

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206099Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 206099
Product Name: Onzetra XSAIL (sumatriptan)

PMR/PMC Description: PMR 3025-1: Conduct a pediatric study under the Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety, including sparse pharmacokinetic (PK) sampling, of Onzetra Xsail (sumatriptan) for the acute treatment of migraine in pediatric patients of ages 12 to 17 years.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>September 2016</u>
	Study/Trial Completion:	<u>November 2019</u>
	Final Report Submission:	<u>June 2020</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Deferred pediatric PREA study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Deferred pediatric PREA study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a pediatric study under the Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety, including sparse pharmacokinetic (PK) sampling, of Onzetra Xsail (sumatriptan) for the acute treatment of migraine in pediatric patients of ages 12 to 17 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
PREA clinical study
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Deferred pediatric PREA study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a pediatric study under the Pediatric Research Equity Act (PREA) for the efficacy and safety of Onzetra Xsail (sumatriptan), including sparse pharmacokinetic sampling, for the acute treatment of migraine in pediatric patients ages 6 to 11 years. Conduct this study after its practicality has been determined based on the review of additional safety and efficacy data from the study of older children of ages 12 to 17 years under PMR 3025-1.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
PREA clinical study
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

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- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

SALLY U YASUDA
01/21/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 22, 2015
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 206099
Product Name and Strength: Onzetra Xsail (sumatriptan) nasal powder
11 mg
Submission Date: December 14, 2015
Applicant/Sponsor Name: Avanir Pharmaceuticals
OSE RCM #: 2015-315-2
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products requested that we review the revised container labels and carton labeling and Instructions for Use for Onzetra Xsail (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container label and carton labeling and Instructions for Use for Onzetra Xsail are acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Harris J. Review of Revised Label and Labeling Review for ONZETRA XSAIL (NDA 206099). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 DEC 02. 14 p. OSE RCM No.: 2015-315-1.

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/s/

JUSTINE HARRIS
12/22/2015

DANIELLE M HARRIS
12/22/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 2, 2015
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 206099
Product Name and Strength: Onzetra Xsail (sumatriptan) nasal powder
11 mg
Submission Date: October 27, 2015
Applicant/Sponsor Name: Avanir Pharmaceuticals
OSE RCM #: 2015-315-1
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products requested that we review the revised container label and carton labeling and Instructions for Use (IFU) for Onzetra Xsail (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹ The sponsor stated that they would submit proposed prescribing information under a separate amendment once final language is agreed upon between the Agency and Avanir. In addition, the instructional video is not included in this submission and therefore, is not reviewed. The sponsor states that the instructional video will be revised to incorporate our previous recommendations prior to its use and will be submitted in the annual report.

We note on September 22, 2015, Avanir submitted an amendment to request proprietary name review to include the device related modifier Xsail in the proprietary name, i.e. Onzetra Xsail.

~~We found the name Onzetra Xsail conditionally approved in OSE review No. 2015-1595257~~

¹ Harris, J. Label and Labeling and Human Factors Results Review for Onzetra (NDA206099). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 18. 23 p. OSE RCM No.: 2015-315.

dated, October 22, 2015. Subsequently, the sponsor has revised label and labeling to include the approved proprietary name 'Onzetra Xsail.'

2 CONCLUSION

The revised container label and carton labeling and Instructions for Use for Onzetra Xsail are unacceptable from a medication error perspective. Our previous recommendations have been partially implemented and therefore, we provide recommendations to Avanir Pharmaceuticals in Section 3. We advise they are implemented prior to approval of the NDA. The changes to the IFU do not require validation in another human factors study.

3 RECOMMENDATIONS FOR AVANIR PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

A. Device Label (Trade and Sample)

1. Revise the label to read:

Onzetra Xsail
(sumatriptan nasal powder)
For use only with Onzetra Xsail nosepieces

B. Pouch (for nosepieces) Labeling (Trade and Sample)

(b) (4)

C. Carton Labeling (Trade)

1. We note that you have included the statement "For use with the Xsail intranasal device only" and placed the statement on the side panel. Relocate this statement to the principle display panel to ensure that this important information is not overlooked.

D. Carton Labeling (Sample)

1. See C.1 above
2. For consistency with the trade carton labeling, relocate the NDC number to the upper right corner of the principal display panel.

E. Instructions for Use (Trade and Sample)

1. We note that you have included the statement "Discard used nosepiece in the trash" in Step 5; however, this information is not stated in the Storage and Care section.

For consistency and to ensure that the nosepiece is properly disposed after use, include this statement in the first bullet of the Storage and Care section of the IFU.

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/s/

JUSTINE HARRIS
12/02/2015

DANIELLE M HARRIS
12/02/2015

LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: September 18, 2015
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 206099
Product Name and Strength: Onzetra (sumatriptan) nasal powder
11 mg
Product Type: Drug-Device Combination Product
Rx or OTC: Rx
Applicant/Sponsor Name: Avanir Pharmaceuticals
Submission Date: May 6, 2015
OSE RCM #: 2015-315
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Team Leader: Danielle Harris, PharmD, BCPS
DMEPA Associate Director: Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Neurology Products (DNP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the submitted results from a Human Factors summative study, labels and labeling, and an instructional video to determine whether the intended population will be able to use the product safely and effectively as intended with the marketed materials.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Human Factors and Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E –N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Onzetra (Sumatriptan Nasal Powder) with Xsail breath powered delivery device is a drug-device combination product. This product is intended for patient self-administration of a powdered form of sumatriptan for treatment of migraine. DMEPA previously reviewed the results of a prior summative human factor study¹ for this product, which was determined to be a failed study. In our previous review, we noted the following deficiencies:

- participants were not able to identify whether capsules were pierced or unpierced, which could result in incomplete treatment doses

¹ Sheppard, J. Label and Labeling Humans Factor Review for Onzetra NDA 206099. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 OCT 23. RCM No.: 2014-315 and 2014-1953

- failure to administer drug to the second nostril, which could result in underdose
- administration of more than two nosepieces per dose, which could result in overdose
- failure to perform administration steps in the correct sequence

The Agency provided a Complete Response Letter citing concerns regarding the results from the human factors validation study. Thus, the Applicant conducted a revised use-error risk analysis, two formative studies evaluating the IFU, a nosepiece sorting evaluation and a pre-summative study prior to conducting another human factors summative study, the results of which are reviewed herein. The applicant implemented several risk mitigation strategies prior to conducting the final study, including streamlining of information, improving clarity of text and graphics, and highlighting critical steps more prone to errors in the Instructions for Use (IFU). Additionally, the Applicant made two modifications to the proposed (IFU) related to capsule piercing. The first modification was to step 5 to include instruction to check the capsule to see if the medication is gone following the use of each nosepiece, i.e., the “check step”. This “check step” is intended to allow users to determine whether the capsules have been pierced and correctly used to deliver the dose. The second modification was to move the instruction about checking for powder residue to confirm piercing of the capsule and delivery of medicine so it is the first reminder listed in the “Did I Do it Right” section of the IFU. Graphics were added to illustrate the appearance of a used capsule versus an unused capsule. Reminders to administer the product in both nostrils with two nosepieces for a complete dose were also added.

Human Factors Summative Study Assessment

We evaluated the new summative human factors validation study (AVA.2015.BRZ.502) submitted on May 5, 2015. Fifteen participants who were clinically diagnosed as having acute migraines and who were currently on a prescription medication treatment regimen for migraines were enrolled in the study. Participants were not trained but were provided a self-familiarization period to review the materials, including the IFU and device, on their own if they wished, but they were not required to. The participants were then observed completing all tasks in the IFU independently for two doses separated by a distracter break.

Fourteen out of 15 users carried out two successful dose simulations and one user delivered a partial dose during the first simulation and a full dose during the second simulation, corresponding to 29 (out of 30) successful dose administrations.

There was one failure reported where a participant administered only a partial dose during one of the simulations (Dose #1). The Applicant notes that this participant (P15) was extremely nervous during the simulation, had minor dexterity limitations and a significant hearing deficiency, which may have contributed to her difficulty with task performance. This participant was primarily confused by the picture and instructions in Step 3 of the IFU (See

Appendix C for details). According to the Applicant, the intent of the Step 3 instruction is for the user to create a seal in the nose by inserting first the nosepiece into the nose and then rotating the device such that the mouthpiece is placed in the mouth for exhalation. However, the IFU reads (b) (4) which is misleading (b) (4)

(b) (4). Although the applicant does not propose further mitigation to address this failure, we recommend that the IFU be revised to state “rotate the device” to improve clarity of the instruction. Furthermore, although not used during the validation study, we note that in the instructional video, the term (b) (4) is used, which also may be misleading and should be revised accordingly.

