

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206099Orig1s000

CHEMISTRY REVIEW(S)



QUALITY ASSESSMENT



Recommendation: Approve

NDA 206099

**Review # 3
January 25, 2016**

Drug Name/Dosage Form	Onzetra (Sumatriptan Nasal Powder)
Strength	11 mg (two nosepieces, each containing 11 mg sumatriptan base)
Route of Administration	Intranasal
Rx/OTC Dispensed	Rx
Applicant	Avanir Pharmaceuticals
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
<i>Reviewed in Review #2, October 10, 2015</i>	
Resubmission	May 6, 2015
Quality Amendment	Aug 6, 2015
Quality Amendment	Aug 10, 2015
Labeling/Container-Carton	Sep 2, 2015
Quality Amendment	Sep 9, 2015
<i>Reviewed in Review #3, October 10, 2015</i>	
Quality Amendment	Oct 21, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	N/A	
Drug Product	Tom Wong	
Process	N/A	
Microbiology	N/A	
Facility	Steve Hertz	
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia A. Woody	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	
CDRH	Jamie Kamon-Branazio	REGO, DMQ, OC, CDRH, OMPT
Environmental Assessment (EA)	N/A	

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Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This review is an addendum to the addendum to the Office of Pharmaceutical Quality (OPQ) integrated review for NDA 206099 dated October 10, 2015. At this time, all outstanding facility issues are resolved and APPROVAL of the application is recommended.

The application and facility history are summarized below.

ONZETRA is a drug-device product used for nasal delivery of a powder form of the drug substance, sumatriptan succinate, via a proprietary breath-powered delivery device. The product is intended for the acute treatment of migraine headache with or without aura. The device consists of a flexible mouthpiece and a (b) (4) nosepiece, containing sumatriptan succinate in a hypromellose capsule, connected via a (b) (4) shell. The device is intended to deliver sumatriptan into the nasal cavity using the patient's exhaled breath and the device (b) (4) while the device is being used to deliver drug.

Avanir Pharmaceuticals (Avanir) submitted a 505 (b)(2) NDA for the product on January 27, 2014. In the original NDA, the firm proposed a contract manufacturer, (b) (4). (b) (4). All quality related issues were resolved during the first review cycle and the application was recommended for approval from a CMC perspective. However, due to outstanding human factors concerns regarding usability of the device and the potential for medication, the Agency issued a complete response (CR) letter on November 26, 2014.

When Avanir resubmitted the NDA on May 26, 2015, the applicant withdrew (b) (4) as a manufacturing site and submitted a new contract manufacturer, UPM Pharmaceuticals, Bristol, Tennessee (UPM). Following an August 14, 2015 inspection, the District Office initially classified the UPM facility as potential official action indicated (pOAI) and made a Withhold recommendation. Thus, the OPQ review dated October 10, 2015 recommended that the Agency issue a second CR letter. Other than the UPM facility status, there were no outstanding quality deficiencies.

On October 21, 2015, Avanir amended the NDA to reinstate (b) (4) as a drug product manufacturing site. This was classified as a major amendment, due to the need to reassess the (b) (4) facility status, and the PDUFA goal date was extended from November 6, 2015 to February 6, 2016. In consultation with the CDRH Office of

Compliance, the OPQ/OPF Facility reviewer, Steve Hertz, has confirmed that the status of (b)(4) remains acceptable from both drug and device perspectives.

During the review clock extension triggered by the amendment that reinstated the (b)(4) facility, the CDER Office of Compliance completed their review of the UPM inspection observations, and UPM's responses. Based on that review, the status of UPM was reclassified from pOAI to voluntary action indicated (VAI) and the Withhold recommendation revised to Acceptable. An overall Acceptable facility recommendation was entered on January 26, 2016.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments

A. Drug Substance Quality Summary

Refer to the Drug Substance Quality Summary in Review # 2. There have been no changes to supporting information for the drug substance since completion of Review #2.

B. Drug Product Quality Summary

Refer to the Drug Product Quality Summary in Review # 2. Other than reinstatement of the (b)(4) manufacturing site, as discussed above, there have been no changes to supporting information for the drug product since completion of Review #2.

C. Summary of Drug Product Intended Use

The product, sumatriptan succinate nasal powder, is a drug-device combination product intended for self-administration of sumatriptan succinate using a provided Xsail™ powered delivery device.

Overall Assessment and Signatures: Executive Summary

Application Technical Lead Signature:

Martha R. Heimann, Ph.D.
CMC Lead, Neurology
Office of New Drug Products

**Martha R.
Heimann -S**

Digitally signed by Martha R. Heimann
-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
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QUALITY ASSESSMENT



Recommendation: Complete Response

**NDA 206099
Review # 2**

Drug Name/Dosage Form	Onzetra (Sumatriptan Nasal Powder)
Strength	22 mg (two nosepieces, each containing 11 mg sumatriptan base)
Route of Administration	Intranasal
Rx/OTC Dispensed	Rx
Applicant	Avanir Pharmaceuticals
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission	May 6, 2015
Quality Amendment	Aug 6, 2015
Quality Amendment	Aug 10, 2015
Labeling/Container-Carton	Sep 2, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	N/A	
Drug Product	Tom Wong	
Process	N/A	
Microbiology	N/A	
Facility	Steve Hertz	
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia A. Woody	
Application Technical Lead		
Laboratory (OTR)	N/A	
CDRH	Jamie Kamon-Branazio	REGO, DMQ, OC, CDRH, OMPT
Environmental Assessment (EA)	N/A	

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

The type II drug substance DMF (b) (4) has been reviewed with adequate status. All other type III DMFs do not need review since sufficient information on the capsule shell and packaging components are provided in the application (see Chemistry Review #1 in DARRTS).

B. Other Documents: IND, RLD, or sister applications

Not Applicable

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Quality (CMC) perspective, approval of NDA 206099 cannot be recommended at this time. Approval of the application was recommended from a CMC perspective at the end of the first review cycle. However; the Agency issued a complete response (CR) letter on November 26, 2014. In the May 26, 2015 resubmission, the applicant withdrew the original drug product manufacturing site (b) (4) and submitted a new contract manufacturer, UPM Pharmaceuticals, Bristol, TN. The UPM facility is currently under a potential official action indicated (OAI) alert. Thus, a Withhold recommendation for the facility and an overall Withhold recommendation have been entered by the Office of Process and Facilities.

There are no other outstanding CMC deficiencies. Therefore, it is recommended that a CR letter citing the CGMP compliance status of the UPM Pharmaceuticals be issued.

