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.

5. (FDA General Comment #1)
Table information, additional DMFs and component information will be reviewed in the next review cycle.

6. (FDA General Comment #2)
Clarify if the protective slip sheet is an anti-static treated liner.

7. (FDA General Comment #8)
Minimize the drug formulation remaining in the reservoir after the system is used and the pads are removed.

8. (FDA General Comment #10)
Provide justification for the (b) (4) hold time of the drug formulation.

9. (FDA General Comment #14)

Establish acceptance limits in the adhesive [redacted] prior to use in the manufacturing of the E-Patch for the following adhesive impurities: [redacted].

10. (FDA General Comment #15)
Determine extractables and leachables of the overtape and [redacted] foam.

11. (FDA General Comment #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.

12. (FDA General Comment #17)
Assure that the sample size for each specification test is of statistical significance.

19. (FDA General Comment #19)
[redacted] 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. (FDA General Comment #21)
Establish a specification and include acceptance criteria for appearance of the electrode card.
- Include an observation for [redacted] of the adhesives.
- Include appearance of each electrode and lack of surface flaws, such as scratches.

21. (FDA General Comment #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.

22. (FDA General Comment #27)
Establish a test and acceptance criteria for in vitro release on stability.

23. (FDA General Comment #28)
Perform crystal growth studies.

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

25. (FDA General Comment #31)
Assess the influence of stacking the individual drug product pouches within a single commercial carton and multiple cartons on each other.

26. (FDA General Comment #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.

27. (FDA General Comment #33)
Provide information regarding the investigation in the [redacted] (b) (4)

28. (FDA General Comment #35)
Assess extractables and leachables for all packaging components.

29. (FDA General Comment #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 should be assessed for potential leachables and extractables.

30. (FDA General Comment #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.

31. (REGARDING USE-RELATED AND MEDICATION ERROR RISKS)
You should 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*.

Additional CMC Deficiencies

32. With regard to the study *NP101-022: A Randomized, Open-Label, Single Center, Single-Dose Study to Determine Residual Sumatriptan Succinate in NP101 Transdermal Patches after Use in Healthy Adult Subjects,* justify the (b) (4) mg difference of drug substance between label claim and assay value measured for the control used in the residual drug clinical study and analyzed by (b) (4).

33. Describe controls utilized to prevent the salt or drug formulation from dripping unintentionally into either well or onto the peripheral (b) (4) reservoir card during the dispensing process.

34. Establish an in-process control (IPC) to assure one and only one pad has been placed into each well. Include 100% monitoring.

35. Because of the importance of proper seal, establish 100% monitoring procedure for the IPC for proper seal.

Biopharmaceutics Deficiencies

36. Explain when approximately (b) (4) mg of sumatriptan is targeted to be delivered to the patient *in-vivo* over 4 hours of application, why the last *in-vitro* release specification proposes a Q = (b) (4) mg after 4 hour.

37. Submit *in-vitro* release data/profiles generated using the final release method from clinical/biobatches. More than one point specification is recommended for this product, especially at the juncture of changing the (b) (4) from (b) (4).

38. The proposed specification with a range of Q ± (b) (4) is not acceptable without an established IVIVC and/or supportive bioequivalence data. FDA recommends a range of Q ± (b) (4). Provide a justification for the proposed Q values.

39. Explain how the sampling area is reproducibly moved without disturbing the integrity of the system.

40. Explain how the electronics is precisely controlled especially in changing the (b) (4) ((b) (4)).

41. Explain how the total amount of drug delivered is calculated.

42. Explain how the system is able to detect and precisely prevent passive transport of the drug.

CDRH Deficiencies

43. Provide the battery specification sheet that includes battery capacity for the 2 (b) (4) batteries.

44. Regarding stability of the clinical and commercially packaged systems after 9 months and 6 months storage, respectively provided to support an expiration date of (b) (4) months, address the following:

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

    b. The document "Post-approval Stability Protocol and Stability Commitment." in section 3.2.P.8.2 of the original submission states that NuPathe intends t (b) (4) Provide a rationale for why these evaluations will not be conducted.

    c. Provide the pass/fail criteria for the (b) (4)

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

45. Regarding biocompatibility, test reports from the completed cytotoxicity, irritation, and dermal sensitization evaluations were provided 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." Confirm that the evaluated test articles are identical to the final device materials intended for commercial distribution. Be advised that biocompatibility should be established for the device you intend to market.