There were five close calls in task performance during the study. The step in which participants committed the most close calls (4/5) was with the “Press and release the white button” task to pierce the medication capsule. The Applicant states that the root causes of these close calls were a temporary “lapse” during the operational sequence, a participant who hurried through the steps, and nervousness which resulted in participant’s confusion. The Applicant notes that previous studies had revealed this step to be more prone to error prompting revision to the IFU prior to this study. Those mitigation strategies included the addition of the red warning box to mitigate against users not pressing the white button and the addition of a “check step” to assess whether the capsule in the nosepiece had been pierced. Despite the 4 close calls on this step, in all 4 cases, the participants identified that the medication had not been delivered after performing the “check step”, self-corrected, and ultimately administered the full dose without moderator intervention. The applicant concluded that the “check step” resulted in an effective rescue step for the participants that experienced a lapse related to pressing the white button. We agree with this conclusion and do not recommend further revision.

The remaining close call was with Step 6 “Blow with your mouth into the device for 2 -3 seconds”, where the participant (P15) first sucked in on the mouthpiece while pressing the white button. This behavior may have been due to negative transfer since the participant was currently using an albuterol inhaler. The participant recognized her mistake, self-corrected and administered a full dose. The IFU contains clear information on this step and therefore, we do not recommend revisions.

Two unanticipated behaviors were observed (the same participant in Dose #1 and Dose #2 simulation) involved IFU step (b) (4) “Check the capsule to see if the medication is gone”. The participant, when checking the nosepiece after using the device, looked into the top screen in the nosepiece rather than at the capsule at the bottom of the nosepiece to determine if the capsule had been pierced. The participant re-reviewed the IFU on his own and noted that it would have been easier to look into the capsule and not through the screen. The Applicant asserts that looking through the screen, although more difficult, does allow for visualization of the capsule. The IFU contains clear information on this step and therefore, we do not recommend revisions. A second unanticipated behavior observed was a participant who held down one of her nostrils as she was carrying out the second dose but immediately corrected

her behavior during the simulation without moderator intervention. We do not recommend revisions to the IFU based on this unanticipated behavior.

Despite the close calls reported in the study, most participants (14/15) delivered two complete doses and 1 participant delivered 1 partial dose and 1 full dose. The Applicant believes that the study results validated the effectiveness of the added “check step” in preventing participants from moving onto the next step until a full dose had been properly administered, thus, they do not recommend any further mitigation strategies. There were no other use errors reported by the Applicant and they report that no participants overdosed.

Labels and Labeling Assessment

We reviewed the IFU, carton and pouch labeling, device label and instructional video for the proposed Onzetra product to determine whether there are any significant concerns that could result in misuse of the product and/or medication errors that may not have been identified during the human factors testing. Our review of the proposed labels and labeling identified areas that can be improved to increase the readability and prominence of important information, to promote the safe and correct use of the product, to mitigate any confusion, and to clarify information. We do not believe these changes to the user interface require validation in another human factors study.

4 CONCLUSION & RECOMMENDATIONS

We find the results from the Human Factors summative study acceptable.

Additional revisions to the IFU, other labels and labeling and instructional video for Onzetra can be made in order to further clarify and simplify the use of the product. We provide recommendations in Section 4.1 for the Division and recommendations to Avanir Pharmaceuticals in Section 4.2 and advise they are implemented prior to approval of the NDA. The changes to the IFU do not require validation in another human factors study.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescriber Information

1. In section 2 *Dosage and Administration*, we note the statement (b) (4)
(b) (4). To avoid confusion, consider revising the statement to “Keeping the nosepiece in the nose, the device is rotated to place the mouthpiece into the mouth”.
2. In Section 17 *Patient Counseling Information*, we note that there is a placeholder (1-xxx-xxx-xxx) for a phone number that healthcare professionals and patients can call for support. The sponsor should provide this number to be included in the PI. In

addition, consider revising the statement, (b) (4)
(b) (4) to read “The device is then rotated and the mouthpiece inserted between the lips” since the mouthpiece is fixed.

3. In the *Patient Information* section we note that there is a placeholder (1-888-xxx-xxx) for a phone number that patients can call for more information. The sponsor should provide this number.

4.2 RECOMMENDATIONS FOR THE AVANIR PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA. The changes do not require validation in another human factors study.

A. Device Label (Trade and Sample)

1. We note that the device label contains the proprietary name and established name with dosage strength. Since the device does not contain medication we recommend the label be revised to read:

Xsail Breath Powered Delivery Device
For use with Onzetra (sumatriptan nasal powder)

B. Pouch (for nosepieces) Labeling (Trade and Sample)



C. Carton Labeling (Trade)

1. We note that the proprietary name and established name lack prominence and the picture of the device and the statement “The breath-powered intranasal migraine medication delivery system” occupy over half of the principal display panel (PDP). Thus, we request that you increase the prominence of the proprietary name and established name by increasing the font size and change the placement to the upper part of the PDP. Additionally, decrease the prominence of the statement “The breath-powered intranasal migraine medication delivery system” so it does not compete in prominence with that of the proprietary name, established name, and strength. Also, include the statement “For use with the Xsail intranasal device only”. Consider decreasing the size of the picture of the device to accommodate.
2. As currently presented, the NDC number is located at the bottom of the carton labeling. Since the NDC number is often used as an additional verification prior to dispensing, it is an important safety feature that should be displayed in the top third of the PDP of the labeling in accordance with 21 CFR 207.35(3)(i).
3. Above the graphic of the nosepieces, revise the statement “Use two for every dose” to read “1 dose = 2 nosepieces”
4. See B.4, B.5 and B.6 above

D. Carton Labeling (Sample)

1. Decrease the prominence of the statement “The breath-powered intranasal migraine medication delivery system” so it does not compete in prominence with that of the proprietary name, established name, and strength. Also, include the statement “For use with the Xsail intranasal device only”. Consider decreasing the size of the picture of the device to accommodate.
2. Add the usual dose statement to the sample carton labeling
3. See B.4, B.5 and B.6 above

E. Instructions for Use

1. Step 3 states to [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (b) (4) To avoid confusion, revise the statement to read
“Insert the nosepiece deeply into your nose. Keep the nosepiece in your nose while you rotate the device to place the mouthpiece into your mouth”
2. Step 5 states to “Discard the used nosepiece”, and the Storage [REDACTED] (b) (4) section states [REDACTED] (b) (4) but does not indicate where to throw away the nosepiece. If the used nosepiece is to be disposed of in the household trash or disposed by some other means, this needs to be stated.

E. Instructional Video

1. [REDACTED] (b) (4) To avoid misinterpretation we recommend that the instructional video be revised to state the “device must be rotated”.
2. The “Check Step” is not presented in the video. As this is important information for patients to verify that a complete dose has been administered, this instruction should be included in the video.
3. There are graphic and verbal instructions to remove two nosepieces contained in individual pouches. The current packaging configuration has one pouch containing 2 nosepieces, therefore revise the video to reflect the commercial packaging configuration and to avoid confusion with dosing.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Onzetra that Avanir Pharmaceuticals submitted on May 6, 2015.

Table 2. Relevant Product Information for Sumatriptan Nasal Powder	
Initial Approval Date	N/A
Active Ingredient	Sumatriptan
Indication	Acute migraine with or without aura
Route of Administration	Intranasal
Dosage Form	Nasal powder
Strength	11 mg Sumatriptan base per nosepiece
Dose and Frequency	Two nosepieces (each 11 mg) for a total of a 22 mg dose. 11 mg is delivered nasally into each nostril via the delivery technology at the first sign of a migraine; if a second dose is needed it can be repeated after 2 hours. Not to exceed more than 44 mg in a 24 hour period.
How Supplied	<p>Commercial Available in kits containing 8 doses.</p> <ul style="list-style-type: none"> • Each kit contains 8 pouches containing two one-time use nosepieces per pouch (each nosepiece contains 11 mg sumatriptan, equivalent to 15.4 mg of sumatriptan succinate) • 2 Xsail reusable devices <p>Professional Sample Each carton contains:</p> <div style="background-color: #cccccc; height: 60px; width: 100%; margin: 5px 0;"></div> <p>Each nosepiece contains a medication capsule</p>
Storage	Store at room temperature between 20° C to 25° C (68° F to 77° F), with excursions permitted between 15° C to 30° C (59° F to 86° F). Do not store in the refrigerator or freezer. Use nosepiece immediately after removing from foil pouch.
Container Closure	Capsule-containing powder in a nosepiece which is packaged in a foil (b) (4) pouch

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 14, 2015, we searched the L:drive using the terms, sumatriptan and Onzetra to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified six previous reviews^{2 3 4 5 6 7}, four proprietary name reviews and two label and labeling and human factors reviews. We confirmed that most of our previous recommendations were implemented, with the exception of changing the dosage strength from 22 mg to 11 mg on all labels and labeling to reflect current dose presentation. However, this revision has been made for this submission.