If there is a change to the facility status, or if the applicant amends the application to provide for a CGMP compliant manufacturing site, the overall Quality recommendation will be updated in an addendum to this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Quality Assessments

A. Drug Substance Quality Summary

The drug substance is sumatriptan succinate, USP. The applicant referred to DMF (b) (4) for detailed information on the drug substance. This DMF has been previously reviewed and the last review was performed by Dr. Maria Manzoni on April 22, 2013. All subsequent submissions have been reviewed by Thomas Wong and the submissions are letters of authorization. The current status of this DMF remains adequate.

Sumatriptan is a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT₁) agonist. It is a small molecule with molecular formula for the succinate salt as C₁₄H₂₁N₃O₂S·C₄H₆O₄ and molecular weight (b) (4). Sumatriptan succinate is a white to almost white crystalline powder (b) (4)

(b) (4)

(b) (4). The drug substance has no chiral centers, non-hygroscopic, and is chemically stable when it is stored at (b) (4)

Available 48 months long-term (b) (4) stability data supports the proposed retest period of (b) (4) months for the drug substance (b) (4)

B. Drug Product Quality Summary

The product, sumatriptan succinate nasal powder, is a drug-device combination product intended for self-administration of sumatriptan succinate. The drug delivery system, Xsail™ powered delivery device, consists of a reusable device body incorporating a flexible mouthpiece device and a single-use, disposable, pre-filled nosepiece containing a filled drug capsule. Each nosepiece contains 11 mg of sumatriptan (as 15.4 mg sumatriptan succinate) and two nosepieces (one used in each nostril) constitute a full 22 mg dose. The trade name for sumatriptan succinate nasal powder is Onzetra™. Each hydroxypropyl methylcellulose contains 11 mg of sumatriptan (as 15.4 mg sumatriptan succinate). The proposed commercial batch size is (b) (4) nosepieces and the manufacturing site of the product has been revised in the resubmission to a contract manufacturing facility, UPM Pharmaceuticals. In the original NDA, the proposed manufacturing site was (b) (4). The capsule containing sumatriptan succinate is housed in a disposable nosepiece. Two nosepieces each containing 11 mg sumatriptan are then placed into (b) (4) foil (b) (4) pouch constituted as one dose. Eight (b) (4) foil pouch containing each foil containing 2 disposable nosepieces with two AVP-825 reusable devices (b) (4) and Instruction for Use and Package Insert are then placed in (b) (4) the (b) (4) for the commercial drug product. The product will be stored at controlled room temperature of 20°C - 25°C with excursions permitted 15°C - 30°C. Although only 12 months long-term stability data is available for the primary registration batches in the resubmission, the additional stability data in the resubmission with 18 months of the supporting stability data for the 2 nosepieces per pouch configuration and 24 months of supporting stability data for the (b) (4) configuration together with 6 months stability (b) (4) pouch configurations at 40°C/75 %RH storage conditions justify the proposed expiry dating of 36 months for the product when packaged in the proposed commercial packages and stored in the afore-mentioned storage conditions.

C. Summary of Drug Product Intended Use

The product, sumatriptan succinate nasal powder, is a drug-device combination product intended for self-administration of sumatriptan succinate using a provided Xsail™ powered delivery device.



OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

APPEARS THIS WAY ON ORIGINAL

Application Technical Lead Signature:

Martha R.
Heimann -S

Digitally signed by Martha R. Heimann -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13C0091527,
cn=Martha R. Heimann -S
Date: 2015.10.07 16:35:17 -0400

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I. Review of Common Technical Document-Quality (CTD-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

(Amendment #0027 dated 9/2/2015)

ONZETRA™ (sumatriptan nasal powder) (b) (4)
Xsail™ (b) (4)

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Onzetra Established Name: Sumatriptan succinate	DEMPA has accepted Onzetra as the proprietary name on 8/13/15 (see review in DARRTS)
Dosage form, route of administration	Dosage: Nasal Powder Route: Intranasal	Acceptable
Controlled drug substance symbol (if applicable)	The product is not a controlled substance.	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	ONZETRA is supplied in a disposable nosepiece containing a capsule with sumatriptan powder and a reusable Xsail Delivery System body. Each capsule contains 11 mg of sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder). (b) (4)	Acceptable. The expression of product strength is the active moiety, sumatriptan, with equivalency statement of the salt form

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Injection	Acceptable
Strengths: in metric system	Each capsule contains 11 mg sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder)	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The capsule is a clear, (b) (4) capsule with 825 printed on one side	Acceptable. The products is used with Xsail Delivery System only.

#11: Description (21CFR 201.57(c)(12))

ONZETRA uses a (b) (4) disposable nosepiece which is attached by the patient to an Xsail Delivery System body which has a mouthpiece and a piercing mechanism. The nosepiece contains a capsule filled with a dry powder form of sumatriptan succinate for nasal administration only with the Xsail Delivery System. Each capsule contains 11 mg sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder), and two nosepieces comprise a single dose. ONZETRA is for nasal administration only. Use of the Xsail Delivery System is for ONZETRA only (b) (4).

The active component of ONZETRA is sumatriptan, a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT₁) agonist. Sumatriptan delivered as the succinate salt is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1), and it has the following structure:



The empirical formula is C₁₄H₂₁N₃O₂S • C₄H₆O₄, representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline. The Xsail Delivery System is used to deliver the dry powder contained in the ONZETRA disposable nosepiece (in a capsule) into the nostril using breath exhaled into the Xsail body (see the Instructions for Use labeling). The Xsail Delivery System has a flexible mouthpiece to adjust to individual anatomic variations. Under standardized *in vitro* testing, the Xsail Delivery System delivers a mean of 10 mg sumatriptan per nosepiece when tested at a flow rate of 30 L/min for 4 seconds (2 L total). The amount of sumatriptan delivered to the nasal cavity will depend on patient factors such as expiratory flow. Delivered dose was measured in patients with migraine headache treated in clinical trials to evaluate the efficacy of the product. In these trials, each nosepiece delivered an average dose of 7.5-8.1 mg, providing a total dose of 15-16.2 mg per treatment episode from two nosepieces.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary: Onzetra Established Name: Sumatriptan succinate	DEMPA has accepted Onzetra as the proprietary name on 8/13/15 (see review in DARRTS)
Dosage form, route of administration	Dosage: Nasal Powder Route: Intranasal	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	ONZETRA is supplied in a disposable nosepiece containing a capsule with sumatriptan powder and a reusable Xsail Delivery System body. Each capsule contains 11 mg of sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder). Use with the Xsail Delivery System only .	Acceptable. The expression of product strength is the active moiety, sumatriptan, with equivalency statement of the salt form
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	N/A	Acceptable. The product contains only the neat drug substance and does not contain any excipient.
Statement of being sterile (if applicable)	N/A	Acceptable. The product is intended for intranasal use.
Pharmacological/ therapeutic class	Sumatriptan is a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT1) agonist and is indicated for the acute treatment of migraine attacks, with or without aura in adults.	Acceptable
Chemical name, structural formula, molecular weight	See the above photocopy of the package insert, Section # 11	Information is accurate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.	Acceptable

