

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202278Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202-278

SUPPL #

HFD # 120

Trade Name Zecuity

Generic Name sumatriptan iontophoretic transdermal system

Applicant Name NuPathe

Approval Date, If Known 1/17/13

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 20-080	Imitrex Injection
NDA 20-132	Imitrex Tablets
NDA 20-626	Imitrex Nasal Spray
NDA 22-239	Sumavel DosePro
NDA 22-377	Alsuma

2. Combination product. (N/A)

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new

clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

NP101-007

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

NP101-007

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 74,877

YES

!
!
! NO
! Explain:

Investigation #2

IND #

YES

!
!
! NO
! Explain:

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

/s/

LANA Y CHEN
02/08/2013

RUSSELL G KATZ
02/08/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 202-278 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Zecuity Established/Proper Name: sumatriptan Dosage Form: iontophoretic transdermal system		Applicant: NuPathe, Inc Agent for Applicant (if applicable): n/a
RPM: Lana Chen		Division: Division of Neurology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>NDA 20-080 Imitrex Injection NDA 20-132 Imitrex Tabs</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Different formulation</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 1/17/13</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>1/17/13</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 	CR 8/29/11
<ul style="list-style-type: none"> If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ 	<input type="checkbox"/> Received
<ul style="list-style-type: none"> Application Characteristics³ <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3S</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<ul style="list-style-type: none"> BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter) 	<input type="checkbox"/> Yes, dates
<ul style="list-style-type: none"> BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Public communications (<i>approvals only</i>) <ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If “Yes,” skip to question (4) below. If “No,” continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If “No,” continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “No,” continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 1/17/13
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	See Tabs L & F
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input type="checkbox"/> DMEPA-see Tab L <input type="checkbox"/> DMPP/PLT -Tab K <input type="checkbox"/> OPDP (DDMAC) – Tab J <input type="checkbox"/> SEALD Tab I <input type="checkbox"/> CSS n/a <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	12/17/12
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	12/17/12
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC (PeRC reviewed 1st cycle) If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	See Tab F
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None see Tab G
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None see Tab G
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None see Tab A
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	see Tab G
• Clinical review(s) (<i>indicate date for each review</i>)	see Tab G
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Tab G
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested see Tab O

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None see Tab S
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None see Tab N
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None See Tab P
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None See Tab P
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None see Tab Q
❖ Microbiology Reviews	<input type="checkbox"/> Not needed See Tab S
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None See Tab 4 for CDRH Reviews

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



NDA 202-278

DISCIPLINE REVIEW LETTER

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

Dear Dr. Sehgal:

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

We also refer to your resubmission dated July 17, 2012.

Our review of the nonclinical section of your submission is complete, and we have identified the following deficiencies:

You have not provided an adequate response to the nonclinical deficiencies (#1 and #2) conveyed in the Agency's Complete Response letter dated August 29, 2011.

- No new data were submitted to document the adequacy of the 9-month chronic dermal toxicity study in miniature swine. We continue to believe that this study is inadequate to assess the dermal toxicity of the sumatriptan iontophoretic transdermal system (TDS) or to dermal application of sumatriptan. Deficiencies include, but are not necessarily limited to, the following:
 - Too few animals were used to test the chronic dermal toxicity of the sumatriptan iontophoretic TDS. Only four animals were treated for the entire 9-month dosing period, and the data from one of these four animals were "...excluded due to it's [*sic*] high rate of patch failure." In addition, two different strains (Yucatan and Hanford) of miniature swine were used (i.e., two animals/strain/group), and, as you note, the data documented notable differences between the strains (*cf. Toxicology Written Summary, page 49*).
 - The dosing regimen did not provide an adequate safety margin compared to the proposed clinical use. Animals were treated with two clinical TDS per week, each delivering 6 mg over 4 hours, at two different application sites. The proposed maximum recommended daily dose in humans is two TDS, each delivering 6.5 mg of sumatriptan over four hours; the proposed label does not state a limit to the number of days per week that the sumatriptan iontophoretic TDS may be used. In addition, the study report did not fully describe how often

the same application site was used in each animal during the 9-month dosing period.

