CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206099Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

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

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
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 the 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/

ERIC P BASTINGS
01/27/2016

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD.
Subject	Summary Review
NDA/BLA # **Supplement #**	206,099
Applicant Name	Avanir Pharmaceuticals, Inc.
Date of Submission	January 27, 2014
PDUFA Goal Date	November 26, 2014
Proprietary Name / **Established (USAN) Name**	Onzetra (Sumatriptan Succinate)
Dosage Forms / Strength	Intranasal
Proposed Indication(s)	Treatment of acute migraine
Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Suhail Kasim, MD
Pharmacology/Toxicology Review	Charles Thompson, Ph.D.
CMC Review	Thomas M. Wong, Ph.D.
CDRH/ODE	Vasant G. Malshet, Ph.D., DABT
CDRH/Human factors	QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer
Clinical Pharmacology Review	Jagan Mohan Parepally, Ph.D.
Statistics	Jingyu (Julia) Luan, Ph.D.
OSE/DMEPA	Jacqueline Sheppard, PharmD
Patient labeling	Twanda Scales, RN, BSN, MSN/Ed.
OSI	Xikui Chen, Ph.D.

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Introduction and Background

Avanir Pharmaceuticals submitted 505(b)(2) new drug application for a new intranasal (powder) formulation of sumatriptan, to the administered with a breath powered delivery device (Xsail). In this document, I will refer to the product by its proposed tradename, Onzetra.

Onzetra is a drug-device combination product intended for self-administration. The drug delivery system consists of a reusable breath powered device body incorporating a flexible mouthpiece device and a disposable pre-filled nosepiece that contains encapsulated sumatriptan succinate nasal powder (15.4 mg of sumatriptan succinate, equivalent to 11 mg sumatriptan base). A full dose of Onzetra is to be administered by use of two nosepieces (one used in each nostril). The drug-filled capsule is not removable from the nosepiece. For commercial distribution, the sponsor expects the kit will contain two device bodies (one for immediate use and a spare), with (b) (4) nosepieces (two per pouch).

For administration, the user must first insert the disposable nosepiece that contains the encapsulated sumatriptan succinate into the drug delivery device body. The users then has to press and release a button integrated in the device body to pierce the capsule in the disposable nosepiece, and insert the nosepiece into the nose to make a complete seal. The mouthpiece is then rotated and inserted between the lips. Exhalation into the mouthpiece propels the sumatriptan powder into the nasal cavity through the nosepiece. The disposable nosepiece is then removed and discarded, and a second nosepiece is used similarly to deliver the second half of the dose into the other nostril.

The applicant references NDAs for three approved formulations of sumatriptan:

- NDA 20,626 (Imitrex Nasal Spray)
- NDA 20,132 (Imitrex Oral Tablet)
- NDA 20,080 (Imitrex injection).

The proposed indication, acute treatment of migraine with or without aura, is shared with the referenced NDAs.

2. CMC/Device

I concur with the conclusions reached by the CMC and biopharmaceutics reviewers that there are no outstanding CMC or biopharmaceutics issues that preclude approval. The submission contains adequate biocompatibility information . The available 12 months primary stability data support the proposed (b) (4) months of product shelf life. Facilities inspections were acceptable.

However, as described below, significant device usability issues have been identified.

3. Nonclinical Pharmacology/Toxicology

No nonclinical data were required to support this application. I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