46. Regarding Software/Firmware the following modes in the software description section of the submission (section 8.2 of 3.2.R.4) are listed and described: 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 provided in attachments 17-48. Address the following:

(b) (4)

47. Regarding Software/Firmware address the following issues with the "self test," "test," "active," and "sleep" modes:

(b) (4)

48. Regarding the Hazard Analysis provided in attachment 17 of the original submission which identified hazards associated with firmware or hardware failure, address the following:

    a. The analysis is incomplete as it did not evaluate potential hazards associated with use of the device in other categories (e.g., electrical, operational, environmental,

mechanical). Update the hazard analysis to include all potential hazards that result from device use. Alternatively, provide a rationale for why identification and evaluation of other hazards have been omitted from the analysis.

b. Burns and blistering have been reported as adverse events for iontophoretic drug delivery patches; however the Hazard Analysis did not identify this hazard. Update the Hazard Analysis to include this risk and all potential causes, along with appropriate mitigating actions.

c. The drug and salt imbibed pads have a very similar appearance and it is possible for users to inadvertently switch the pads between the anode and cathode. Address the potential for such an occurrence and discuss the potential hazards to the patient. Update the Hazard Analysis accordingly.

d. The Software Safety Report in attachment 17 states the analysis was performed on software Version (b) (4) 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).

49. All validation and verification activities were completed 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. A memo in attachment 48 stated 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. Provide the test report (method, results, discussion) for these completed tests and provide a rationale for why these two tests alone are sufficient. Alternatively, complete a full validation and verification of the firmware version you intend to use in the commercial product.

50. Section 2 of 3.2.R.4 of the original submission declares conformity to several standards, including IEC 60601-2-2 (2006), and 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 the device as the device does not generate or deliver high frequency current. Explain the extent to which the device conforms to this standard.

51. Evaluation of patch conformability was conducted according to IEC 60601-2-2 standard. All patches met the acceptance criteria of the standard (less than (b) (4)% lift after 1 hour of placement on the forearm); however, multiple patches showed signs of lift at the edges and near the power supply. Based on this evaluation, it is not clear if the patches will adhere completely for the full 4 hour dosing period. Incomplete adherence of the electrodes could result in injury to the patient. Conduct an evaluation of the conformability of the patch (or extent of patch lift) for the full 4 hour duration of use.

52. The current density distribution evaluation was conducted using FEA modeling and determined that the highest degree of non-uniformity occurs at (b) (4) and is less evident

at the skin surface when used correctly (i.e., imbibed pads completely cover the electrode areas and entire pad area contacts skin). The 120 day safety update you provided lists several adverse events relating to administration site conditions including 2 instances of moderate burns and 3 instances of severe burns. Burns under electrodes typically occur due to areas of high focused current delivery. Conduct an evaluation of the current density distribution of the device in use for complete and incomplete patch adherence scenarios. Additionally, provide a discussion on scenarios that would result in burns using the device.

53. Regarding the documents SOP QS-003, TM-0002, TM-0003, TM-0004, SOP QS-009, SOP QS-001, SOP QS-002, SOP QS-004, SOP 10-005, SOP QS-007, SOP QS-008, SOP QS-009, SOP QS-101, SOP QS-011, SOP QS-013, SOP 10-015, SOP QS0916, SOP 25-001, SOP QA-002, SOP QA-014, SOP QA-020 and SOP RA-001 provided in order to satisfy the requirements of 21 CFR 820, the objective, responsibilities, procedure steps, and references related to each procedure have been adequately described. However, none of the procedures contain a scope, which should identify the limits as to when and where a procedure is to be applied. Provide updated procedures that contain relevant scopes as to when and where the procedures are to be applied.

54. Regarding SOP QA-002: *Processing Marketed Product Related Complaints and Inquiries* provided in order to satisfy the requirements of 21 CFR 820.198, Complaint Files:

55. Regarding SOP QS-003 *Design Control and Pharmaceutical Development, Revision .03,* provided to satisfy the requirements of 21 CFR 820.30(c), Design Input:

(b) (4)

56. Regarding SOP QS-003 *Design Control and Pharmaceutical Development, Revision .03,* provided to satisfy the requirements of 21 CFR 820.30(d), Design Output, the procedure describes how and where design outputs are to be (b) (4) Provide a revised Design Control procedure that contains or makes reference to acceptance criteria for the device that satisfies the requirements of 21 CFR 820.30(d).