² Myers, D. Proprietary Name Review for Onzetra NDA 206099. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 13. RCM No. 2015-546766

³ Harris, J. Revised Human Factor Protocol Review Memo for Onzetra NDA 206099. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAY 04. RCM No.: 2015-509

⁴ Sheppard, J. Label and Labeling Humans Factor Review for Onzetra NDA 206099. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 OCT 23. RCM No.: 2014-315 and 2014-1953

⁵ Sheppard, J. Proprietary Name Review for Onzetra NDA 206099. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JUL 14. RCM No. 2014-17318

⁶ Sheppard, J. Proprietary Name Review for (b) (4) NDA 206099. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 MAR 04. RCM No. 2014-16850

⁷ Sheppard, J. Proprietary Name Review Memo for Onzetra NDA 206099. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 SEP 25. RCM No. 2014-17318-01

APPENDIX C. HUMAN FACTORS STUDY

We evaluated the Human Factor Study Results for the summative study submitted on May 6, 2015. This study was conducted as a follow-up summative study after the results of the first summative study were found to be inadequate to support the safe use of the device. Below is a brief overview of the study objectives, descriptions of study participants, study design, data collection, and data analysis.

C.1 Study Design

Study Objective

The study was focused on validating that the design improvements implemented in the IFU and packaging were effective in mitigating user errors and to validate that the product can be used safely and effectively by the intended target user group. In addition, the study assessed the effectiveness of the step where users were prompted to inspect the capsule inside the nosepiece as a means to verify if drug was fully delivered following each administration.

Study Participants

Fifteen participants who had been clinically diagnosed as having acute migraines and who are currently on a prescription medication treatment regimen for migraines were enrolled in the study. Participants had varying levels of physiological capabilities and limitations.

Training

Participants were not trained but were provided the IFU in the to-be-marketed packaging. They were provided a self-familiarization period in which they had the opportunity to review the materials and device on their own but were not required to view any of the materials. Distractor breaks were introduced to simulate the cognitive delay associated with a product like this as it is interventional-based and not maintenance-based.

Study Materials

Participants were provided intend-to-market versions of the nasal delivery system with nosepieces containing lactose placebo and packaging containing complete product labeling and the updated IFU. The applicant implemented several risk mitigation strategies prior to conducting the final study, including streamlining of information, improving clarity of text and graphics, and highlighting critical steps more prone to errors. Additionally, the Applicant made two modifications to the proposed Instructions for Use (IFU) related to capsule piercing. The first modification was the addition to step 5 of an instruction to check the capsule to see if the medication is gone following the use of each nosepiece, i.e., the “check step”. This “check step” is intended to allow users to determine whether the capsules have been pierced and correctly used to deliver the dose. The second modification was to move the instruction about checking for powder residue to confirm piercing of the capsule and delivery of medicine so it is the first reminder listed in the “Did I Do it Right” section of the IFU. Graphics were added to illustrate the appearance of a used capsule versus an unused capsule. Additional modifications

made to the IFU included the addition of reminders to administer the product in both nostrils with two nosepieces for a complete dose.

Study Workflow

Table 3. Study Workflow

Step	Description
1. Study Introduction and Informed Consent Review	Moderator provided the study introduction and reviewed the informed consent material with the participant. Moderator answered any questions and ensured that the participant had been clinically diagnosed with migraine headaches.
2. IFU Familiarization	Moderator brought the participant into the simulated living environment and reminded the participant of the study intent emphasizing that the study moderator would not be able to provide any help during the study. The moderator provided a scenario to the participant that he/she had just received a prescription from the doctor and had picked it up from the pharmacy. The moderator left the participant alone after asking the participant to do whatever he/she would do in a real situation after picking up a new prescription from the pharmacy to treat their migraines.
3. Distractor Break	Moderator administered various assessments during a distractor break that included the following assessments: Near Visual Acuity ¹ Test and Cochlin Hand Function Scale ² . This was done to simulate the time lapse between receiving the prescription and actually using the device for the first time.
4. Dose Simulation 1	Participants returned to the simulation area for the first dose simulation. They were asked to imagine they were feeling the onset of an acute migraine and in order to relieve the pain, they needed to deliver a full dose using this new device. The moderator indicated that participants could use any of the materials to carry out the simulation. The moderator remained in the room during the simulation to ensure study safety and to better visualize the user steps for data integrity. A study staff observer also viewed from a remote viewing room and noted administration performance. Once the participant indicated they completed the simulation, the moderator asked the participant how he/she knew the dose had been fully administered. The moderator asked no further questions. The participant was then led back to the “break room” to carry out two additional distractor tasks. At no point in the study, did the moderator point out that these tasks were in fact distractor tasks meant to prevent rehearsal of information.
5. Distractor Break	Participants were administered Self-Hearing Assessment ³ and Health Assessment Questionnaire ⁴ during this distractor break.
6. Dose Simulation 2	After the required time elapsed, participants were led back to the simulation area for simulation 2. Participants were asked to re-imagine they were feeling the onset of an acute migraine and in order to relieve the pain they needed to deliver a full dose. Once the participant indicated they had administered the full dose, the moderator asked how the participant knew the dose had been fully administered.
7. Root cause investigation	Following the second simulation, the moderator asked the participant how well they thought they had performed during each simulation. If the participant recalled use errors on his or her own, the moderator probed as to why the use error occurred. If a participant, for instance, indicated, “forgetting,” the moderator probed further as to why steps may have been forgotten. Once the participant has provided their own use error recollections, the moderator walked through any remaining use errors noted during the simulation to better understand what the root cause behind those use errors may have been.
8. Post session interview and debrief	Some aspects of device use may not be effectively evaluated through observation of performance during simulated use. Therefore, the moderator asked a few post-session interview questions (See Section 9.4) in order to evaluate whether participants understand all critical and essential aspects of device use.

Tasks

Each participant performed two full simulated dose administrations separated by a period of distractor activities. Following the administration of the two doses, each participant was individually interviewed to obtain subjective data not readily observed during the dose simulations.

Definitions of critical and essential tasks:

1. critical task – one in which the result affects the patient or user safety, which in this case is tasks that could result in an under or overdose as defined within the user FMEA.
2. Essential Task – associated with ensuring an effective outcome of the device

Performance Scoring

During completion of the tasks, participant performance on critical and essential user tasks were classified into two main categories:

- a) successful performance of the task
- b) close call – participant almost committed a user error but self-corrected without moderator direction, and
- c) failure to complete the task or failure to perform the task correctly.

Results

Successful performance:

Failures:(1/15 participants)

There was one failure reported where a participant administered only a partial dose during one of the simulations (Dose #1). Rather than press the button and release to pierce the capsule, the participant continued to hold the button while blowing into the mouthpiece which resulted in a partial dose. When questioned by the moderator during the post-test assessment, the participant stated that she was nervous and was confused by the picture and instructions in Step 3 of the IFU. According to the Applicant, the intent of the Step 3 instruction is for the user to create a seal in the nose by inserting first the nosepiece into the nose and then rotating the device such that the mouthpiece is placed in the mouth for exhalation. Of note, the Applicant stated this participant had minor dexterity limitations and significant hearing handicap which may have contributed to her level having difficulty with the task sequence.

Close Calls:

There were five close calls in task performance during the study. The step in which participants committed the most close calls (4/5) was with the “Press and release the white button” task to pierce the medication capsule. The Applicant states that the root causes of these close calls were a temporary “lapse” during the operational sequence, a participant who hurried through the steps, and nervousness which resulted in participant’s confusion. The Applicant notes that previous studies had revealed this step to be more prone to error prompting revision to the IFU prior to this study. Those mitigation strategies included the addition of the red warning box to mitigate against users not pressing the white button and the addition of a “check step” to assess whether the capsule in the nosepiece had been pierced. Despite the 4 close calls on this step, in all 4 cases, the participants identified that the medication had not been delivered after

performing the “check step”, self-corrected, and ultimately administered the full dose without moderator intervention. The applicant concluded that the “check step” resulted in an effective rescue step for the participants that experienced a lapse related to pressing the white button.

The remaining close call was with Step ^(b)₍₄₎ “Blow with your mouth into the device for 2 -3 seconds”, where the participant first sucked in on the mouthpiece while pressing the white button. According to the Applicant, this behavior may have been due to negative transfer since the participant was currently using an albuterol inhaler. The participant recognized her mistake, self-corrected and administered a full dose.