- The lack of a TDS control group or site. Although, as you note, untreated skin was examined in each animal, the lack of an assessment of the dermal toxicity of a control TDS precluded an evaluation of the dermal toxicity of sumatriptan itself. This is of particular importance when considering whether or not an assessment of dermal carcinogenicity may be necessary.
- No new data were submitted relevant to the feasibility of conducting an assessment of the carcinogenic potential of dermally applied sumatriptan. An *in vitro* test of the use of penetration enhancers was conducted only using bovine udder skin and human epidermis. No *in vitro* or *in vivo* assays were conducted to test the effect of various penetration enhancers on absorption of sumatriptan by rodent skin. Published literature suggests that rodent skin is more permeable to a variety of compounds than is human skin (e.g., Calabrese EJ *Drug Metab Rev* 15(5&6):1013-1032, 1984; Scott RC *et al. J Invest Dermatol* 96(6):921-925, 1991; van Ravenzwaay B, Leibold E *Toxic in Vitro* 18:219-225, 2004; Williams AC, Barry BW *Adv Drug Deliv Rev* 56:603-618, 2004; Ross JH *et al. Reg Toxicol Pharm* 41:82-91, 2005). The relevance of the *in vitro* data provided to address the issue of the feasibility of assessing carcinogenic potential appears questionable.

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, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Lois Freed, PhD
Supervisory Pharmacologist
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

J EDWARD FISHER
12/21/2012
signed for Dr. Freed



NDA 202-278

INFORMATION REQUEST

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

Dear Dr. Sehgal:

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

Please also refer to your July 17, 2012, submission, containing your response to our Complete Response letter.

We have reviewed the carton and container section of your labeling submission, and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Identifying Label of the Transdermal System

1. Revise [REDACTED] ^{(b) (4)} to read “6.5 mg/4 hours” or equivalent presentation, for clarity. In addition, ensure that there is a space between the number and the unit for improved readability. For example, revise “6.5mg” to read “6.5 mg.”

Container Label

2. All uses of the word “patch” should be replaced with one of the following “iontophoretic transdermal system,” “iontophoretic device,” “system,” or “device” as applicable.
3. Revise the strength of the product [REDACTED] ^{(b) (4)} to read “6.5 mg/4 hours” or equivalent presentation. In addition, increase the font size of the strength statement “6.5 mg/4 hours.”
4. Remove the graphic appearing to the left of the proposed proprietary name, Zecuity. This graphic detracts from other important information on the label and could be misinterpreted as an additional letter in the proprietary name.

5. Present the established name as “(sumatriptan iontophoretic transdermal system)”. The font size should appear at least 50% as large as the proprietary name per 21 CFR 201.10(g)(2) and be of the same typography and color.
6. Add the statement “For transdermal use only” on the principal display panel per 21 CFR 201.100(b)(3).
7. Debold the “Rx Only” statement on the back panel since it is overly prominent.
8. Change (b) (4) to “86 mg” in the statement (b) (4)
9. Negative warnings, such as “do not do that” can be misread as an affirmative warning “do this.”² The negative warning should be changed to an affirmative to prevent misinterpretation. Therefore, we request you revise the statement (b) (4) to read “Single-use only. Discard after initial use.”
10. Revise the statement (b) (4) to read “Store Zecuity at room temperature 20°C to 25°C (68 °F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F)”. Removing the hyphens and replacing with ‘to’ will help to improve readability and increase clarity of the information presented.
11. Revise statements in all upper case to title case. For example, revise “BEFORE OPENING POUCH, READ INSTRUCTIONS FOR USE” to “Before Opening Pouch, Read Instructions for Use” for improved readability.
12. Decrease the size of the NuPathe logo since it detracts from other important information.
13. Revise the statement (b) (4) to read “Press firmly while tracing arrow 3 times around” for clarity.