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

ONZETRA is available in (b) (4) disposable nosepieces containing 11 mg sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate). (b) (4)

The following table provides a description of the packaging configurations:

Description	Contents	NDC Code
8 Dose Kit	8 pouches containing 2 nosepieces per pouch, 22 mg sumatriptan nasal powder, (each nosepiece contains 11 mg sumatriptan) 2 Xsail Delivery System bodies	64597-311-08

Storage Recommendations

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.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	See above photo copy of package insert, Section #16	Acceptable
Available units (e.g., bottles of 100 tablets)	8 Dose kit - 8 pouches containing 2 nosepieces per pouch, 22 mg sumatriptan nasal powder, (each nosepiece contains 11 mg sumatriptan) 2 Xsail Delivery System bodies	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC numbers are provided	Acceptable
Special handling (e.g., protect from light, do not freeze)	Do not store in the refrigerator or freezer. Use nosepiece immediately after removing from foil pouch	Acceptable
Storage conditions	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)	Acceptable

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by UPM Pharmaceuticals Bristol, TN 37620 for Avanir Pharmaceuticals, Inc. Aliso Viejo, CA 92656	Acceptable. Obtained from Patient Information.

Conclusion: Acceptable. Final container label will be finalized with other review disciplines during labeling meetings.

2. Labels

1) Immediate Container Label (Amendment #0027 dated 9/2/2015)

POUCH FRONT

POUCH BACK



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The font size and prominence of both proprietary and establish name is adequate.	Final decisions will be made jointly with DMEPA
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Expression of product strength is in free form.	Acceptable
Net contents (21 CFR 201.51(a))	2 nosepieces	Acceptable
Lot number per 21 CFR 201.18	No space is provided for entry.	Need to confirm with the applicant that the lot number will be printed on the pouch
Expiration date per 21 CFR 201.17	No space is provided for entry.	Need to confirm with the applicant that the expiration date will be printed on the pouch
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" statement is present	Acceptable
Storage (not required)	Not required. Stated in cartoon container	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number is printed on the label	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Printed on the label	Acceptable
Name of manufacturer/distributor	Printed on the label	Acceptable
Others	For use with Xsail™ intranasal device only	Acceptable

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Acceptable. Final container label will be finalized with other review disciplines during labeling meetings.

2) Cartons (Amendment #0027 dated 9/2/2015)

(b) (4)



QUALITY ASSESSMENT



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The font size and prominence of both proprietary and establish name is adequate.	Final decisions will be made jointly with DMEPA
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Expression of product strength is in free form.	Acceptable
Net contents (21 CFR 201.51(a))	(b) (4)	Acceptable
Lot number per 21 CFR 201.18	Space is provided for entry.	Acceptable
Expiration date per 21 CFR 201.17	Space is provided for entry.	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables[201.10(a), 21CFR201.100(b)(5)(iii)]	N/A	Acceptable. The product contains only the neat drug substance and does not contain any excipient.
Sterility Information (if applicable)	N/A	
"Rx only" statement per 21 CFR 201.100(b)(1)	Statement is in label	Acceptable
Storage Conditions		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number is printed on the container label.	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Printed on carton label	Acceptable
Name of manufacturer/distributor	Printed on the label	Acceptable
"See package insert for dosage information" (21 CFR 201.55)	"Before use, please read Instruction for Use" is printed on the carton label.	Acceptable
"Keep out of reach of children" (optional for Rx, required for OTC)	The statement is printed on the carton label.	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	For intranasal use only	Acceptable
Other	Do not refrigerate. (b) (4). Dispose of nosepieces after use (b) (4)	Acceptable



QUALITY ASSESSMENT



Conclusion: Acceptable. Final container label will be finalized with other review disciplines during labeling meetings.

Conclusion: Acceptable

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Acceptable

Thomas Wong, Ph.D., ONDP/Division of New Drug Products I/Branch I

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, Ph.D., Branch Chief (Acting), ONDP/DNDP1/Branch 1

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

4. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Initial Risks	Current status	Final Recommendation
(b) (4)	(b) (4)	(b) (4)	Medium (VAI classification history)	Acceptable	Acceptable
UPM PHARMACEUTICALS INC.	1000208638	CSS, CTL	Medium (DS and DP manufacturing)	pOAI (QA functions)	Withhold
(b) (4)	(b) (4)	CTL	Medium (VAI classification history)	Acceptable	Acceptable

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)	(b) (4)	(b) (4)	See below	7	6	5	18	File review
UPM PHARMACEUTICALS INC.	1000208638	CSS	See below	8	10	5	23	File review
(b) (4)	(b) (4)	CTL	See below	8	5	5	18	File review

Applicant's Response:

Reviewer's Assessment: The (b) (4)
(b) (4) facility was inspected on (b) (4) and was classified VAI.

(b) (4)

The district office made an acceptable recommendation based on file review. The UPM PHARMACEUTICALS INC facility was inspected on 8/14/15 for profiles CSS and CTL and was classified OAI (final classification pending) for inadequate quality assurance at the facility. The firm is responsible for release of the API, storage, (b) (4) testing and release, release of nosepiece components, (b) (4) (b) (4) nosepiece assembly, (b) (4) testing, release and stability testing, primary and secondary packaging, labeling, finished product and retain samples storage. The district office made a withhold recommendation based on the recent inspection classification. The (b) (4) (b) (4) facility was inspected on (b) (4) for profile CTL and was classified VAI. The firm performs analytical testing and release of the drug substance and drug product release and stability testing. The district office made an acceptable recommendation based on file review.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

5. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Initial Risks	Current status	Final Recommendation
UPM PHARMACEUTICALS INC.	1000208638	DKA, CTL	High (DS and DP [i.e. DKA] manufacturing)	pOAI (QA functions)	Withhold
		^{(b) (4)} CTL	Medium (VAI inspection history)	Acceptable	Acceptable
			^{(b) (4)} High (prior compliance status with CDRH)	Acceptable	Acceptable
			High (prior inspection history)	No Further Evaluation	No Further Evaluation

