

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206099Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	(electronic stamp)
<b>From</b>	Eric Bastings, MD
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	206,099
<b>Supplement #</b>	
<b>Applicant Name</b>	Avanir Pharmaceuticals
<b>Date of Submission</b>	May 6, 2015
<b>PDUFA Goal Date</b>	February 6, 2016
<b>Proprietary Name / Established (USAN) Name</b>	Onzetra Xsail (sumatriptan) nasal powder
<b>Dosage Forms / Strength</b>	Intranasal Breath Powered Delivery Device (22 mg)
<b>Proposed Indication(s)</b>	Acute Treatment of Migraine
<b>Action</b>	Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	<b>Names of discipline reviewers</b>
CMC Review/OBP Review	Martha Heimann, Ph.D.
CDTL Review	Nick Kozauer, MD
OSE/DMEPA	Justine Harris, RPh

## 1. Introduction and Background

The application under review is a response to a CR letter issued on November 26, 2014, for Avanir Pharmaceuticals' 505(b)(2) NDA for a new intranasal (powder) formulation of sumatriptan, to be administered with a breath powered delivery device (Xsail).

The application was issued a CR letter because of human factors deficiencies. The human factors validation study did not support that the intended population would be able to use the product safely and effectively. In that study, only a fraction of patients were able to successfully complete the delivery of a full treatment dose, while the others had various types of errors. Most of the task failures noted in the study would have resulted in patients receiving either an underdose or not receiving the medication at all, resulting in possible treatment failures or reduced efficacy.

The applicant was asked to evaluate the root cause(s) of the failures seen in the study, and implement mitigations to address the failures and concerns described above. The applicant was also requested to conduct an updated use-related risk analysis, and validate all user interface changes (including labeling, IFU, training, and/or device) in a new human factors study, to demonstrate that the changes are effective and that they did not introduce any new risks.

## 2. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. At the time of resubmission of this NDA, the applicant withdrew the original manufacturing site (b)(4) and proposed a new contract manufacturer, UPM Pharmaceuticals (UPM). Upon inspection, the District Office initially classified the UPM facility as potential official action indicated (pOAI) and made a "Withhold" recommendation. In response, the applicant amended the NDA to reinstate (b)(4) as a manufacturing site. The (b)(4) facility status was reassessed, and found acceptable. In addition, the status of UPM was reclassified from pOAI to voluntary action indicated (VAI) and the "Withhold" recommendation was revised to "Acceptable". Manufacturing site inspections are therefore acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues.

## 3. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

## **4. Clinical Pharmacology/Biopharmaceutics**

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

## **5. Clinical Microbiology**

Not applicable.

## **6. Clinical/Statistical-Efficacy**

There was no outstanding efficacy issue in the first cycle.

## **7. Safety**

There was no outstanding safety issue in the first cycle.

## **8. Advisory Committee Meeting**

An Advisory Committee Meeting was not necessary for this application.

## **9. Pediatrics**

PREA was triggered for this new dosage form.

We will be waiving the pediatric study requirement for ages 0 months up to 6 years because necessary studies are impossible or highly impracticable in that age group.

We will be deferring submission of pediatric studies for ages 6-17 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected (in patients 12 to 17 years).

These required studies are listed below:

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.

Protocol Submission: September 2016  
Study Completion: November 2019  
Final Report Submission: June 2020

3025-2 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.

Protocol Submission: December 2020  
Study Completion: June 2024  
Final Report Submission: December 2024

## 10. Other Relevant Regulatory Issues

### Human factors

Justine Harris, DMEPA reviewer, notes that the applicant conducted a revised use-error risk analysis, two formative studies evaluating the information for use (IFU), a nosepiece sorting evaluation and a pre-summative study prior to conducting another human factors summative study.

Justine Harris notes that 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 IFU. Additionally, the applicant modified the proposed IFU related to capsule piercing, which led to confusion among patients in its prior version.

Justine Harris also evaluated the new summative human factors validation study (AVA.2015.BRZ.502). She notes that in that study, 14 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 29/30 successful dose administrations. Justine Harris notes that there were five close calls in task performance during the study, mostly (4/5) in a step during which patients have to press and release a white button to pierce the medication capsule. Justine Harris notes that those patients nevertheless identified that the medication had not been delivered, self-corrected, and ultimately administered the full dose without moderator intervention. Justine Harris finds the results from the Human Factors summative study acceptable. She also reviewed the IFU, carton and pouch labeling, device label and instructional video. Justine Harris 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. These were implemented by the applicant.

There are no other unresolved relevant regulatory issues.

## **11. Labeling**

Proprietary name was accepted by DMEPA. The DMEPA reviewer notes that the revised container label and carton labeling and Instructions for Use for Onzetra Xsail are acceptable from a medication error perspective. There are no outstanding labeling issues.

## **12. Decision/Action/Risk Benefit Assessment**

The sponsor has adequately addressed the device usability issues that led to the complete response action in the first cycle. Therefore, I will issue an approval letter for this application.

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/s/  
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ERIC P BASTINGS  
01/27/2016