Carton Label

14. Apply comments 2 through 12 to the carton label.
15. The Quick Response (QR) Code that appears on the principal display panel should be relocated to a side or back panel, away from the barcode. The size of the QR Code should also be minimized so that it does not detract from other important information on the panel.
16. Revise the statement “(b) (4)” per comment 2.
17. Decrease the font size of the net quantity statement, currently reading (b) (4),” since it is overly prominent.

² Institute for Safe Medication Practices (ISMP). August 12, 2010. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Medication Safety Alert, 15(16).

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

Sincerely,

{See appended electronic signature page}

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

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/s/

ERIC P BASTINGS
12/11/2012



NDA 202278

INFORMATION REQUEST

NuPathe Inc.

Attention: Sanjay Sehgal, Ph.D., Vice President, Regulatory Affairs
227 Washington Street, Suite 200
Conshohocken, PA 19428

Dear Dr. Sehgal:

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

We also refer to your July 17, 2012 resubmission.

We are reviewing the Product Quality 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.

1. In your response to Deficiency 46b in our Additional Information request dated July 15, 2011, you reference Section 3.2.R.4.2.3.3 of your submission, which describe the (b) (4) mode as a method of (b) (4). However, you did not provide a detailed description of this mode. Please provide a description of the (b) (4).
2. In your response to Deficiency 47a in our Additional Information request dated July 15, 2011, you state “the Self-Test mode (b) (4).” You provided the Self-Test Mode Flowchart in Figure 9 of Section 3.2.R.4.2.4.1.3 of your submission. Figure 9 indicates (b) (4). However, you did not indicate the pass/fail criteria for each of the evaluated parameters. Therefore, please provide the pass/fail criteria for each of the evaluated parameters (i.e. (b) (4)).
3. In your response to Deficiency 47d in our Additional Information request dated July 15, 2011, you state “(b) (4).” In the Architecture Design Chart, the device enters Inactive Mode following failed test mode.

However, you did not address concerns with restarting the device following failed test mode. Therefore, please address the following:

a. Clarify how the device transitions from [REDACTED] (b) (4)

[REDACTED]

b. The LED indicator for [REDACTED] (b) (4). Please indicate how is it possible for a user to differentiate between a device that is in Sleep Mode versus a device that has entered Fail Mode.

4. In your response to Deficiency 47e in our Additional Information request dated July 15, 2011, you reference Section 3.2.R.4.2.3.4 of your submission, which states “[REDACTED] (b) (4)

[REDACTED]” However, Section 3.2.R.4.1.1.2 states that [REDACTED] (b) (4)

[REDACTED] There appears to be inconsistency in the current profile of your device. Please clarify wh [REDACTED] (b) (4)

5. In your response to Deficiency 48a in our Additional Information request dated July 15, 2011, you provided a revised hazard analysis in the REP-DHF-NP101-296 report. However, the analysis is incomplete as it did not fully evaluate the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards. Therefore, please update the hazard analysis to include a description of all potential hazards (e.g., electrical, operational, environmental, mechanical) presented by this device, the causes and severity of the hazards, the method of control of the hazards and the testing done to verify the correct implementation of that method of control, and any residual hazards.

Note: This is typically done in an enumerated columnar form, wherein the first column identifies the hazard to the patient, the second column identifies from where in the system that hazard could be caused, the third column presents, for software caused hazards, where in the software the hazard could be caused, the fourth column provides the specific details of the mitigation including identifying the enumerated tests, and the fifth column identifies any residual hazards.

6. In your response to Deficiency 49 in our Additional Information request dated July 15, 2011, you state “*The final version of firmware in the proposed to be marketed product is [REDACTED] (b) (4). Verification and validation of this final firmware version is discussed*

more specifically in Section 3.2.R.4.2.7.” However, the Verification and Validation documentation of this final firmware version in Section 3.2.R.4.2.7 does not provide a complete description of the validation and verification activities at the unit, integration, and system level. Therefore, please provide unit, integration, and system level test protocol, including pass/fail criteria, test report, summary, and test results.