4. Clinical Pharmacology

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

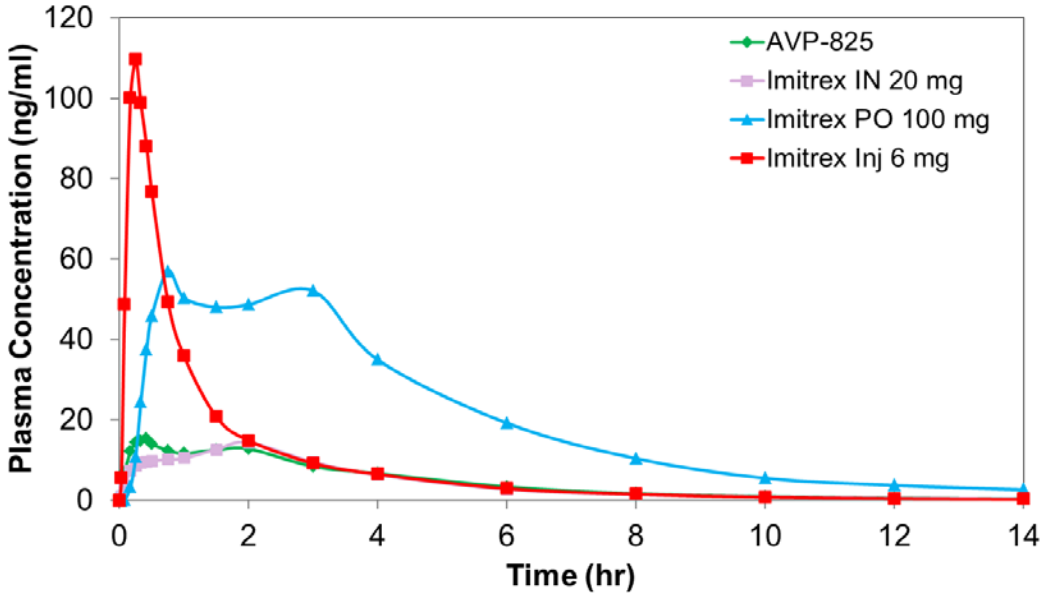
The applicant conducted a bioavailability study (OPN-SUM-1302) to compare the pharmacokinetics of Onzetra with those of Imitrex 6 mg Injection, Imitrex 100 mg Tablet, and Imitrex 20 mg Nasal Spray. Onzetra produced a higher C_{max} and a higher early exposure ($AUC_{0\text{-}30\ min}$) compared to Imitrex 20 mg Nasal Spray. The overall systemic exposure (AUC0-∞) of Onzetra was slightly higher than that of Imitrex 20 mg Nasal Spray, but lower than that of both Imitrex 100 mg Oral Tablet and Imitrex 6 mg Injection (Table 1, Figure 1).

Table 1: Comparative bioavailability of Onzetra, Imitrex nasal spray, Imitrex oral tablet, and Imitrex injection (adapted from Table 6 of OCPB review).

	Cmax (ng/mL)	AUC0-30 min (ng·hr/mL)	AUC0-inf (ng·hr/mL)
Imitrex Nasal Spray, 20 mg	16 ± 6	3.6 ± 1.9	61 ± 18
Onzetra 22 mg	21 ± 12	5.8 ± 4.1	65 ± 21
Imitrex Oral Tablet 100 mg	70 ± 25	8.1 ± 5	128 ± 17
Imitrex Injection, 6 mg	112 ± 22	39.7 ± 7.1	309 ± 92

The Tmax of sumatriptan following administration of Onzetra was between 20 and 40 minutes, compared to between 1 and 1.5 hours for Imitrex Nasal Spray (Figure 1).

Figure 1: Comparison of Sumatriptan Plasma Concentration-Time Profiles between Onzetra (AVP-825) and Imitrex nasal spray, oral tablet, and injection (adapted from "Figure 7" of OCPB review)



AVP-825 = Onzetra

The bracketing of Onzetra pharmacokinetics between those of Imitrex Nasal Spray and Imitrex Tablet and Injection is adequate to support the systemic safety and efficacy of Onzetra.

5. Clinical/Statistical-Efficacy

As discussed above, the efficacy of Onzetra is supported by pharmacodynamic bridging to referenced formulations of Imitrex.

In addition, the sponsor conducted two efficacy studies (OPTUK-MSPP-PRO002 and OPN-SUM-MIG-3301). Study OPTUK-MSPP-PRO002 was a supportive phase 2 study which I will not further discuss here. Study OPN-SUM-MIG-3301 was a randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of a 22 mg dose of Onzetra in adults with acute migraine with or without aura. In that study, patients were instructed to use the study drug to treat the first qualifying migraine headache following the randomization visit, and to initiate treatment as soon as the headache severity reached moderate or severe intensity. The primary efficacy endpoint was the percentage of subjects with headache pain relief at 2 hour after treatment, defined as a reduction from moderate or severe pain to no pain or mild pain. The migraine-associated symptoms of nausea, phonophobia, and photophobia were also evaluated.

At total of 212 subjects were included in the efficacy analysis. The primary endpoint was met, with 68% of responders on Onzetra vs. 45% on placebo (p=0.0016).

As shown in Table 2, the proportion of patients with migraine-related symptoms was numerically lower in the Onzetra group than in the placebo group (the study was not designed or powered to show a treatment effect on these endpoints).

Table 2: Migraine-associated symptoms in Study OPN-SUM-MIG-3301 (adapted from Dr. Kasim's review)

Migraine Associated Symptoms	Dose		p-value
	Onzetra 22 mg (N=108)	Placebo (N=104)	
Nausea-free	82%	79%	0.75
Photophobia-free	52%	40%	0.12
Phonophobia-free	68%	56%	0.10

6. Safety

As discussed above, the systemic safety of Onzetra is supported by pharmacodynamic bridging to referenced formulations of Imitrex. The applicant was also asked to address the local (intranasal) safety of Onzetra. In particular, the applicant had to address whether some segments of the nasal cavity (e.g., olfactory region) would be exposed to higher doses of sumatriptan, in which case additional long-term local safety data may be required.