57. Regarding SOP QS-003 *Design Control and Pharmaceutical Development, Revision .03,* forms F-QS-010 and F-QS-009 provided to satisfy the requirements of 21 CFR 820.30(e), Design Review:

(b) (4)

58. Regarding SOP QS-003 *Design Control and Pharmaceutical Development, Revision .03,* provided to satisfy the requirements of 21 CFR 820.30(g), Design Validation, which defines Design Validation and the potential methods to conduct Design Validation, (b) (4)

59. Regarding SOP QS-003 *Design Control and Pharmaceutical Development,* sections 3.9 and 4.9, provided to satisfy the requirements of 21 CFR 820.30(h), Design Transfer:

(b) (4)

60. Regarding SOP QS-003 *Design Control and Pharmaceutical Development,* sections 4.11, provided to satisfy the requirements of 21 CFR 820.30(i), Design Changes:

(b) (4)

(b) (4)

61. Regarding SOP-QS-011: *Non-Conformance and CAPA Management* provided to satisfy the requirements of 21 CFR 820.100:

(b) (4)

62. Regarding SOP-QS-012: *Purchasing (revision .02)* provided in order to satisfy the requirements of 21 CFR 820.50, Purchasing Controls:

a. The SOP states that (b) (4)

(b) (4)

63. Regarding SOP-QS-012: *Purchasing (revision .02)* and SOP QS-016: *External Auditing* provided in order to satisfy the requirements of 21 CFR 820.50, Purchasing Controls, which describes how purchases are made by (b) (4)

64. Regarding SOP 75-009: *Operation and Maintenance of the* (b) (4) *Battery Tester* provided to satisfy the requirements of 21 CFR 820.72, Inspection, Measuring, and Test Equipment how to operate the Battery Tester is described; however, the procedure does not describe the need to calibrate the instrument, and if it is required, how often, by whom, and where the calibration record will be stored. Provide a procedure for the (b) (4) Battery Tester that addresses the requirements for calibration of 21 CFR 820.72(b), Calibration.

65. Four procedures, SOP 75-002, SOP 75-003, SOP 75-007, and SOP 75-009 are provided to describe (b) (4)

(b) (4)
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66. Regarding the document (b) (4)

67. Regarding the (b) (4)

(b) (4)

68. Regarding the provided [redacted] (b) (4)

69. Regarding the provided [redacted] (b) (4)

70. Regarding [redacted] (b) (4)

71. Section [redacted] (b) (4)

MICROBIOLOGY

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 methylparaben 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.

CLINICAL PHARMACOLOGY

The clinical portion of Study NP101-013 (which was designed to assess the bioequivalence of the NP101 patch used in pivotal efficacy Study NP101-007 and that intended for commercial use, compared to oral Imitrex) is not acceptable for review, because Prism Research failed 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 at Prism Research, authenticity of the test and reference products used in Study NP101-013 cannot be assured. Since the data from NP101-013 generated at Prism Research are not acceptable for review, the results obtained from the pivotal BE Study NP101-013 are not acceptable. That study must therefore be repeated.

NONCLINICAL

1. You have not adequately assessed the chronic dermal toxicity of the NP101 drug formulation since the 9-month dermal toxicity study in miniature swine (PROT-55-NP101-006/S08719) was inadequate by design and conduct. The study needs to be repeated using:
    a. A clinically relevant formulation and dosing regimen. Justification would need to be provided for less than daily dosing at the same site.
    b. A sufficient number of animals to allow for meaningful interpretation (4/sex/group).
    c. Untreated and vehicle control groups. It is possible that assessment of untreated skin could be conducted in animals from other groups, i.e., a separate group may not be needed.
    d. Three dose levels to allow assessment of the dose-dependent nature of any toxicity observed, up to a dose documented to be either a maximum tolerated or maximum feasible dose.
    e. Toxicokinetic analysis to document drug delivery through the skin.

2. You have not provided adequate justification to allow for a waiver of the requirement for conducting a dermal carcinogenicity study for NP101. We understand that the NP101 patch cannot be used to dose rodents. However, you have failed to address the feasibility of conducting a carcinogenicity study in which the components of the drug product are painted onto the skin. Unless the results of an adequately conducted chronic dermal toxicity study in non-rodent demonstrate the lack of any histopathological changes in locally exposed tissue, you will need to either conduct a dermal carcinogenicity study (preferably in mouse) or provide adequate justification for why a dermal painting carcinogenicity study is not feasible or would not provide data relevant to humans.
3. If substantial changes are made to the clinical product, additional nonclinical studies may be required.

CLINICAL

1. We have serious concerns about the potential for your product to cause severe burns, and permanent skin lesions. You cross-referenced in section 2.1.5.1.4 of your summary of clinical safety 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". We note that you described these events in a section titled "Improper Application". We reject 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 attributable to product design issues rather than to patient misuse. We consider 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. We also note that there were 3 adverse event reports (0.4%) of severe burns, and 2 reports of moderate burns (0.3%) in long-term safety studies, and one report of "mild scar". In addition, we can not rule out that your database includes additional cases of permanent skin lesions that were not described in your summary of clinical safety. Unless you can provide evidence that cases of significant administration site adverse events (e.g., burn, scar, discoloration or abnormal pigmentation) in your database ultimately resolved, we believe that the risk of skin lesions (in particular with permanent sequelae) is not justified by the benefits of the product.