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
UPM PHARMACEUTICALS INC.	1000208638	DKA	See below	8	45	5	61	PAI
		^{(b) (4)} CTL	See below	8	5	5	18	File review
		^{(b) (4)}	See below	27	8	5	80	CDRH consult
		^{(b) (4)}	See below	33	8	5	43	CDRH consult

Applicant's Response:

Reviewer's Assessment: The UPM PHARMACEUTICALS INC facility was inspected on 8/14/15 for profiles DKA and CTL and was classified OAI (final classification pending) for inadequate quality assurance at the facility. The firm is responsible for release of the API, storage, ^{(b) (4)} testing and release, release of nosepiece components, ^{(b) (4)}, nosepiece assembly, ^{(b) (4)} testing, release and stability testing, primary and secondary

packaging, labeling, finished product and retain samples storage. The district office made a withhold recommendation based on the recent inspection classification. The (b)(4) facility was inspected on (b)(4) for profile CTL and was classified VAI. The firm performs analytical testing and release of the drug substance and drug product release and stability testing. The district office made an acceptable recommendation based on file review. A consult was sent to CDRH to evaluate the (b)(4) facility. Per CDRH, “An inspection at (b)(4) was conducted on (b)(4). The inspection was classified VAI, and the district recommended to withhold the NDA application. The firm was cited for the following observations: 1) (b)(4) results cannot be fully verified by subsequent inspection and test has not been validated according to established procedures; and 2) Procedures (b)(4) have not been adequately established. However, the firm provided sufficient information (b)(4) (b)(4) in their response (b)(4). Therefore, a pre-approval inspection is not needed for this firm at this time.” (b)(4) - (b)(4) The district office (CDRH) made an acceptable recommendation based on file review. A consult was sent to CDRH to evaluate the (b)(4) facility. Per CDRH, “No inspectional history was found in FACTS or Turbo EIR for (b)(4). The firm is responsible for manufacturing (b)(4). Since the firm is a (b)(4) supplier controlled by the applicant, an inspection is not required. However, the applicant must show how supplier controls are established and maintained, including receiving and acceptance activities for the device constituent.” The district office (CDRH) recommendation was for no further evaluation of the facility.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES



QUALITY ASSESSMENT



Reviewer's Assessment and Signature: The overall manufacturing inspection recommendation for this application is to withhold, due to the current facility compliance classification of UPM PHARMACEUTICALS, INC. | FEI: 1000208638 | DUNS: 032125469.

Steven Hertz
10/5/15

Secondary Review Comments and Concurrence:

I concur with the facility reviewer's recommendation to withhold this application.

Zhihao Peter Qiu, Ph.D.
OPQ/OPF/DIA
10/5/2015

MEMORANDUM

To: NDA 206-099
From: Thomas M. Wong, Ph.D., Chemist
Date: 12-Nov-14
Drug: Onzetra™ (Sumatriptan Succinate) Nasal Powder
Route of administration: Intranasal
Strength: 11 mg
Subject: "Approval" recommendation for NDA 206-099 pending OC recommendation on facilities

This memorandum updates the status of the CMC review. Based on the information summarized below, ONDQA recommends an Approval recommendation for NDA 206-099 pending on the Office of Compliance's overall Acceptable recommendation on the manufacturing sites.

On September 17, 2014, it was stated in the Chemistry review #1 that CMC recommendation on the NDA 206-099 for Onzetra™ (Sumatriptan Succinate) Nasal Powder, 22 mg will depend on the resolution of the issues of Office of Compliance's final overall recommendation; results of transportation simulation studies; Biopharmaceutics reviewer and CDRH consults recommendations. Below is the updated information on these issues.

EES: As of 12 Nov, 2014, the Office of Compliance has not provided an overall recommendation for the manufacturing sites.

Results of transportation simulation studies: On Sep 12, 2014, the applicant provided satisfactory transportation simulation studies.

Biopharmaceutics reviewer's recommendation: Oct 16, 2014, an Approval recommendation is provided.

CDRH consults: The device portion of the submission has been reviewed by Dr. Sageev George on March 11, 2014 and Dr. Vasant Malshet on March 6, 2014. There is no comment to be sent to the applicant.

Amendment #0014 review

The applicant provided two responses in amendment #0014 dated 9/12/2014. One is to respond to our IR letter dated 7/3/2014 on the simulated distribution study and the other is to provide 18 months stability data on LTSS batches and comparative long-term stability data for (b) (4) (18 months) and (b) (4) (6 months).

Simulated distribution study results:

Our IR letter dated 7/3/2014 was to request the applicant to demonstrate that there is no effect on the performance of the nosepiece during product transportation, provide data to show the effect of transit on emitted dose content uniformity and particle size distribution. Below is the information of the study and results provided in this amendment.

(b) (4) packaging configurations presented in the NDA (b) (4)
(b) (4) were tested for the effect of the shipping on the emitted dose content uniformity and particle size

distribution in a simulated distribution study

(b) (4)

(b) (4)



(b) (4)

(b) (4) packaging configurations met specifications. The results were comparable to those at release.

(b) (4)

Evaluation: The simulated study data show that there is no effect on the performance of the nosepiece during product transportation.

Updated stability data in amendment #0014:

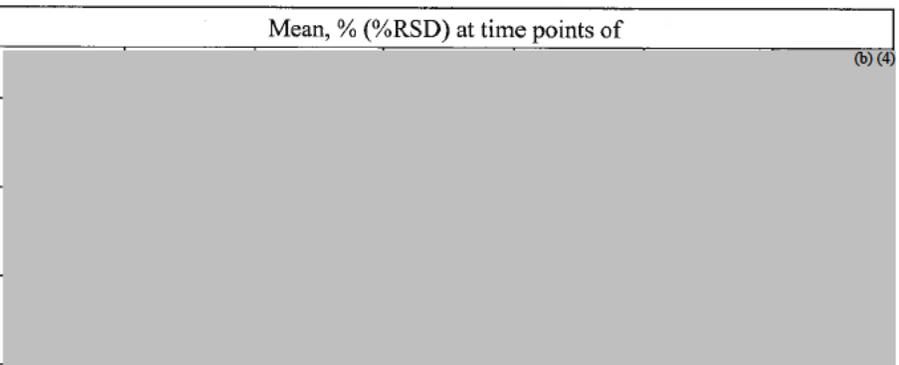
The applicant provided 18 months long-term stability results on LTSS batches and comparative long-term stability data for the (b) (4) registration batches (18 months) and (b) (4) registration batches (6 months).