Unanticipated Behaviors: (2/15 participants; both resulted in complete dose)

Two unanticipated behaviors were observed (the same participant in Dose #1 and Dose #2 simulation) involved IFU step ^(b)₍₄₎ “Check the capsule to see if the medication is gone”. The participant, when checking the nosepiece after using the device, looked into the top screen in the nosepiece rather than at the capsule at the bottom of the nosepiece to determine if the capsule had been pierced. The participant re-reviewed the IFU on his own and noted that it would have been easier to look into the capsule and not through the screen. The Applicant asserts that looking through the screen, although more difficult, does allow for visualization of the capsule. A second unanticipated behavior was a participant who held down one of her nostrils as she was carrying out the second dose but immediately corrected her behavior during the simulation without moderator intervention.

Pass	Close Call	Failure
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Table 4. Task Performance - Dose Administration #1

Instruction Step	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15
1. Remove Device Body from packaging.															
2. Open the pouch and remove a nosepiece.															
3. Remove device cover. Insert nosepiece into the device body until...															
4. Press and Release the white button to pierce the medication capsule														E4.1	E4.4 E4.6 UE2
5. Insert the nosepiece deeply into your nose and rotate the 'mouthpiece ...															
6. Blow with your mouth into the device for 2-3 seconds...															
7. Check the capsule to see if the medication is gone.				E7.2											
8. Insert second nosepiece into device.															
9. Don't forget to pierce the capsule in the second nosepiece.															
10. Use on opposite nostril. Repeat steps in 2 nd nostril.															
Dose Delivery	Full	Partial													

Table 5. Task Performance - Dose Administration #2

Instruction Step	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15
1. Remove Device Body from packaging.															
2. Open the pouch and remove a nosepiece.															
3. Remove device cover. Insert nosepiece into the device body until...															
4. Press and Release the white button to pierce the medication capsule								E4.1					E4.1		E4.4 E4.6 UE2
5. Insert the nosepiece deeply into your nose and rotate the 'mouthpiece ...								UE1							
6. Blow with your mouth into the device for 2-3 seconds...															E6.3
7. Check the capsule to see if the medication is gone.				E7.2											
8. Insert second nosepiece into device.															
9. Don't forget to pierce the capsule in the second nosepiece.															
10. Use on opposite nostril. Repeat steps in 2 nd nostril.															
Dose Delivery	Full														

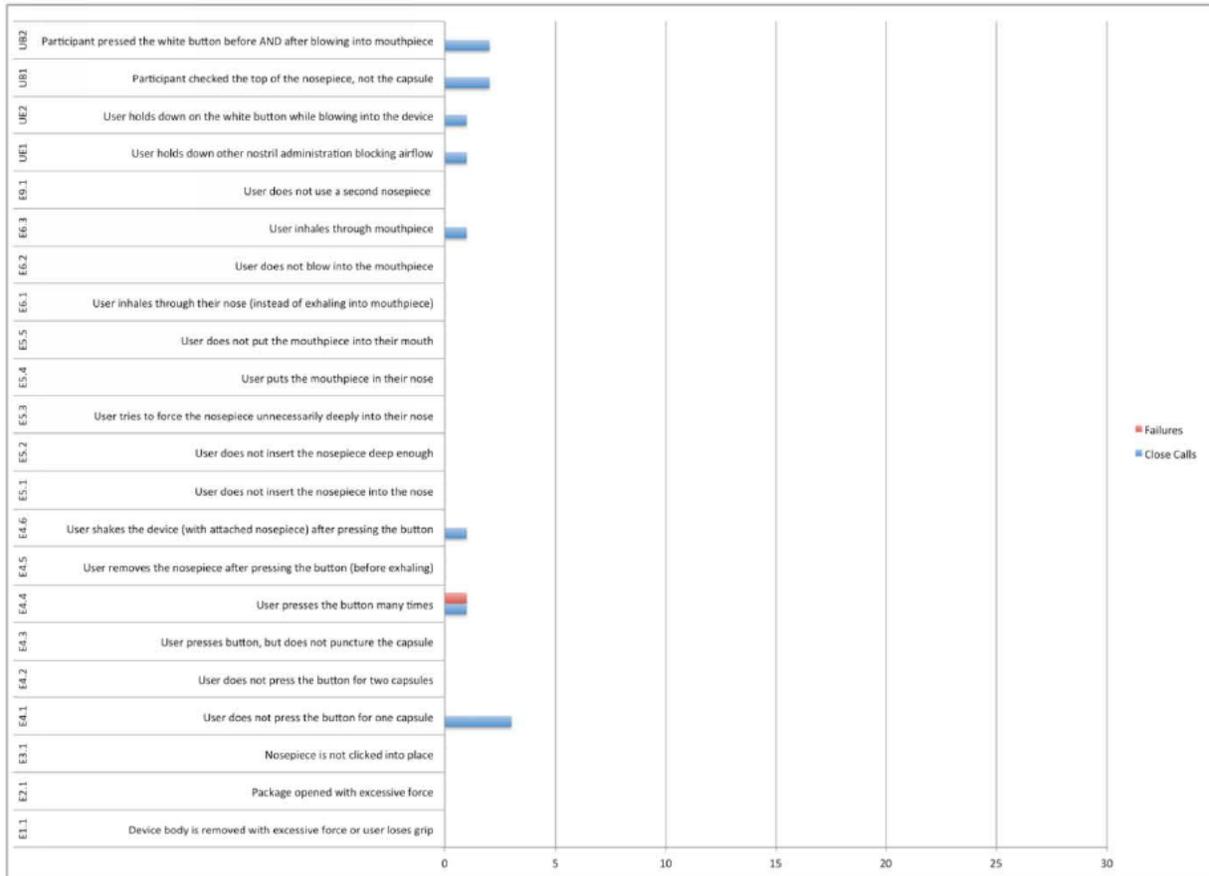


Figure 7. User Error Summary Graph

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/s/

JUSTINE HARRIS
09/18/2015

DANIELLE M HARRIS
09/18/2015

IRENE Z CHAN
09/23/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 24, 2015

To: Kellie Taylor, PharmD, MPH
Acting Director
**Division of Medication Error Prevention and Analysis
(DMEPA)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): ONZENTRA (sumatriptan nasal powder)

Dosage Form and Route: Xsail breath powdered delivery

Application Type/Number: NDA 206099

Applicant: Avanir

1 INTRODUCTION

On February 4, 2015, Avanir submitted to the Agency a Preliminary Response and Request for FDA Review of the Human Factors Usability Validation Study Protocol for AVP-825, ONZENTRA (Sumatriptan Nasal Powder), 22 mg in the Xsail Breath Powered Delivery. AVP-825, ONZENTRA (sumatriptan nasal powder) proposes an indication for the treatment of migraine with or without aura.

Reference is made to the initial application submitted on January 27, 2014, the Agency's Discipline Review Letter dated October 29, 2014, as well as the Complete Response Letter dated November 26, 2014, in which the the Division of Medication Error Prevention and Analysis (DMEPA) cited concerns with observations from the human factors validation study to support the safety and efficacy of the AVP-825 product-user interface. This submission included a proposed updated IFU labeling incorporating modifications to mitigate the previous use errors.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Medication Error Prevention and Analysis (DMEPA) on April 9, 2015, for DMPP to review the Applicant's proposed Instructions for Use (IFU) ONZENTRA (Sumatriptan Nasal Powder), 22 mg in the Xsail Breath Powered Delivery, that will be used for the Applicant's HFE usability study.

2 MATERIAL REVIEWED

- Draft AVP-825, ONZENTRA (Sumatriptan Nasal Powder), 22 mg in the Xsail Breath Powered Delivery IFU received on February 5, 2015, and received by DMPP on April 20, 2015.
- Avanir Response to the Agency's April 14, 2014, e-mail request for information dated April 18, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the IFUs using the Arial font, size 11.