7. You provided SOP GN-005, Rev 00, and SOP QS-008, Rev 3, in order to satisfy the requirements of 21 CFR 820.50, Purchasing Controls. In these procedures, you describe how purchases are made (b) (4)

[Redacted]

8. You provided a response to deficiencies regarding Process Validation, 820.75(a). In the response, you state that (b) (4) packaging (b) (4)

[Redacted] Please provide a validation protocol for the (b) (4) packaging process.

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

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MARTHA R HEIMANN
12/11/2012
For Ramesh Sood



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 202278

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

NuPathe Inc.
227 Washington Street
Suite 200
Conshohocken, PA 19428

ATTENTION: Sanjay Sehgal, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Sehgal:

Please refer to your New Drug Application (NDA) submission dated and received October 29, 2010, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Iontophoretic Transdermal System, 6.5 mg over 4 hours.

We also refer to:

- your Class 2 resubmission, dated July 16, 2012, received July 17, 2012; and
- your correspondence, dated and received August 17, 2012, requesting review of your proposed proprietary name, Zecuity.

We have completed our review of the proposed proprietary name, Zecuity and have concluded that it is acceptable.

The proposed proprietary name, Zecuity, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 16, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lana Chen at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LAURIE A KELLEY
11/09/2012

CAROL A HOLQUIST
11/09/2012



NDA 202-278

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

NuPathe, Inc.
Attention: Sanjay Sehgal, PhD
Vice-President, Regulatory Affairs
227 Washington Street, Suite 200
Conshohocken, PA 19428

Dear Dr. Sehgal:

We acknowledge receipt on July 17, 2012, of your July 16, 2012, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zecuity (sumatriptan) iontophoretic transdermal system.

We consider this a complete, class 2 response to our August 29, 2011, action letter. Therefore, the user fee goal date is January 17, 2013.

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

Sincerely,

{See appended electronic signature page}

Lana Y. Chen, R.Ph., CAPT-USPHS
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

LANA Y CHEN
07/30/2012

Bouie, Teshara

From: Bouie, Teshara
Sent: Tuesday, August 02, 2011 1:57 PM
To: 'Michele Roy'
Cc: Chen, Lana Y
Subject: RE: NDA 202278, NP101 (sumatriptan) iontophoretic transdermal system

Hi Michele,

Due to scheduling conflicts we will not be able to meet Thursday August 4, 2011. However we have the following response to your question below regarding Comment # 17 of the July 15, 2011 Discipline Review Letter.

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

FDA Response (7/15/2011): The response is not adequate. The sample size for all specification testing must reflect statistical significance.

NuPathe: We are unclear as to exactly what additional information is needed to address this comment and would greatly appreciate if you could clarify or provide more detail as to what we need to provide to satisfy this requirement.

FDA Response: Due to the complexity of the dosage form a [REDACTED] (b) (4); however the justification provided for [REDACTED] (b) (4) for the identification methods appears reasonable. The number of samples for the appearance tests should be representative of the quality of the batch, across the batch (e.g. beginning, middle, and end).

We hope this provides more clarity. Please let me know if have any other questions.

Regards,

Teshara G. Bouie

From: Michele Roy [mailto:MRoy@NuPathe.com]
Sent: Friday, July 22, 2011 11:41 AM
To: Chen, Lana Y; Bouie, Teshara
Subject: FW: NDA 202278, NP101 (sumatriptan) iontophoretic transdermal system
Importance: High

Good morning Lana and Teshara,

I hope this finds you well and surviving the hot weather! I wanted to let you know that the remaining items listed in the e-mail below, for information committed to be sent to you as part of our response on 10 June to your 16 May Information Request Letter, are being submitted to the NDA today, as Sequence 0022.

I also wanted to let you know that yesterday we received your CMC Discipline Review Letter, dated 15 July 2011, and are working to expeditiously provide additional information to address the comments and/or issues identified as needing further attention. We would, however, like to request your help to clarify Comment #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.

We are unclear as to exactly what additional information is needed to address this comment and would greatly appreciate if you could clarify or provide more detail as to what we need to provide to satisfy this requirement.