Particle size distribution of emitted dose at 25 °C/60% RH storage conditions (Amendment #0014)

Batch	Time points (0, 1, 3, 6, 9,12, and 18 months)
-------	---

0012R	
0022R	
0032R	

Content uniformity of emitted dose at 25 °C/60% RH storage conditions (Amendment #0014)

Batch	Mean, % (%RSD) at time points of
0012R	
0022R	
0032R	



The applicant also provided comparative stability on [redacted] (b) (4) batches stored at 25°C/60%RH and 40°C/75%RH. Below are the data for related substance, emitted dose content uniformity and particle size distribution at 25°C/60%RH storage conditions:

Test	Method	Acceptance Criteria	Stability Data Range from Initial Time-point to 18 Months			Stability Data Range from Initial Time-point to 6 Months		
			0012R	0022R	0032R	0023R	0043R	0053R
Date of Manufacture			28Nov2012	29Nov2012	30Nov2012	21Oct2013	23Oct2013	24Oct2013
Related Substances (HPLC)	CTMLP-2679	NMT (b) (4)	[redacted] (b) (4)					
Impurity (b) (4)								
Impurity (4)								
Any unspecified Impurity		NMT						
Total Impurities		NMT						

Emitted Dose Content Uniformity, target 10 mg	CTMLP-2680	(b) (4)
Particle Size Distribution of Emittted Dose	CTMLP-2770	

(b) (4)

The applicant proposed a shelf-life of 24 months is proposed for AVP-825 packaged in (b) (4) 2 nosepieces per pouch.

Evaluation: The updated 18 months stability results are acceptable and all results were within specification. The comparative stability data for (b) (4) 2 nosepieces per pouch show that, as expected, the stability of sumatriptan in the 2 nosepieces per pouch is equally stable (b) (4) (see Review #1 for details in pouch packaging).

The available stability data support the proposed expiry dating of 24 months for (b) (4) 2 nosepieces per pouch.

Thomas M.
Wong -S

Digitally signed by Thomas M. Wong -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Thomas M. Wong -S, 0.9.2342.19200300.100.1.1=1300437649
 Date: 2014.11.12 07:36:46 -05'00'

Olen Stephens -S

Digitally signed by Olen Stephens -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
 Date: 2014.11.12 09:40:13 -05'00'

NDA 206-099

OnzetraTM (Sumatriptan Succinate) Nasal Powder

Avanir Pharmaceuticals, Inc.

Thomas M. Wong, Ph.D.

Division of New Drug Quality Assessment I

Office of New Drug Quality Assessment

Division of Neurology Drug Products

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet NDA 206-099

Chemistry Review Data Sheet

1. NDA 206-099
2. REVIEW #: 1
3. REVIEW DATE: September 17, 2014
4. REVIEWER: Thomas M. Wong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

IND 110,090

Document Date

Commercial IND

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original submission
Submission # S004
Submission # S006
Submission # S007
Submission # S008
Submission # S010
Submission # S011
Submission # S013

Document Date

27-Jan-2014
30-Apr-2014
26-Jun-2014
09-Jul-2014
11-Jul-2014
25-Jul-2014
28-Jul-2014
28-Aug-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Avanir Pharmaceuticals, Inc.
Address: 30 Enterprise
(Submission #S013) Suite 400
Aliso Viejo, CA 92656

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Onzetra™
b) Non-Proprietary Name: Sumatriptan succinate

Chemistry Review Data Sheet NDA 206-099

- c) Code Name/#: AVP-825
d) Chem. Type/Submission Priority (ONDC only):
• Chem. Type: 3
• Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Anti-migraine

11. DOSAGE FORM: Nasal powder

12. STRENGTH/POTENCY: 22 mg (two nosepieces, each containing 11 mg sumatriptan base)

13. ROUTE OF ADMINISTRATION: Intranasal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN Name: Sumatriptan Succinate, USP

CAS Name: 1H-indole-5-methanesulfonamide, 3-[2-(dimethylamino) ethyl]-N-methylbutanedioate
3-[2-(Dimethylamino)ethyl]-N-methylindole-5-methanesulfonamide succinate

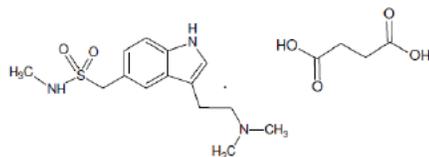
CAS registry #: 103628-48-4

Molecular weight: 413.49 (salt), (b) (4)

Molecular formula: C₁₄H₂₁N₃O₂S · C₄H₆O₄

Chemistry Review Data Sheet NDA 206-099

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug substance	1	Adequate	July 31, 2014	Reviewed by Thomas Wong
(b) (4)	III	(b) (4)	(b) (4)	4			Sufficient information in application
(b) (4)	III	(b) (4)	(b) (4)	4			Sufficient information in application
(b) (4)	III	(b) (4)	(b) (4)	4			Sufficient information in application
(b) (4)	III	(b) (4)	(b) (4)	4			Sufficient information in application
(b) (4)	III	(b) (4)	(b) (4)	4			Sufficient information in application
(b) (4)	III	(b) (4)	(b) (4)	4			Sufficient information in application
(b) (4)	III	(b) (4)	(b) (4)	4			Sufficient information in application

Chemistry Review Data Sheet NDA 206-099

(b) (4)		(b) (4)				
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")



CHEMISTRY REVIEW



Chemistry Review Data Sheet NDA 206-099

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	110,090	Commercial IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Pending		
LNC	N/A		
Methods Validation	N/A		
DMFPA	N/A		
EA	Acceptable	Jul 30, 2014	Dr. Thomas Wong
Microbiology	Approval	Feb 26, 2014	Dr. Bryan Riley
CDRH HF	Pending		
CDRH DOENT	Pending		

Executive Summary Section

The Chemistry Review for NDA 206-099

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final CMC recommendation on the NDA 206-099 for Onzetra™ (Sumatriptan Succinate) Nasal Powder, 22 mg will depend on the resolution of the following issues :

- The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspection.
- Awaiting results of emitted dose content uniformity and particle size distribution on the transportation simulation studies
- Awaiting Biopharmaceutics review on the acceptance of dissolution specification.
- Awaiting CDRH consults recommendations.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

CBE-30 supplement for comparability protocols for changing of nosepiece assembly method from manual operation to automation, and foil pouching from containing one nosepiece to two nosepieces.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The drug substance is sumatriptan succinate, USP. The applicant referred to DMF (b) (4) for detailed information on the drug substance. This DMF has been previously reviewed and the last review was performed by Dr. Maria Manzoni on January 24, 2012 and Dr. Kathleen Uhl on June 4, 2013. All subsequent submissions have been reviewed by Thomas Wong and the submissions are letters of authorization. The current status of this DMF remains adequate.