In our review of the IFU we have:

- simplified wording and clarified concepts where possible

- removed unnecessary or redundant information
- ensured that the IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes for use in the Applicant's HFE usability study.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the IFU is appended to this memorandum. Consult DMPP regarding additional changes to the IFU to be used in the HFE usability study.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
04/24/2015

MELISSA I HULETT
04/24/2015

LASHAWN M GRIFFITHS
04/24/2015



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Review

*** This document contains proprietary information that cannot be released to the public***

DATE: October 14, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Nushin Todd, Medical Officer, CDER/OND/ODEI/DNP
Vandna Kishore, Regulator Project Manager, CDER/OND/ODEI/DNP

SUBJECT: **NDA 206099**
Applicant: Avanir Pharm
Drug: (b) (4) Xsail
Device: Nasal powder inhaler
Intended Use: migraine
CDRH CTS Tracking No. 1400080

Digitally signed by Quynhnhu T. Nguyen -S
Date: 2014.10.15 16:08:56 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist
(Human Factors Premarket Evaluation Team - HFPMET)

Ronald D. Kaye -S

Digitally signed by Ronald D. Kaye -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Ronald D. Kaye -S,
0.9.2342.19200300.100.1.1=1300110677
Date: 2014.10.15 16:25:59 -04'00'

Ron Kaye, Human Factors and Device Use-Safety Team Leader (HFPMET)

CDRH Human Factors Review

Overview and Recommendation

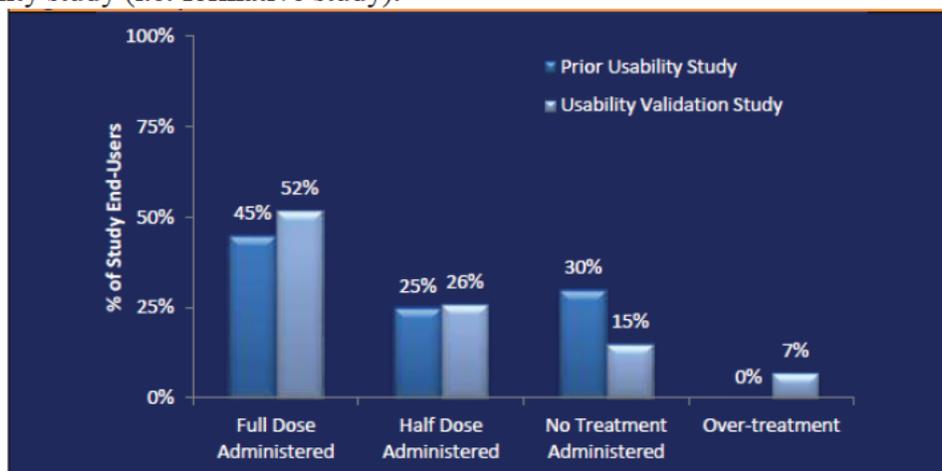
The Division of Neurology Products, Office of New Drugs, Center for Drug Evaluation and Research requested a Human Factors consultative review human factors validation study report submitted under NDA 206099 by Avanir Pharm, for the (b) (4) sumatriptan nasal powder inhaler to treat migraine.

The human factors validation study included a total of 27 adult study participants with a history of migraine headaches, age 18 to 70 years old (inclusive). The study participants represented the intended user population. The study was designed to evaluate performance of tasks required for typical use to administer a full dose, consisting of two administrations, one to each nostril.

There were 12 use errors, 2 unanticipated use errors, and 3 close calls. The study results show that participants do not understand what constitutes a full dose. Of the 27 participants, there were 14 participants who were able to successfully complete the delivery of a full treatment dose i.e. two administrations, one to each nostril. Of the 13 participants that did not deliver a full treatment dose, 7 participants were able to administer one nosepiece to one nostril, 4 participants failed to simulate administering any treatment. Of these, one (1) did not pierce the capsule of either of the two nosepieces; two (2) blew into the device and then pierced the drug capsule; and one (1) kept the button depressed while blowing into the device during the delivery step. The remaining 2 participants used more than two nosepieces to simulate administration of a total dose. One of these end-users used three (3) nosepieces despite understanding that the correct dose was two (2) nosepieces, and the other used four (4) nosepieces.

Based on the follow up and feedback obtained from study participants, the root-causes for task included confusions or misinterpretation of the Instructions for Use (IFU) that were associated with failure to understand the requirement to blow into the device to administer the medication, the lack of knowledge that two nosepieces (one for each nostril) are required to achieve a full dose of medication, and participants unable to pierce a nosepiece drug capsule.

The following Figure shows the comparison for the results between the validation study and the prior usability study (i.e. formative study).



Recommendation: As shown above, the validation study results continue to show pattern of use errors that were previously observed in the prior usability study indicating that the modifications are not effective in addressing the problems. This human factors reviewer believes that the IFU and training should be further enhanced to address these observed issues, and that additional validation is necessary to demonstrate the effectiveness of the enhancements. This reviewer would like to communicate the following deficiency to the Sponsor:

We do not find the validations study results supported the conclusion that representative users can use your device safely and effectively. It was evident that a relatively high number of study participants did not deliver a full treatment dose resulting in underdosing. Furthermore, two participants experienced use errors that resulted in overdosing. In addition, the results showed that the modifications made to the IFU and packaging prior to the validation study were effective for reducing use-errors because the validation study results continue to show pattern of use errors that were previously observed in the prior usability study. We believe that the device user interface (including IFU and training) should be further enhanced to address these observed issues, and that additional validation with at least 15 representative users is necessary to demonstrate the effectiveness of the enhancements.

CDRH Human Factors Review

Combination Product Device Information

Submission No.: NDA 206099

Applicant: Avanir Pharm

Drug: (b)(4) Xsail

Device: Nasal powder inhaler

Intended Use: migraine

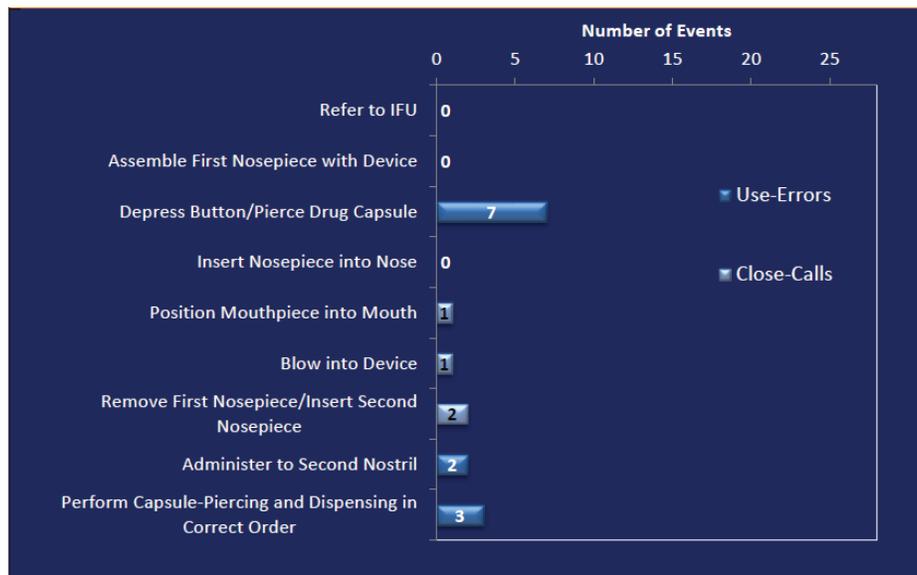
CDRH Human Factors Involvement History

- 1/31/2014: CDRH HFPMET was consulted to review human factors validation study report available at: EDR Location: <\\CDSESUB1\evsprod\NDA206099\206099.enx>
- 10/14/2014: CDRH HFPMET provided review recommendations to CDER/DMIP.

Summary of Human Factors Related Information

The human factors validation study included a total of twenty-seven (27) adult study participants with a history of migraine headaches, age 18 to 70 years old (inclusive). The study participants represented the intended user population and the range in education, literacy, cognition, visual acuity, and physical dexterity levels expected in the general United States population. The study was designed to evaluate performance of tasks required for typical use to administer a full dose, consisting of two administrations, one to each nostril.

All twenty-seven (27) participants chose to use the product IFU, without prompting, in order to obtain information on how to use the device during their use-scenarios; three (3) of the 27 relied on the IFU and web video equally. The following Figure shows the number of use errors and close calls by tasks.



Detailed Discussion and Analysis of Use Errors and Close Calls:

Use Errors

- 1 participant did not press the button after inserting either of the two nosepieces prior to simulating administration. This participant understood that she needed to press the button but said she didn't because she knew there was no medication in the nosepieces.
- 5 participants pressed the button on the first nosepiece for the first administration but did not press the button after inserting the second nosepiece for the second administration. 3/5 indicated that they had to but just forgot. 1/5 reported that she didn't see to press the button for the second nosepiece in the IFU. 1/5 stated that he misunderstood the information in the IFU at first and thought he had made a mistake by pressing the button for the first nosepiece so he didn't press it for the second nosepiece.
- 1 participant did not release the button before stimulating administration to both nostrils. He thought that he was supposed to press while blowing.
- 1 participant only administered to one nostril using one nosepiece. She stated that she overlooked the information in the IFU.
- 1 participant administered two doses into the first nostril. She did not know she had to administer to both nostrils but dispensed a second dose to the first nostril because she wanted to try using the product again.
- 1 participant used the correct sequence for the first nosepiece but during simulated administration of the second nosepiece blew into the device and then pressed the button. He indicated that he forgot the instructions for the second administration.
- 2 participants blew into the device and then pressed the button when simulating use of both nosepieces. They believed the IFU indicated for them to blow first and then press the button.

Unanticipated Use Errors

- 1 participant used four nosepieces to simulate administration of a treatment dose. He misinterpreted that the (b) (4) on the last page of the IFU meant he had to administer to both nostrils a second time.
- 1 participant used three nosepieces during the use task. She was aware that the correct dose was 2 nosepieces, but did not feel she had inserted the nosepiece deep enough when administering to the first nostril, so after administering to the second nostril she repeated dispensing to the first nostril again using a third nosepiece.