We would also like to request a meeting with the Review Team. We feel that having the opportunity for our team to discuss the NP101 product with your Review Team would facilitate an understanding of the product and the issues that remain, as identified in the Discipline Review Letter. We prefer a face to face meeting but understand that a teleconference might be quicker to schedule. Again, we believe a meeting would be of great benefit in resolving the outstanding issues.

Please let me know if you have any questions. We look forward to your clarification of comment #17 and to the opportunity for further discussion regarding the NP101 product and the outstanding issues. Thank you very much for your help and support – Michele

From: Michele Roy
Sent: Friday, July 15, 2011 1:45 PM
To: Chen, Lana Y; 'Bouie, Teshara'
Subject: NDA 202278, NP101 (sumatriptan) iontophoretic transdermal system

Hi Lana and Teshara – I hope this finds you well. I wanted to provide you with a quick update regarding our submissions and commitments. This week we submitted the usability study report, the impurity acceptance limits for the foam, and today the crystal study report confirming the (b) (4) in both the drug and salt formulations. This leaves two items (updates in blue text):

FDA Comment #	Description	Submission
15	Expose clinically relevant amounts of overtape and (b) (4) foam, in terms of surface area that comes in contact with the skin, to the drug and salt formulations for 4 hours and 8 hours, then test both formulations for the known adhesive impurities ((b) (4))	In progress; pushing for final report by 21 July
35	Provide an extractable and leachable test report for the (b) (4) material (b) (4), equivalent to that provided for the (b) (4)	In progress; pushing for 27 July

I hope you find this helpful. Please let me know if you have any questions or if I can provide more information. Thank you and have a very nice weekend! Michele

Michele Roy RN, MS | Director of Regulatory Affairs | NuPathe Inc. (Nasdaq: PATH) | 227 Washington Street, Suite 200, Conshohocken, PA 19428 | Tel: 484-567-0130
 Ext. 1103 | Cell Phone: 610-217-7536 | Fax: 484-567-0136 | www.nupathe.com | mroy@nupathe.com

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/s/

TESHARA G BOUIE
08/02/2011



NDA 202-278

**METHODS VALIDATION
MATERIALS RECEIVED**

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

Dear Michele Roy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zelrix (Sumatriptan iontophoretic Transdermal system, 6.5 mg and to our 07/13/2011 letter requesting sample materials for methods validation testing.

We acknowledge receipt on 7/21/2011 and 7/26/2011, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
07/26/2011



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) 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 impurities of (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 (b) (4) 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 (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 (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)

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

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/s/

TERRANCE W OCHELTRIE
07/15/2011



NDA202-278

REQUEST FOR METHODS VALIDATION MATERIALS

NuPathe Inc.
Attention: Michele A. Roy, RN, MS
227 Washington Street
Suite 200
Conshohocken, PA 19428
Telephone: 484-567-0130 x 1103

Dear Michele 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, 6.5 mg.

We will be performing methods validation studies on Zelrix (Sumatriptan) iontophoretic transdermal system, 6.5 mg, as described in NDA 202-278.

In order to perform the necessary testing, we request the following sample materials and equipments:

- 70- Zelrix (Sumatriptan) iontophoretic Transdermal systems
- 5- Placebo patches
- 200 mg – Methyl Paraben Reference Standard
- 200 mg- Sumatriptan Succinate Reference Standard
- 50 mg- Sumatriptan Succinate Related Impurities Reference Standard
- 1- HPLC Column, Spherisorb ODS-1, 250 mm x 4.6 mm, 5 μ m

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
07/13/2011

Chen, Lana Y

From: Chen, Lana Y
Sent: Thursday, May 19, 2011 11:14 AM
To: Michele Roy
Cc: Chen, Lana Y; Summers, Kelly
Subject: NDA 202-278 Zelrix: No REMS

Hi Michele,

On October 29, 2010, in your NDA submission, you proposed a risk evaluation and mitigation strategy (REMS) for Zelrix (sumatriptan iontophoretic transdermal system) to ensure that the benefits of the drug outweigh the potential for increased risk in patients who fail to use the product properly. You proposed that your REMS include a Medication Guide ^{(b) (4)}

You may be aware that 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, we do not think that is not necessary for the Medication Guide to be part of a REMS to ensure that the benefits of Zelrix (sumatriptan iontophoretic transdermal system) outweigh its risks. We do believe, however, that the Medication Guide is still necessary for patients' safe and effective use of Zelrix (sumatriptan iontophoretic transdermal system). 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.