Sumatriptan is a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT₁) agonist. It is a small molecule with molecular formula for the succinate salt as C₁₄H₂₁N₃O₂S · C₄H₆O₄ and molecular weight (b) (4). Sumatriptan succinate is a white to almost white crystalline powder (b) (4)

(w) (4). The drug substance has no chiral centers, non-hygroscopic, and is chemically stable when it is stored (b) (4).

Available 48 months long-term (b) (4) stability data supports the proposed retest period of (b) (4) months for the drug substance (b) (4).

Executive Summary Section

Drug Product

The product, sumatriptan succinate nasal powder, is a drug-device combination product intended for self-administration of sumatriptan succinate. The drug delivery system, Xsail™ breath powered delivery device, consists of a reusable device body incorporating a flexible mouthpiece device and a single-use, disposable, pre-filled nosepiece containing a filled drug capsule. Each nosepiece contains 11 mg of sumatriptan (as 15.4 mg sumatriptan succinate) and two nosepieces (one used in each nostril) constitute a full 22 mg dose. The trade name for sumatriptan succinate nasal powder is Onzetra™. Each (b) (4) contains 11 mg of sumatriptan (as 15.4 mg sumatriptan succinate). The proposed commercial batch size is (b) (4) nosepieces and the product will be manufactured at a contract manufacturing facility, (b) (4). The capsule containing sumatriptan succinate is housed in a disposable nosepiece. The nosepiece is then placed into the primary foil laminate pouch. The drug product in pre-printed pouches is packaged in a cardboard carton (b) (4)

(b) (4) and package insert. The product will be stored at controlled room temperature of 20°C - 25°C with excursions permitted 15°C - 30°C. The available 12 months primary stability data supports the proposed (b) (4) months of product shelf-life. An expiry period of (b) (4) months is granted for the product when packaged in the proposed commercial packages and stored in the aforementioned storage conditions.

Additional Items

DMFs: All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Methods Validation: The applicant provided analytical method validation information for both drug substance and drug product. The analytical methods used in the testing procedures (release, stability and in-process) are either compendial methods or common well known methods used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.

EES: As of to date, the Office of Compliance has not yet provided an overall acceptable recommendation for the manufacturing sites.

Post-Approval Agreements: (b) (4)

(b) (4)

B. Description of How the Drug Product is Intended to be Used

The product, sumatriptan succinate nasal powder, is a drug-device combination product intended for self-administration of sumatriptan succinate using a provided Xsail™ breath powered delivery device.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP are manufactured and packaged

Executive Summary Section

in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. However, the final CMC recommendation on this NDA will depend on the resolution of the issues mentioned in the Recommendation and Conclusion on Approvability of this review.

Labeling negotiations have not concluded. Recommendations will continue to be routed through the clinical PM with concurrence from DMEPA.

Executive Summary Section

D. Risk Assessment

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Rank ing	Risk Mitigation	Risk Evaluation	Lifecycle Considerations / Comments
Assay	Impurity formation due to degradation	L	- The drug substance as a dry powder is less susceptible to degradation.	Acceptable	None
Content uniformity	Dose to dose variation	L	- The capsule filling equipment can fill very accurately the required amount of drug substance. And have the capability of weight checking each individual filled capsule.	Acceptable	None
Emitted dose content uniformity (EDCU)	- Lower than target fill of capsule. - Failure of protective packaging (moisture ingress). - Device malfunction. - Particle size of drug substance. - Static charge of drug substance.	L	There is no other excipient in the formulation. - The capsule filling equipment can fill very accurately the required amount of drug substance. And have the capability of weight checking each individual filled capsule. - The nosepiece containing the filled capsule is packaged in foil laminate pouch and sealed. - Study has demonstrated the ruggedness of the device. - The drug substance particle size has proven to be acceptable for use in nasal powder. - No evidence of static charge developed.	Acceptable	None
Emitted dose particle size distribution	- Low potency assay. - Lower than target fill of capsule. - Failure of protective packaging (moisture ingress). - Device malfunction. - Particle size of drug substance. - Static charge of drug substance.	L	Same as Emitted dose content uniformity (EDCU)	Acceptable	None