Close Calls

- 1 participant realized after looking at the picture in the IFU that she had the device backwards and corrected so that the mouthpiece was in her mouth.
- 2 participants used the first nosepiece to simulate dosing to the second nostril but indicated that they then saw in the IFU that they needed to use a second nosepiece for the second nostril. Both end-users corrected themselves by changing the nosepiece and simulating delivery to the second nostril.

Appendix 1: Device Related Information

AVP-825, also referred to as (b) (4) SUMATRIPTAN (sumatriptan delivered with the Breath Powered™ (b) (4) Nasal delivery system). This nasal delivery system is specifically designed to optimize the delivery of sumatriptan powder for nasal absorption without lung deposition.

(b) (4)

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/s/

VANDNA N KISHORE
10/28/2014

LABEL AND LABELING, HUMAN FACTORS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: October 23, 2014
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 206099
Product Name and Strength: Onzetra (Sumatriptan) Nasal Powder, 11 mg
Product Type: Combination Product (Drug-Device)
Rx or OTC: Rx
Applicant/Sponsor Name: Avanir Pharmaceuticals
Submission Date: January 27, 2014
OSE RCM #: 2014-315 and 2014-1953
DMEPA Primary Reviewer: Jacqueline Sheppard, PharmD
DMEPA Acting Team Leader: Tingting Gao, PharmD
DMEPA Associate Director: Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

Onzetra (Sumatriptan Nasal Powder) with Xsail breath powered delivery device is a drug-device combination product used for nasal delivery of a powder form of sumatriptan succinate via a proprietary breath powered delivery device.

This review responds to a request from the Division of Neurology Products to review the results of the Human Factors/Usability Study of Onzetra (Sumatriptan Nasal Powder) with Xsail Breath Powered Delivery System, NDA 206099 to ensure the intended population is able to use the product safely and effectively. This review also responds to the additional request to evaluate the container label and carton labeling for the Onzetra (Sumatriptan Nasal Powder) with Xsail Breath Powered Delivery System, NDA 206099, submitted on July 28, 2014 for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Human Factors (HF) study did not demonstrate that the Sumatriptan Nasal Powder with Xsail Breath Powered Delivery System can be used safely and effectively by patients with a history of migraine. We note the participants experienced the following errors in the validation study and accompanying labels:

General Assessment of Human Factor Study

Only Fourteen (14) users (52%) safely and effectively completed the product use process by simulating delivery of a “full treatment dose.” Seven users were unsuccessful at administering the second nosepiece. Four users failed to simulate administering any treatment. Two users used more than two nosepieces to simulate administration of a total dose. The type of errors and their clinical implications are provided in the table below.

Error	Use-Errors (n=27)	% Failure Rate	Clinical Implication
Failure to fully Depress Button/Pierce Capsule	7	26%	Failure to dose medication; may result in increased emergency room visits and treatment failures due to delays or omissions in therapy
Failure to perform piercing/dispensing in correct order	2	7.4%	
Failure to administer dose to second nostril	2	7.4%	Under-dose of medication
Administration of more than two nosepieces per dose	3	11.1%	Overdose of medication

Failure to Pierce the Capsule and Failure to Perform Piercing/Inhalation Tasks in Correct Order

Seven of the 56 capsules used by 27 participants during testing scenarios remained unpierced. Five users pressed the medication piercing button for the first nosepiece but did not press the medication piercing button after inserting the second nosepiece. One user did not release the medication piercing button before simulating administration to both nostrils. One user stated she understood she needed to push the medication piercing button to pierce the capsule but did not because she knew there was no medication in it, thus this failure was an artifact of

testing. Failure to pierce the capsule would result in patients receiving either an under-dose or not receiving the medication at all.

Additionally, four users had failures performing the piercing/inhalation tasks in the correct order to achieve effective dosing of Onzetra. One user performed the correct sequence of piercing the capsule first and then blowing into the device correctly for the first nostril but performed the sequence incorrectly for the second nostril. Two users blew into the device and then pierced the drug capsule. One user kept the button depressed while blowing into the device during the delivery step as she felt the picture in the IFU indicated she should press the button while blowing. Failure to perform the piercing/inhalation tasks in the correct order would result in patients receiving either an under-dose or not receiving the medication at all.

We evaluated the use errors and note that currently, there is no mechanism in the device to provide feedback to the patients to ascertain whether or not the piercing process was successful and the device was ready for use. Lack of feedback may falsely lead users to believe that they have received a dose of medication. This may result in treatment failures due to delay in therapy. Therefore, we recommend, if feasible, the Applicant consider redesigning the device with an effective feedback mechanism that enables users to identify the successful piercing of the capsules and the delivery of the dose. The Applicant has noted that although the device does not have a signaling feature to indicate to the patient that the capsule was pierced or the drug was delivered, they explained that a patient may be able to visually inspect the capsule inside the nosepiece after use and see if there is powder remaining in the capsule (See Appendix F). Although patients may be instructed to inspect the capsules after dosing to determine if the capsules have been pierced, this procedure would need to be detailed extensively in the IFU and the IFU would need to be validated to confirm that patients were successful in identifying pierced/used versus unpierced/unused capsules. We suggest modifying the IFU to add detailed instructions for viewing the used and unused capsules in a manner similar to that provided in the IFU for Tobi Podhaler. Additionally while the IFU states the need to fully press and release the piercing mechanism prior to positioning the device into the mouth and nose, users had difficulty performing the tasks in the correct order. We suggest modifying the IFU (b) (4)

(b) (4)

While, we first recommend the applicant consider redesigning the product with an effective feedback mechanism, if it is not feasible, modification to the IFU may be used to help mitigate the error.

Failure to administer dose to second nostril

Two users failed to administer medication to the second nostril. One user only administered to one nostril using one nosepiece because she overlooked the information in the IFU stating to administer to the second nostril. One user administered two doses into the first nostril. She stated that she did not know she had to administer to both nostrils but wanted to try the product again. The clinical significance of delivering both doses of Onzetra to the same nostril is unknown. Upon review of the IFU, it is noted that the instructions for the preparation for the second nostril can be made more prominent. While it is clear that the user will need to use both nosepieces for full delivery of a dose, the instructions for the use of a second nostril can be easily overlooked. We suggest modifying the IFU to illustrate the use of a second nostril with either a pictorial depiction of the second nostril or by the use of color and increased font size to bring prominence to the need to use both nostrils for full delivery of the medication.

Not Using the Appropriate Number of Nosepieces

Two users used more than two nosepieces to simulate administration of a total dose. One user thought the (b) (4) on the last page of the IFU meant that he had to administer to both nostrils a second time. An additional user did not feel that she had inserted the nosepiece deep enough into the first nostril and repeated the administration process using the first nostril. Using more than two nosepieces may lead to medication overdose. We recommend removing the (b) (4) from the back of the IFU or included as a separate piece of labeling (i.e. Wallet card, pamphlet) if the Applicant desires. Additionally, although the Applicant is intending to market this product (b) (4) (b) (4) with a two nosepiece per pouch packaging configuration (b) (4) (b) (4). Since there were two close calls and two errors were patients were confused about the number of nosepieces they needed to use to achieve an appropriate dose, we are concerned that if the product is approved (b) (4) (b) (4) there may be a risk of patients (b) (4) (b) (4) overdosing. We recommend the Applicant consider this risk and provide appropriate mitigation strategies and confirm (via validation study) that this risk is appropriately mitigated.

Labeling

Additionally, we reviewed the labels and labeling submitted on July 28, 2014. While we will provide a general recommendation to the carton and container labels, we will defer a more detailed label and labeling review until after the submission of the results of the revised human

factor study as the results of the study will have a significant impact on the label and labeling design for this application. The current submitted label and labeling does not reflect the change in strength, and utilized the 2 nosepiece per pouch configuration that was not tested during human factors study.

4 CONCLUSION & RECOMMENDATIONS

The human factors validation study was unable to show that the intended population is able to use the product safely and effectively. Only Fourteen (14) users (52%) safely and effectively completed the product use process by simulating delivery of a “full treatment dose.” Most of the task failures noted in the study would result in patients receiving either an under-dose or not receiving the medication at all resulting in treatment failures. Thus, we recommend the Applicant implement corrective and preventative measures to improve the product-user interface and validate these changes in another human factors study prior to approval. However, we defer to the Review Division for determination of whether the benefits of introducing this sumatriptan product with its existing user interface outweighs the risk for use errors that can result in improper dosing. We provide recommendations below;

4.1 RECOMMENDATIONS FOR THE DIVISION

A. General Comments

The human factors validation study was unable to show that the intended population is able to use the product safely and effectively. Seven of the 56 capsules used by 27 participants during testing scenarios remained unpierced. Four users had failures performing the piercing/inhalation tasks in the correct order to achieve effective dosing of Onzetra. Additionally, two users failed to administer medication to the second nostril. All of these task failures would result in patients receiving either an under-dose or not receiving the medication at all resulting in treatment failures. Although, we recommend the Applicant implement corrective and preventative measures to improve the product-user interface and validate these changes in another human factors study prior to approval. We defer to the Review Division for determination of whether the benefits of introducing this sumatriptan product with its existing user interface outweighs the risk for use errors that can result in improper dosing. We recommend the Review Division take into consideration the risks of dosing errors and their clinical consequence (lack of efficacy) when assessing the approvability of this product.