Please send me an email to acknowledge your agreement of "no REMS" for NDA 202278 Zelrix (sumatriptan iontophoretic transdermal system).

If you have any questions, please feel free to contact me.

thanks,
Lana

Lana Y. Chen, R.Ph., CAPT-USPHS
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
Phone 301-796-1056
Fax 301-796-9842
Email: lane.chen@fda.hhs.gov

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/s/

LANA Y CHEN
05/19/2011



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 (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. 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).
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

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/s/

TERRANCE W OCHELTRIE
05/16/2011



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 acknowledge your submission dated March 18, 2011 in response to our February 23, 2011 communication. We request that the drug substance specification table be further modified to include a single regulatory test and acceptance criterion for each parameter. An alternate test (but not acceptance criterion) may be included in the specification table. It is expected that the USP test be the primary method unless appropriate justification is provided for using an alternate method. These changes will aid in clarifying the final regulatory specification and avoid confusing (e.g. Related Compound ^(b)₍₄₎/ Impurity ^(b)₍₄₎) or apparently duplicated (e.g. Related Compound ^(b)₍₄₎/Impurity ^(b)₍₄₎) tests/limits.

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

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/s/

TERRANCE W OCHELTRIE
05/06/2011



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:

1. The microbial limits specifications for the sumatriptan and salt pads. The recommended microbial limits for transdermal patches can be found in USP <1111>.
2. The results of (b) (4) testing on the sumatriptan pads and salt pads using USP <51> methodology or equivalent. Tests should be conducted using the minimum amount of preservative content specified in the stability protocol.

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

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

KASTURI SRINIVASACHAR
04/21/2011



NDA 202278

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

NuPathe Inc.
227 Washington Street, Suite 200
Conshohocken, Pennsylvania 19428

ATTENTION: Michele A. Roy, RN, MS
Director of Regulatory Affairs

Dear Ms. Roy:

Please refer to your New Drug Application (NDA) dated October 29, 2010, received October 29, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Iontophoretic Transdermal System, 6.5 mg.

We also refer to your December 17, 2010, correspondence, received December 17, 2010, requesting review of your proposed proprietary name, Zelrix. We have completed our review of this proposed proprietary name, Zelrix, and have concluded that this name is unacceptable for the following reasons:

1. The proposed proprietary name, Zelrix is orthographically and phonetically similar to and shares similar product characteristics with the marketed product, Salvax. The orthographic similarity of this name pair stems from the similar length and shape of the names. This name pair begins with letters that look similar when scripted (Z and S) and share two letters that appear in the same positions (l and x).

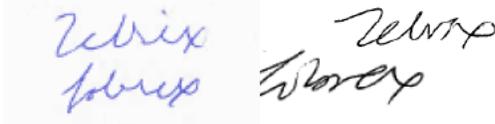
The image shows four handwritten examples of the names 'Zelrix' and 'Salvax' in cursive script. The top row shows 'Zelrix' on the left and 'Salvax' on the right. The bottom row shows 'Salvax' on the left and 'Zelrix' on the right. This visual comparison highlights the orthographic similarities between the two names, particularly in the length and shape of the letters and the shared 'l' and 'x' characters.

The phonetic similarity stems from the fact that both names include two syllables. The first syllable in each name is essentially the same when spoken (“Zel-” vs. “Sal-”). The second syllable includes a vowel followed by the letter ‘x’ which provides for similar sounding endings (“-ex” vs. “-ax”).

In addition to the orthographic and phonetic similarity of this name pair, these products share similar product characteristics which include the following: a numerically similar single strength (6 % vs. 6.5 mg), and route of administration (topical). The numeric similarity of the strengths may be exacerbated by the use of trailing zeros (e.g. 6.0% vs. 6.5 mg). In addition, since both products are available in a single strength, the omission of the strength during the prescribing and procurements steps of the medication use process is likely. Further, we note that the directions for

use of Zelrix and Salvax can be written as “Apply or use as directed” which contributes to the risk of confusion leading to medication error.