The applicant noted that the proposed dose of Onzetra per nostril (11 mg) is less than the highest approved dose of Imitrex Nasal Spray (20 mg to one nostril). The applicant also argued that as approximately 83% of the dose is delivered, the comparison should be between a dose of 8.06 mg of Onzetra and 20 mg of Imitrex nasal spray. The applicant also compared the nasal deposition patterns between a traditional nasal spray and the Onzetra delivery device by gamma scintigraphy. Dr. Kasim discusses that the gamma scintigraphy studies show that the distribution patterns associated with each delivery method are similar in all areas of the nasal cavity. Dr. Kasim concludes that the local nasal mucosal safety of Onzetra 22 mg is predicted to be comparable to that of Imitrex Nasal Spray. I agree.

7. Advisory Committee Meeting

No advisory committee meeting was necessary for this application, which is for a new dosage form of an already approved active moiety.

8. Pediatrics

This application triggered PREA as a new active ingredient, dosage form, and route of administration. FDA agrees with the waiver requested by the applicant for studies in patients ages birth to less than 6 years because studies would be impossible or highly impractical, as

there are too few patients. FDA also agrees to a deferral for studies in patients 6 to 17 years because the product is ready for approval in adults.

9. Other Relevant Regulatory Issues

OSI

The results from the clinical and bioanalytical portions of Study OPN-SUM-1302 were found to be acceptable for Agency review.

Device Usability

The device usability was reviewed both by DMEPA and by CDRH.

DMEPA review

DMEPA notes that the Human Factors study conducted by the applicant was inadequate to establish that Onzetra can be used both safely and effectively by patients.

DMEPA observes that only 14 users (52%) completed the product use process by simulating delivery of a "full treatment dose" (see Table 3). 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.

Table 3: Participant errors in the human factors study (copied from DMEPA review)

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

DMEPA notes that there is currently 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. DMEPA believes that lack of feedback may falsely lead users to believe that they have received a dose of medication. DMEPA recommends that 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. DMEPA notes that modification to the Instructions for Use (IFU) may also possibly be used to help mitigate the error.

DMEPA notes that most of the task failures seen in the study would result in patients receiving either an underdose or not receiving the medication at all. This has obvious efficacy implications, as these users would receive less than the targeted dose of sumatriptan.

DMEPA recommends the applicant to implement corrective and preventive measures to improve the product-user interface. DMEPA also provided a number of recommendations for modifications of the IFU. DMEPA asks that the revised IFU (and possibly revised device) be evaluated in a new simulated use study to confirm that patients were successful in identifying pierced/used versus unpierced/unused capsules and the other observed use-errors were successfully mitigated.

CDRH

CDRH makes similar conclusions about the usability study. CDRH notes that based on the follow up and feedback obtained from study participants, the root-causes for errors included confusions or misinterpretation of the 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.

CDRH observes that the validation study results continue to show pattern of use errors that were observed in a prior usability study, indicating that the modifications were not effective in addressing the problems. CDRH 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.

Of note, I do not consider the fact that efficacy for the treatment of acute migraine was seen in Study OPN-SUM-MIG-3301 as indicative that patients will be able to effectively use the device “in real life”, because these patients received training that will not be systematically provided to patients prescribed Onzetra.

There are no other unresolved relevant regulatory issues.

10. Labeling

Due to the significant issues with device usability, labeling was not reviewed in this cycle.

11. Decision/Action/Risk Benefit Assessment

The applicant provided adequate bracketing pharmacokinetics information to bridge the systemic safety and efficacy of Onzetra to those of the referenced NDAs for approved formulations of sumatriptan: NDA 20,626 (Imitrex Nasal Spray), NDA 20,132 (Imitrex Oral Tablet), and NDA 20,080 (Imitrex Injection). The applicant also provided adequate information to support the local safety of the new product.

However, the usability study does not support that patients will be able to use the product effectively in "real life". The root causes of this problem may be related to the design of the device, to deficiencies in the Instruction for Use, or to a combination of both.

I agree with the DMEPA and CDRH review teams that these issues must be resolved before the product can be approved. Therefore, I will issue a Complete Response letter for Onzetra.

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/s/

ERIC P BASTINGS
11/26/2014