If the Division decides to proceed with an approval action on this product, we recommend the Applicant revise the IFU based on our recommendations in section 4.2

If the Division decides to proceed with a Complete Response action for this product, we provide the following comments for the Applicant.

1. We note that there is no mechanism in the device to provide feedback to the patients to ascertain whether or not the piercing process was successful and the device was ready for use. Therefore, we recommend you consider redesigning the device with an effective feedback mechanism that enables users to identify the successful piercing of the capsules.
2. If redesigning is not feasible, we recommend you outline in detail the procedure to inspect the capsules after dosing to determine if the capsules have been pierced in the IFU. The revised IFU would need to be validated to confirm that patients were successful in identifying pierced/used versus unpierced/unused capsules. We suggest modifying the IFU to add detailed instructions for viewing the used and unused capsules (see IFU for Tobi Podhaler).
3. Validate the revised IFU (incorporating all changes recommended in section 4.2) via a supplemental simulated use testing to confirm that patients were successful in identifying pierced/used versus unpierced/unused capsules and the other observed use-errors were successfully mitigated.
4. We note that you intend to market this product (b) (4) with a two nosepiece per pouch packaging configuration (b) (4). We are concerned (b) (4) there may be a risk of patients (b) (4) overdosing. We recommend you consider this risk and provide appropriate mitigation strategies and confirm (via validation study) that this risk is appropriately mitigated.

4.2 RECOMMENDATIONS FOR THE APPLICANT

A. Instructions for Use

1. (b) (4) should be removed from the back of the IFU. (b) (4)
(b) (4)
(b) (4) may be incorporated as a separate piece of labeling (ie. Wallet card) if desired.
2. Revise the IFU to include detailed instructions on inspecting the capsules after dosing to determine if the capsules have been pierced/used (see IFU for Tobi Podhaler).
3. The IFU states the need to fully press and release the piercing mechanism prior to positioning the device into the mouth and nose; users had difficulty performing the tasks in the correct order. Modify the IFU (b) (4)
(b) (4)
(b) (4).
4. Illustrate the use of a second nostril with either a pictorial depiction of the second nostril or by the use of color and increased font size to bring prominence to the need to use both nostrils for full delivery of the medication.

B. Labels and Labeling

- a. Change strength (b) (4) to 11 mg on all labels and labeling to reflect current dose presentation.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Onzetra that Avanir Pharmaceuticals submitted on January 27, 2014.

Table 2. Relevant Product Information for Sumatriptan Nasal Powder	
Active Ingredient	Sumatriptan
Indication	Acute migraine with or without aura
Route of Administration	Intranasal
Dosage Form	Nasal powder formulation
Strength	11 mg Sumatriptan base per nosepiece
Dose and Frequency	Two nosepieces (each 11 mg) for a total of a 22 mg dose. 11 mg is delivered nasally into each nostril via the delivery technology at the first sign of a migraine; if a second dose is needed it can be repeated after 2 hours. Not to exceed more than 44 mg in a 24 hour period.
How Supplied	<p>Commercial Each carton contains:</p> <ul style="list-style-type: none"> • 2 reusable (b) (4) device bodies <p>(b) (4)</p> <ul style="list-style-type: none"> ○ Each nosepiece contains a medication capsule <p>Professional Sample Each carton contains:</p> <p>(b) (4)</p>
Storage	Store in a clean, cool dry place
Container Closure	Capsule-containing powder in a nosepiece which is packaged in a foil (b) (4) pouch

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on June 20, 2014 using the terms, [REDACTED] (b) (4), Onzetra, and Sumatriptan to identify reviews previously performed by DMEPA.

C.2 Results

Two previous reviews concerning sumatriptan nasal powder were conducted by DMEPA. The July 22, 2013 review (OSE RCM 2013-1230; IND 110090) makes recommendations to the proposed user verification and validation study including re-evaluating the identification of essential and critical tasks, classifying subtask use errors as close call errors that require further evaluation, and ensuring the usability study include participants reflect the range in education and literacy levels expected in the general US population. Additionally, there were comments detailing concerns with the IFU including the abbreviated steps on the coversheet of the IFU. The March 4, 2014 review (OSE RCM 2014-16850; NDA 206099) denied the named [REDACTED] (b) (4) [REDACTED] (b) (4).

1. Neshiewat, J. Type B Pre-NDA Meeting for Sumatriptan Nasal Delivery System (IND 110090). FDA/CDER/OSE/DMEPA. 2013 Jul 22. 3 p. RCM 2013-1230.
2. Sheppard, J. Proprietary Name Review of [REDACTED] (b) (4) (Sumatriptan) (NDA 206099). FDA/CDER/OSE/DMEPA. 2014 Mar 4. 2 p. RCM 2014-16850.

APPENDIX D. HUMAN FACTORS STUDY

D.1 Objective

The primary objective of the study was to validate if Sumatriptan Nasal Powder delivery system is safe and effective for use by the intended untrained user population without unspecified patterns or preventable use errors or difficulties that could result to harm to the end user.

The secondary objective of this study was to validate that recent modifications to the IFU and packaging informed by the previous study were evaluated for their effectiveness to mitigate use errors without presenting new risks.

D.2 Study Population

- 27 patients aged 18-70 with a self-reported history of migraine headache

D.3 Design

Participants did not receive formal training on proper device use. Participants were provided with the same labeling and instructions that will be packaged with the commercial device and were allowed to read the IFU and watch the video if desired. Participants were given production versions with nosepieces containing unfilled drug capsules that provided auditory and tactile clues if the device was used properly. The use-error evaluations of the product was both objective (performance-based, simulated-use evaluations) as well as subjective (user-feedback based evaluations).

D.4 Human Factors and Usability Results

Table 6. Use-errors Observed by Sub-Task		
Sub-Task / Use-Step	Use-Errors (n = 27)	Close- Calls
• <i>Assemble First Nosepiece with Device</i>	0	1
• <i>Depress Button/Pierce Drug Capsule (for both nosepieces)</i>	7	0
• <i>Insert Nosepiece into Nose</i>	0	0
• <i>Position Mouthpiece into Mouth</i>	0	1
• <i>Blow into Device</i>	0	1

Table 6. Use-errors Observed by Sub-Task		
Sub-Task / Use-Step	Use-Errors (n = 27)	Close- Calls
• <i>Remove First Nosepiece/Insert Second Nosepiece</i>	0	2
• <i>Administer to Second Nostril</i>	2	0
• <i>Perform Capsule-Piercing/Dispensing in Correct Order</i>	2	0

The expected use-errors related to the Sumatriptan Nasal Powder delivery system are detailed below.

1. Did not fully depress the device button/pierce drug capsule (n=7)

- One user did not press the button after inserting either of the two nose pieces. She indicated she saw in the IFU not to press the button while administering. While looking back at the IFU, she said she understood she needed to push the button but did not because she knew there was no medication in it.
- Five users pressed the button on the first nosepiece but did not press the button after inserting the second nosepiece. Three users said they just forgot, one user said she didn't see to press the button for the second nosepiece, and one user thought he had made a mistake by pushing it for the first nosepiece so he did not push it for the second.
- One user did not release the button before stimulating administration to both nostrils. She thought the picture indicated she should press the button while blowing.

2. Administer to second nostril (n=2)

- One user administered two doses into the first nostril.

- One user did not know she had to administer to both nostrils but dispensed a second dose to the first nostril because she wanted to try to the product again.

3. Perform capsule-piercing/dispensing in correct order (n=3)

- Two users blew into the device and then pressed the button when simulating use of both nosepieces.
- One user used the correct sequence for the first nosepiece but during the administration of the second nosepiece blew into the device and then pressed the button.

The expected use close-calls related to the Sumatriptan Nasal Powder delivery system are detailed below.

1. Did not correctly position mouthpiece into mouth (n=1)

- One user experienced a close call when after looking at the picture in the IFU she realized she had the device backwards. She self-corrected so that the mouthpiece was in her mouth.

2. Did not blow into device (n=1)

- One user experienced confusion before blowing into the device as she indicated she wanted to inhale at first but knew she needed to blow based on information in the IFU.