- The proposed proprietary name, Zelrix, is orthographically similar to and shares similar product characteristics with the marketed product, Tobrex. The orthographic similarity of these names stem from the similar length, similar appearance of the first letter in each name when scripted (T vs. Z), and nearly similar ending three letters (‘-rix’ vs. ‘-rex’). Adding to the visual similarity are the upstrokes (b vs. l) in the middle of each name.



In addition to the orthographic similarity of this name pair, the products share product characteristics such as a single strength which may be omitted in the prescribing and procurements steps of the medication use process, both are topically applied products (ophthalmic ointment vs., transdermal system), and both can be prescribed with directions for use written as “Apply or use as directed” which we believe adds to the risk of confusion leading to medication error.

- The proposed proprietary name, Zelrix, is orthographically similar to and shares similar product characteristics with the once marketed and now discontinued product, Lidex. Although, Lidex is discontinued, drug use data demonstrates healthcare providers continue to use the name, Lidex, in clinical practice when prescribing fluocinonide topical products. In the event a prescription is written for Lidex, although not available, the prescription will be filled with the generic equivalent fluocinonide topical product. Thus, we must consider this name still active. The orthographic similarity of this name pair stems from the similar appearance of the first letters (L vs. Z) and the second letters (i vs. e) when scripted. In addition, both names end with the same two letters ‘-ex.’ Adding to the visual similarity are the upstrokes (d vs. l) in the middle of each name.



In addition to the orthographic similarity of the name pair, these products share similar product characteristics which include the following: single strength availability (which may be omitted in the prescribing and procurements steps of the medication use process), route of administration (topical), and the directions for use (both can be written as “Apply or use as directed”). DMEPA acknowledges Lidex is a proprietary name for discontinued topical products. However, preliminary drug use data demonstrates prescribers continue to use the name, Lidex, in clinical practice and prescribers write “as directed” as the directions for use on these prescriptions

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*,

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm> and “Pdufa Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Beverly Conner at (301) 796-1171.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LAURIE A KELLEY
03/07/2011

CAROL A HOLQUIST
03/09/2011



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.

Provide the proposed regulatory drug substance specification in a single table that includes all tests, analytical procedures and acceptance criteria. This table may include footnotes listing the tests that will be routinely done on all batches and tests for which results may be taken from the suppliers Certificate of Analysis. The table can also include footnotes for the tests that will be applicable to the material obtained from a specific source.

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

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/s/

TERRANCE W OCHELTRIE
02/23/2011



NDA 202-278

FILING COMMUNICATION

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 Zelrix (sumatriptan) iontophoretic transdermal system.

We also refer to your submissions dated November 23, 2010 and December 17, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is August 29, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 29, 2011.

Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We have the following requests for information:

CMC

With respect to the Environmental Assessment (Module 1.12.14), please clarify whether you are claiming categorical exclusions under 21 CFR 25.31(b) and 21 CFR 25.34(a).

With regard to the drug substance specification, the document referred to as "NuPathe specification MS-0001" does not constitute a specification. Submit the regulatory acceptance specification for sumatriptan (i.e., test, analytical procedures, and acceptance criteria). The specification should include adequate tests and analytical procedures to allow verification of each parameter reported on the manufacturer's certificate of analysis, regardless of whether the test is performed routinely on lot receipt or periodically for vendor requalification. Note that although USP compendial methods may be incorporated by reference, copies of any European Pharmacopeial procedures referenced in the specification should be provided in the application.

With regard to adhesives used in the product, the DMF supporting (b) (4) is deficient. We recommend that you discuss the nature of the deficiencies with the DMF holder. Reviews of other referenced DMFs have not been completed at this time. If deficiencies are identified in other DMFs during the review cycle, you will be notified at that time.