2. Site discoloration was reported as an adverse event in 4.3% of patients in long-term safety studies. You have not provided sufficient information to allow us to determine the time course and reversibility of the discoloration. Please provide that information.

Permanent discoloration of the skin would typically not represent an acceptable side effect for a product indicated for the acute treatment of migraine.

3. We are concerned about the significant irritation and sensitization potential of your product. In long-term safety studies, bruising was reported as an adverse event in 2.4% of patients, and vesicles were reported in 2.4% of patients. In addition, intense redness at the site of treatment was observed in 6% of patients 4 hours post-treatment, and in 2.7% of patients 24 hours after treatment. Blisters or broken skin were observed in 0.5% of patients 24 hours after treatment. Unless these findings can be dismissed as non clinically significant, we do not believe that the benefits of the product justify the side effects at the site of administration.

4. We were not able to estimate the exact incidence of adverse events because they were often reported by non-specific terms such as "site reactions" or "adverse drug reactions". For your updated integrated summary of safety, you need to re-examine and recode adverse events that were described using non-specific terms, and also provide updated datasets.

5. You 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 per month, as there was no specific analysis of patients using the treatment under these conditions in your NDA, and limited information of patients treating more than 2 attacks per month, on average. You need to submit sufficient and adequate 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.

6. You have not provided sufficient information to allow us to determine the minimal amount to time necessary to safely reapply the product at the same site. Your NDA provides evidence that the product has a significant irritation potential and is sensitizing. Therefore, it is particularly important to establish how soon the product can be reapplied at the same site. Your 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" is not supported by empirical evidence that it is safe to do so. Your application must include adequate and sufficient safety information to establish the minimum time between treatments that is necessary to safely reapply the product, particularly in patients who exhibited local signs of irritation with the previous treatment.

7. There was a high rate of discontinuation in long-term safety studies (55%). The most common reason for discontinuation was "withdrawal of consent" (20% of patients

across treatment groups). The reason for the "withdrawal of consent" was not described in your database. As adverse events often lead to patients withdrawing consent, it is critical to determine whether patients who withdrew consent experienced an adverse reaction before withdrawing from the study. For patients who discontinued because of "withdrawal of consent", provide a description of adverse events occurring in the previous 30 days.

8. Your 6-month safety database includes a lower number of patients who have treated an average of at least 2 migraine attacks per month than discussed with you during the development program. Specifically, our typical requirement for acute migraine products is for data on at least 300 subjects who treated an average of at least 2 migraine attacks per month for six months, and 100 subjects who treated an average of at least two migraine attacks for one year. At the pre-NDA meeting, the division agreed to your proposal for a database of at least 300 patients treated with an average of three patches per month for six months, and 50 patients treated with an average of three patches per month for 12 months. We acknowledge that your database includes a sufficient number of patients exposed for 12 months. However, your 6-month database provides data on only 165 patients who treated an average of greater than 2 attacks per month, and 74 patients who treated an average of greater than 3 attacks per month[1]. Assuming you adequately address the clinical safety issues described above (under clinical comments 1-7), additional 6-month long-term safety data may be required.

9. While we acknowledge that pivotal efficacy Study NP101-007 established the efficacy of your product in the overall migraine population, we note there was essentially no treatment benefit for the 2-hour pain-free rate in non-White patients (active patch 12.5%; placebo patch 11.4%). In addition, clinical pharmacology studies suggest that sumatriptan exposure (Cmax and AUC) may be lower in non-White patients than in White patients, which gives credence to a possible lack of efficacy in non-White patients. Please address these findings, and provide evidence supporting the efficacy of the product in non-White patients.

REMS

You proposed a REMS consisting of a Medication Guide (b) (4) . As communicated during the review cycle, we made a preliminary determination 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. We may reconsider that position after we review your response to the deficiencies identified above. At this time, we do not believe that a Medication Guide would be by itself sufficient to mitigate the risks associated with the product, as significant skin toxicity did occur in clinical trials, despite instructing the patients on how to use the product. We have also not yet determined whether

[1] Because of the way your data presentation was structured, we could derive the number of patients who treated an average of greater than 2 attacks per month, but not the number of patients who treated an average of at least 2 attacks per month.

other REMS elements may be necessary for your product. A final decision on the appropriate risk management strategy will be undertaken after you submit a satisfactory response to this letter.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
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/

RUSSELL G KATZ
08/29/2011