3. Remove first nosepiece / insert second nosepiece (n=2)

- Two users initially did not change nosepieces before simulating delivery to the second nostril but indicated that they then saw in the IFU that they needed to change nosepieces. Both users self-corrected and performed successfully.

Table 8. Unexpected Use-Errors			
Failure Mode	Error Count	Causal assessment	Error Type
Administration of more than two nosepieces.	<p>2 Use-Error</p> <p>One (1) end-user used four nosepieces to simulate administration of a treatment dose.</p> <p>One (1) end-user used three nosepieces during the use-task.</p>	<ul style="list-style-type: none"> One (1) end-user (002-029) thought that the (b)(4) (b)(4) on the last page of the IFU meant he had to administer to both nostrils a second time. One (1) end-user (002-046) was aware that the correct dose was 2 nosepieces, but did not feel she had inserted the nosepiece deep enough when administering to the first nostril, so after administering to the second nostril she repeated dispensing to the first nostril again using a third nosepiece. 	<p>1 IFU-based misinterpretation</p> <p>1 Misuse</p>

D.5 Usability Validation Study

Results:

- C. No mechanical functions were observed in the 27 devices used by the users during their scenarios
- D. Seven of the 56 capsules used during scenarios were not pierced and were attributed to observed use-errors
- E. Fourteen (14) users (52%) safely and effectively completed the product use process by simulating delivery of a “full treatment dose.” Seven users were successful at administering one nosepiece. Only four users failed to simulate administering any treatment. Two users used more than two nosepieces to simulate administration of a total dose. None of the twenty-seven (27) users performed any action that would result in direct harm from the device.
- F. Two users used more than two nosepieces to simulate administration of a total dose. The first of these end-users thought (b)(4) on the last page of the IFU meant that he had to administer to both nostrils a second time. The second user did not feel

that she had inserted the nosepiece deep enough into the first nostril and repeated dispensing again using the first nostril.

- G. There was a slight increase in the number of errors in one subtask of the validation study (perform capsule-piercing/dispensing in correct order) than in the prior usability study. However, it appears that there is an overall decrease in the total number of errors from the prior usability studies.

Conclusions:

1. We note a discrepancy in the user-observed error table (Table 6). It appears that it was an oversight and that a participant was counted as a close call in the table and another participant was omitted in the error section of the table. These numbers are different from the written account of the errors.
2. The Applicant is intending go to market (b) (4) pending the stability results for two nosepieces in each pouch (b) (4). There is concern over this plan. There were two close calls and two errors were patients were confused about the number of nosepieces they needed to use to achieve an appropriate dose. If the product is approved (b) (4) there will need to be either education or another study to determine the risk of patients (b) (4) overdosing on the medication.
3. One user thought (b) (4) on the last page of the IFU meant that he had to administer to both nostrils a second time which would have resulted in an overdose. (b) (4) should be removed from the back of the IFU or made into a separate wallet card.

APPENDIX F. Pictures of Used and Unused nosepieces submitted by Avanir Pharmaceuticals on October 6, 2014

Figure 1: Used Nosepiece (Top) Unused Nosepiece (Bottom)



Figure 2: Unused Nosepiece

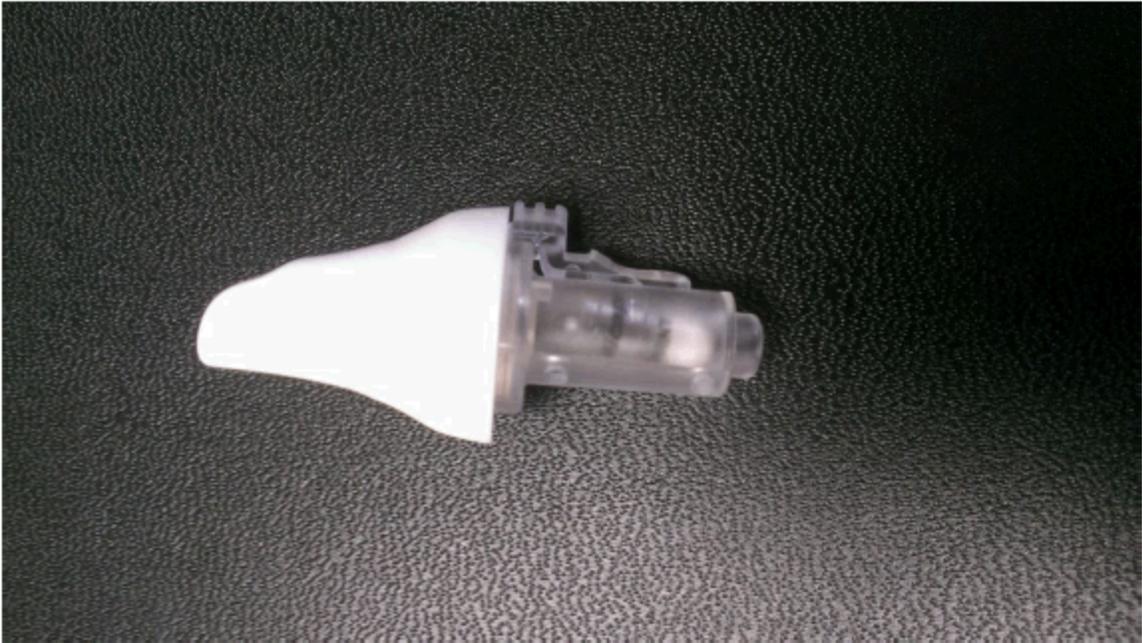


Figure 3: Used Nosepiece



6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JACQUELINE E SHEPPARD
10/23/2014

TINGTING N GAO
10/23/2014

LUBNA A MERCHANT
10/23/2014

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: October 17, 2014

TO: Billy Dunn, M.D.
Director, Division of Neurology Products (DNP)
Office of Drug Evaluation I
Office of New Drugs

FROM: Xikui Chen, Ph.D., Pharmacologist
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations (OSI)
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs covering NDA 206099, (b) (4)
(Sumatriptan Nasal Powder) 22 mg in the Xsail Breath
Powered Delivery Device, sponsored by Avanir
Pharmaceuticals, Inc.

At the request of the Division of Neurology Products, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following comparative bioavailability study:

Study Number: OPN-SUM-1302
Study Title: "An Open-Label Single Dose, Randomized, Crossover Study to Compare the Bioavailability of Intranasal Administration of 20 mg (b) (4) SUMATRIPTAN with IMITREX Oral Tablet and 6 mg IMITREX Subcutaneous Injection in Health Subjects"

Page 2 - NDA 206099, (b)(4) (Sumatriptan Nasal Powder) 22 mg
in the Xsail Breath Powered Delivery Device, sponsored
by Avanir Pharmaceuticals, Inc.

The inspection of the clinical portion of the study was
conducted by Michael Serrano (ORA Investigator, (b)(4)) at
Celerion, in Neptune, New Jersey, from October 8 to October 16,
2014. There were no objectionable findings during the
inspection and Form FDA-483 was not issued. Mr. Serrano did not
collect reserve samples for study OPN-SUM-1302, because the
unused test product was shipped back to Optinose on January 23,
2013, and reference products were destroyed on January 23, 2013,
at (b)(4) according to the study protocol.

The inspection of the bioanalytical portion of the study was
conducted by Joseph Lambert (ORA Investigator, (b)(4)), and
Xikui Chen (DBGLPC) (b)(4) from
(b)(4). There were no objectionable
findings for study OPN-SUM-1302; Form FDA-483 was issued for
observations concerning NDA 201849, also audited during the
inspection. These observations have no impact on the evaluation
of study OPN-SUM-1302.

Conclusion:

Following review of the inspectional findings, I recommend that:

- The results from the clinical and bioanalytical portions of
study OPN-SUM-1302 are acceptable for Agency review of
pharmacokinetics.

Xikui Chen, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

NAI - Celerion, Neptune, NJ
(FEI# 3003583366)

VAI - (b)(4)
(FEI# (b)(4))

Page 3 - NDA 206099, (b)(4) (Sumatriptan Nasal Powder) 22 mg
in the Xsail Breath Powered Delivery Device, sponsored
by Avanir Pharmaceuticals, Inc.

DARRTS CC:

OSI/DBGLPC/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Chen

OSI/DBGLPC/Dejernett/Nkah/Fenty-Stewart/Johnson

CDER/OND/ODEI/DNP/Billy Dunn/Vandna Kishore

ORA (b)(4)/Lambert

ORA (b)(4)/Serrano

Draft: XC 10/17/2014

Edits: MFS 10/17/2014; WHT 10/17/2014

OSI: File#: BE 6690

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical

(b)(4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Celerion, Neptune, NJ

FACTS: (b)(4)

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/s/

XIKUI CHEN
10/17/2014

WILLIAM H TAYLOR
10/17/2014