III. Administrative**A. Reviewer's Signature**

See DARRTS

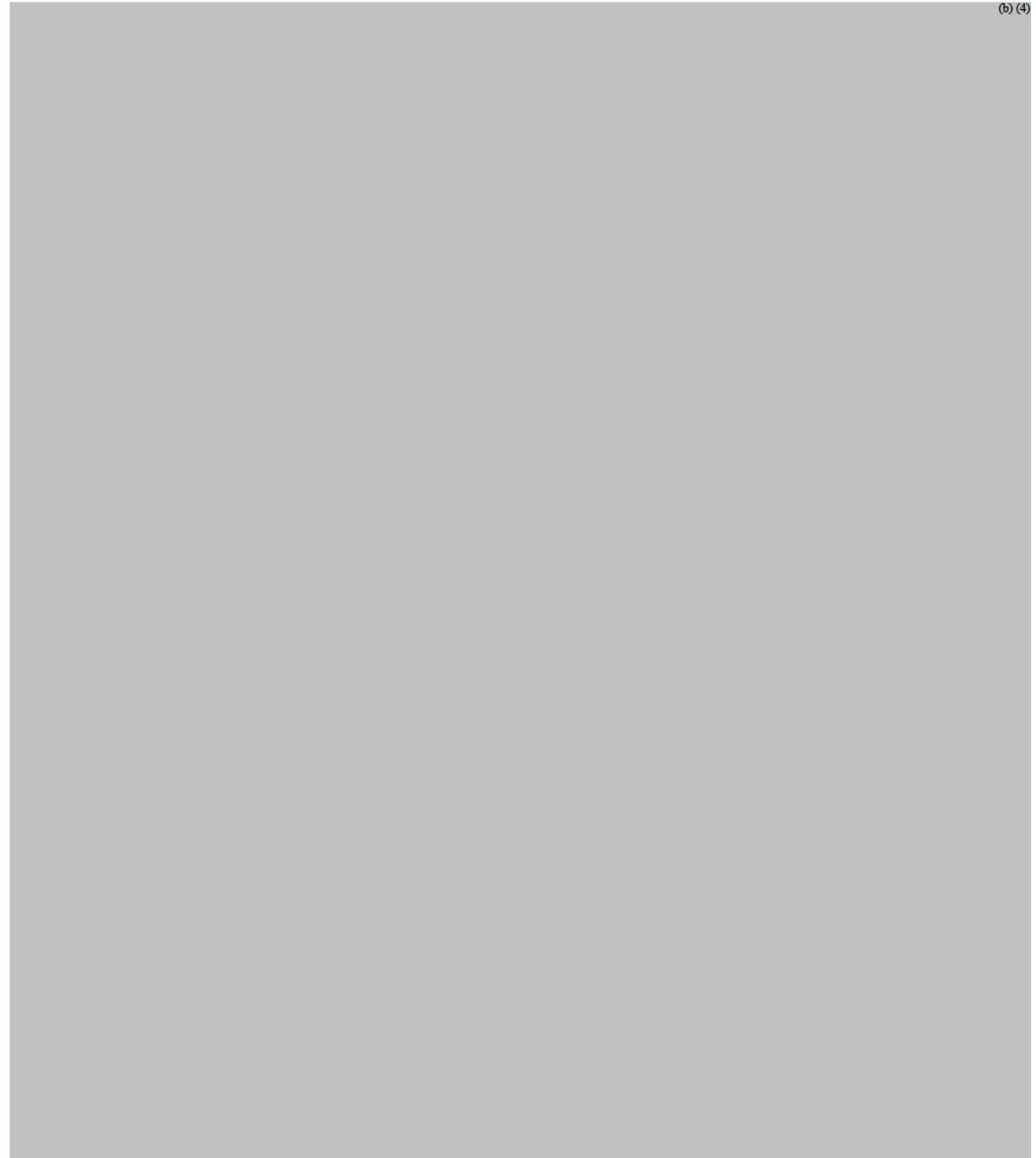
B. Endorsement Block

See DARRTS

C. CC Block

See DARRTS

105 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

**II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1****A. Labeling & Package Insert**

EVALUATION: Adequate. The CMC related information provided is sufficient and accurate.

Full Prescribing Information

1. Indication:

Onzetra™ (b) (4) Xsail™ (b) (4) is indicated for the acute treatment of migraine attacks, with or without aura in adults.

2. Dosage and Administration:

(b) (4)

3. Dosage Forms and Strengths:

Onzetra™ is supplied in a disposable nosepiece containing a capsule and a reusable (b) (4) (b) (4) delivery device body. Each capsule contains 11 mg sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder) in a clear (b) (4) capsule with 825 printed on one side.

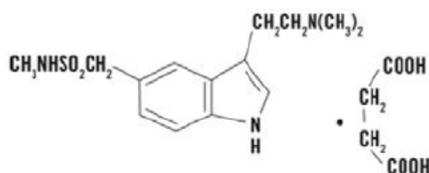
11. Description:

Onzetra™ uses a (b) (4) disposable nosepiece which is attached by the patient to an (b) (4) (b) (4) delivery device body which has a mouthpiece and a piercing mechanism. The nosepiece

Chemistry Assessment Section NDA 206-099

contains a capsule filled with (b) (4)
(b) (4) 11 mg sumatriptan base (equivalent to 15.4 mg (b) (4)
of sumatriptan succinate nasal powder), and two nosepieces comprise a single dose (b) (4)

The active component of Onzetra™ is sumatriptan, a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT₁) agonist. Sumatriptan (b) (4) succinate (b) (4) is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1), and it has the following structure:



The empirical formula is C₁₄H₂₁N₃O₂S • C₄H₆O₄, representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.

(b) (4) breath powered delivery device is used to deliver the dry powder contained in the (b) (4) disposable nosepiece (in a capsule) into the nostril using breath exhaled into the (b) (4) device (b) (4). The Xsail device has a flexible mouthpiece to adjust to individual anatomic variations. Under standardized *in vitro* testing, the Xsail device delivers a mean of 10 mg sumatriptan per nosepiece when tested at a flow rate of 30 L/min for 4 seconds (2 L total). The amount of sumatriptan delivered to the nasal cavity will depend on patient factors such as expiratory flow. Delivered dose was measured in patients with migraine headache treated in clinical trials to evaluate the efficacy of the product. In these trials, each nosepiece delivered an average dose of 7.5 - 8.1 mg, providing a total dose of 15 - 16.2 mg per treatment episode from two nosepieces.

Comment: The (b) (4) should be replaced by hypromellose capsule.

In the residual studies, the clinical returns showed (b) (4) mg of sumatriptan succinate was left in the nosepiece which is equivalent to (b) (4) (b) (4) sumatriptan free base. Thus, the calculated amount of sumatriptan succinate delivered was (b) (4) which is equivalent to (b) (4) (b) (4) delivered (see section P.2.2.1 Formulation Development - Residual Sumatriptan Studies for details).

16. How Supplied/Storage and Handling:

(b) (4)

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The following table provides a description of the packaging configurations:

Description	Contents	NDC Code
(b) (4)		

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.

Evaluation: Adequate. The CMC related information provided is sufficient and accurate. In Section 11- Description, the (b) (4) should be replaced by hypromellose capsule. Details will be discussed during labeling review meetings. The TRADE NAME will be replaced by Onzetra (trade name accepted by DMEPA on 7/14/2014).

Container labels:

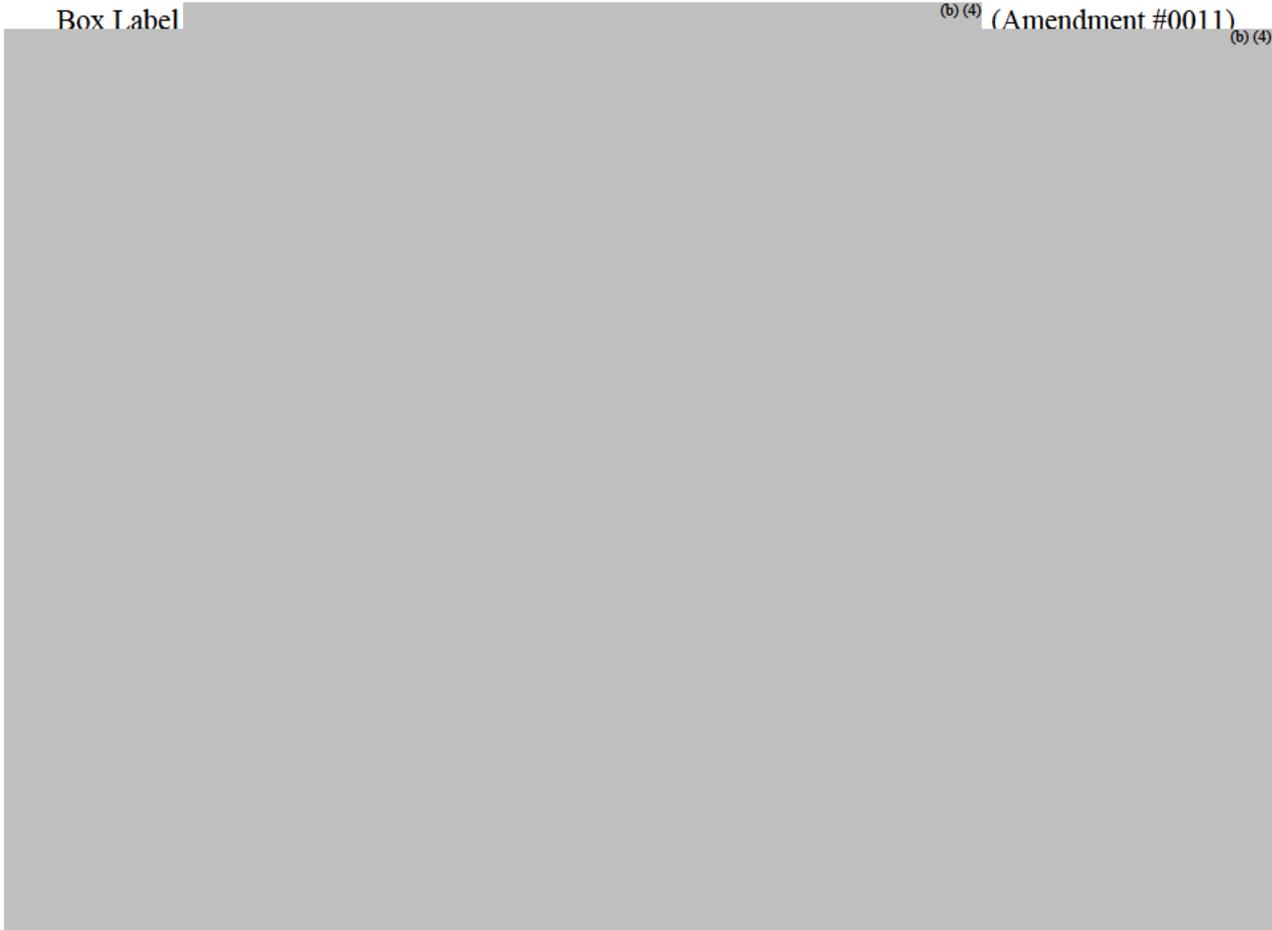
The applicant provided label samples for pouch and box (b) (4)
(b) (4)

(b) (4)

Chemistry Assessment Section NDA 206-099

Box Label

(b) (4) (Amendment #0011) (b) (4)



Pouch label (two nosepiece per pouch) – (b) (4) Amendment #0011)

(b) (4)



EVALUATION: Adequate. The (b) (4) label sample contains the following required information: Rx only; NDC number; number of doses, quantity of pouches in the box, ; the trade name and established name; the total dose (22 mg sumatriptan) the strength per nosepiece, the company Avanir Pharmaceuticals and address; lot number and expiration date; and storage condition. (b) (4)

(b) (4). Details of the container labels especially the number of nosepieces per pouch/sleeve, will be discussed with DMEPA in labeling meetings. There is a discussion to revise the strength (b) (4) with a note indicating that each nosepiece contains 11 mg sumatriptan. Final decision will be made during labeling review sessions.

B. Environmental Assessment Or Claim Of Categorical Exclusion

A request for categorical exclusion under 21 CFR 25.31 (b) is submitted in the original submission. The applicant mentioned that the calculated expected introduction concentration (EIC) introduced into the environment for AVP-825 is (b) (4) ppb. Avanir Pharmaceuticals, Inc. is unaware of any data which would indicate that the product might be toxic to organisms in the environment at the expected levels of exposure.

EVALUATION: Adequate. A categorical exclusion is, therefore, can be granted as per 21 CFR 25.31 (b) for this NDA.

III. List Of Deficiencies To Be Communicated:

We are still waiting for the results of emitted dose content uniformity and particle size distribution on the transportation simulation studies. All other deficiencies have been satisfactorily resolved.



CHEMISTRY REVIEW



Chemistry Assessment Section NDA 206-099

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 206099/000	Sponsor:	AVANIR PHARMS
Org. Code:	120		30 ENTERPRISE STE 400
Priority:	3		ALISO VIEJO, CA 92856
Stamp Date:	27-JAN-2014	Brand Name:	(b) (4) SUMATRIPTAN NASAL POWDER) 22
PDUFA Date:	27-NOV-2014		M
Action Goal:		Estab. Name:	SUMATRIPTAN SUCCINATE
District Goal:	28-SEP-2014	Generic Name:	

Product Number; Dosage Form; Ingredient; Strengths
 001; POWDER, FOR INHALATION; SUMATRIPTAN SUCCINATE;
 11MG

FDA Contacts:	T. WONG	Prod Qual Reviewer	(HFD-810)	3017961608
	T. BOUIE	Product Quality PM		3017961649
	V. KISHORE	Regulatory Project Mgr		3017964193
	M. HEIMANN	Team Leader		3017961678

Overall Recommendation:	PENDING	on 06-MAY-2014	by EES_PROD
	PENDING	on 14-MAR-2014	by EES_PROD
	PENDING	on 14-MAR-2014	by EES_PROD
	PENDING	on 13-MAR-2014	by EES_PROD
	PENDING	on 26-FEB-2014	by EES_PROD

Establishment:	CFN:	FEI:	(b) (4)	
			(b) (4)	
DMF No:		AADA:		
Responsibilities:				
Profile:		OAI Status:	NONE	
Last Milestone:	ASSIGNED INSPECTION TO IB			
Milestone Date:	06-MAY-2014			

Chemistry Assessment Section NDA 206-099

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities:
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-MAY-2014
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities:
Profile: OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 31-JUL-2014

Profile: (b) (4) OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 19-AUG-2014

Profile: (b) (4) OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 31-JUL-2014



CHEMISTRY REVIEW



Chemistry Assessment Section NDA 206-099

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFN: FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: OAI Status: NONE
Profile: SUBMITTED TO OC
Last Milestone: 26-FEB-2014
Milestone Date:

Establishment: CFN: FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: OAI Status: NONE
Profile: DO RECOMMENDATION
Last Milestone: 08-SEP-2014
Milestone Date: WITHHOLD
Decision: BUILDING/FACILITIES
Reason: SCALE UP (VALIDATION) OR PROCESS VALIDATION PROTOCOL

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

/s/

THOMAS M WONG
09/17/2014

OLEN M STEPHENS
09/17/2014