With regard to the drug product specification, you have presented separate specifications in Module 3.2.P.5 for the Sumatriptan Pad (Table 1), the Salt Pad (Table 2) and "Co-Packaged Drug/Device Combination Product." Adopt a single specification for the to-be marketed product, which incorporates all critical drug and device performance parameters and will be valid through the proposed product shelf life.

With regard to residual drug, provide the residual drug amount of the proposed commercial patch (mean \pm SD, max, min) after prescribed use in humans. This assessment should be of the sumatriptan succinate remaining in the transdermal system after use, not a calculation or estimation based on *in vitro* permeation studies. The study may be on a subset of patients/volunteers in a clinical/PK study.

Additionally, the residual drug in the NP101 patch is not appropriately justified. The provided literature and the study of the relationship between sumatriptan concentration and iontophoretic drug delivery using a representative *in vitro* system provided in section 2.1.5.1 do not support the amount of drug remaining in the NP101 patch for (but not limited to) the following reasons:

- The currents used in the *in vitro* study do not correlate to the current to be applied in prescribed use.
- The time evaluated in the *in vitro* study does not correlate to the time of intended application.
- Figure 2 indicates that the desired (b) (4) mg of total delivery was achieved within 3 hours of delivery by the (b) (4) mA condition.

With regard to product stability, we remind you that, as communicated during the pre-NDA meeting held on November 24, 2009, product stability testing should be reflective of the finished product *in the intended commercial configuration*. Although you have provided supportive stability data for drug and device components tested separately, you have provided stability for a single lot of the combination product in the commercial packaging configuration. Data for this lot is limited to six months. Additionally, you have only provided 4 months stability data for the

adhesive component. Given this, there are not sufficient data available to support establishment of an expiration dating period for the combination product.

Additionally, with regard to stability, perform the following additional tests:

- 1) Functionality testing of the device as a regular part of stability testing in the co-packaged commercial packaging configuration.
- 2) Functionality testing of the device as a regular part of stability testing after it is assembled for 4 hours but not applied. Additionally, update the device hazard analysis to address the potential risks associated with delayed application and use of the device after assembly. This would assess the functionality of the device if a patient were to assemble but not immediately apply the patch.

To facilitate our review of the Zelrix Iontophoretic Transdermal System, we request the following:

- 5 samples of the product in the intended commercial packaging configuration
- 5 samples of each stability storage configuration including reservoir and salt cards, co-packaged in clinical packaging, co-packaged in commercial packaging, and adhesive coated materials stability with co-packaged product in commercial packaging.

BIOPHARMACEUTICS

We recommend that you submit within the first 3 months of the review cycle in-vitro release data to justify the proposed in-vitro release specification.

DEVICE

The drug imbibed patches that are intended to be placed over the electrode are larger than the conductive area of the electrode. Please perform a dispersion test, or equivalent, to demonstrate that the current is evenly distributed over the conductive area of the electrode and the drug imbibed patches, and ensure that an area of unintended focal current does not occur and harm the patient when the device is in use.

According to Table 1 of ANSI/AAMI/ISO 10993-1; *Biological evaluation of medical devices- Part 1: Evaluation and testing*, your device is considered a surface device with limited contact duration to the skin. As such, all patient contacting components/materials should be evaluated for the following biological effects; cytotoxicity, sensitization, and irritation or intracutaneous reactivity. You have provided only the biocompatibility test report for cytotoxicity (per ISO 10993-5: 1999) in section 4.2.3.7.7 of the submission. Please conduct and provide the sensitization and irritation or intracutaneous reactivity evaluations per the respective ISO standards for all patient contacting device components/materials.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult our division. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We note that you have submitted a Proposed Pediatric Development Plan, but no formal request for a waiver or deferral of pediatric studies. Our understanding is that you are seeking to obtain a partial deferral of pediatric studies for patients ages 6-17 years, and a partial waiver of pediatric studies for patients ages 0-5 years. Please submit a formal request for partial waiver and/or partial deferral of pediatric studies.

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

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/s/

ERIC P BASTINGS

01/10/2011

Signed for Dr. Katz