

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206099Orig1s000

PHARMACOLOGY REVIEW(S)



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

REVIEW OF TOXICOLOGY DATA

Date: March 6, 2014

From: Vasant G. Malshet, Ph.D., DABT

Division/Branch: DONED/ENTB

To: Vandna Kishore

Division/Branch: OMPT/CDER/
OND/ODEI/DNP

Trade Name : (b) (4) XSAIL™ (sumatriptan and delivery device)

NDA #: 206-099

Applicant: Avanir Pharmaceuticals

Checklist: Biocompatibility Evaluation of Medical Devices

Indications for Use: Acute migraine with or without aura

Brief Device Description: The drug delivery system consists of a reusable device body incorporating a flexible mouthpiece (Flexible Mouthpiece Device) and a disposable, pre-filled drug-containing nosepiece (Disposable Nosepiece). For administration, the disposable nosepiece that contains the encapsulated Sumatriptan Succinate, USP is inserted into the drug delivery device body. A button integrated in the device body is then pressed and released to pierce the capsule in the disposable nosepiece. The nosepiece of the device is then inserted into the nose and the mouthpiece inserted into the mouth. Exhalation into the mouthpiece propels the sumatriptan powder into the nasal cavity through the attached disposable nosepiece. The disposable nosepiece (including the now dose-expended drug containing capsule) is then removed and discarded, and a second nosepiece is used to similarly deliver the remainder (i.e. a second 11 mg nosepiece) into the opposite side of the nose to complete the dosing. The majority of the delivery system components are custom molded. Mold capability studies using key component dimensions have been performed on all individual injection molded components. (b) (4) components ((b) (4)) are supplied to controlled specifications.

Disposable Nosepiece Components

The nosepiece, including sub-parts thereof (Figure 3.2.R.4.3-1), is the disposable component of the AVP-825 device. It is intended for a single dose administration and it is not refillable. Each disposable nosepiece contains a Size 3 HPMC capsule filled with 15.4 mg Sumatriptan Succinate, USP (equivalent to 11 mg Sumatriptan base). The drug filled capsule is not removable from the nosepiece. Each fully assembled disposable nosepiece, which includes the plastic nozzle, grid, chamber and capsule (Figure 3.2.R.4.3-2) is packaged individually in a foil (b) (4) pouch. See 3.2.P.7 for detailed information regarding the packaging for the nosepiece.

(b) (4)



Assembled Disposable Nosepiece



Flexible mouthpiece device Components

The Flexible mouthpiece device (b) (4) (see [Figure 3.2.R.4.3-3](#)), is the reusable component of the AVP-825 drug delivery system. The disposable nosepiece component is designed to fit into the Flexible mouthpiece device (see [Figure 3.2.R.4.3-](#)

(b) (4)

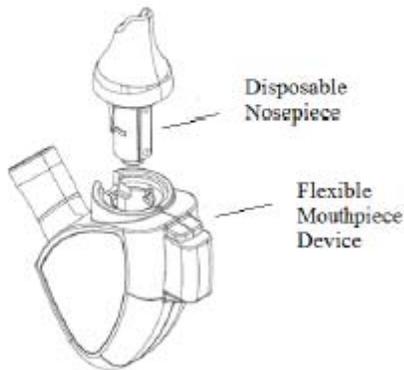


Flexible Mouthpiece Device

Flexible Mouthpiece Device



Insertion of the Disposable Nosepiece into the Flexible Mouthpiece Device



A drug/device combination that delivers a powder formulation nasally by leveraging a patient's own breath to propel the drug deep into the nasal cavity. The drug is then quickly absorbed via the nasal mucosa into the bloodstream.

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, can be repeated after 2 hours

Component Materials:

(b) (4)

(b) (4)

Type of Tissue Contact: (check one)

- Surface device: skin
- Surface device: mucosal membrane
- Surface device: breached or compromised surfaces
- External communicating device: blood path, indirect
- External communicating device: tissue/bone/dentin
- External communicating device: circulating blood
- Implant device: tissue/bone
- Implant device: blood

Duration of Contact: (check one)

- < 24 hours
- > 24 hours, but less than 30 days
- > 30 days
- potential for repeat exposure (If so, please explain)

Biocompatibility Testing Submitted: (See Table 2.) For suggested Biocompatibility Testing for Devices, see Attachments 1-x.

	FDA Recommended See Attached (will plan to add links to tests)	Firm Provided	Firm Should Provide
Cytotoxicity	X	X	
Sensitization	X	X	
Irritation or intracutaneous reactivity	X	X	
Acute systemic toxicity			
Material mediated pyrogenicity			
Hemocompatibility			
Hemolysis			
Complement activation			
Thrombogenicity			
For tests listed below, check with Division Focal Point			
Implantation			
Genotoxicity			
Gene mutations in bacteria			
Gene mutations in mammalian cells			
Clastogenicity in mammalian cells			
Sub-chronic toxicity			
Chronic toxicity			
Carcinogenicity			
Reproductive/developmental			
Biodegradation			

Cytotoxicity Study Using the ISO Elution Method

The test article, (b)(4) Sumatriptan (breath powered), was evaluated for potential cytotoxic effects following the guidelines of ISO 10993-5, Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity. A single preparation of the test article was extracted in single strength Minimum Essential Medium (IX MEM) at 37°C for 24 hours. The negative control, reagent control, and positive control were similarly prepared. Triplicate monolayers of L-929 mouse fibroblast cells were dosed with each extract and incubated at 37°C in the presence of 5% CO₂ for 48 hours. Following incubation, the monolayers were examined microscopically for abnormal cell morphology and cellular degeneration.

The test article extract showed no evidence of causing cell lysis or toxicity. The test article extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity).

ISO Intracutaneous Study in Rabbits

The test article, (b) (4) Sumatriptan (breath powered), was evaluated for the potential to cause irritation following intracutaneous injection in rabbits. This study was conducted based on ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP solution (SC), sesame oil, NF (SO), alcohol in saline (AS) and polyethylene glycol (PEG). A 0.2 mL dose of the appropriate test article extract was injected intracutaneously into five separate sites on the right side of the back of each of three animals. Similarly, the extract vehicle alone (control) was injected on the left side of the back of each animal. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection.

The test article met the requirements of the test since the difference between each test extract overall mean score and corresponding control overall mean score was 0.0, 0.0, 0.0 and 0.0 for the SC, SO, AS and PEG test extracts, respectively.

ISO Guinea Pig Maximization Sensitization Test

The test article, (b) (4) Sumatriptan (breath powered), was evaluated for the potential to cause delayed dermal contact sensitization in a guinea pig maximization test. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP and sesame oil, NF. Each extract was intradermally injected and occlusively patched to ten test guinea pigs (per extract). The extraction vehicle was similarly injected and occlusively patched to five control guinea pigs (per vehicle). Following a recovery period, the test and control animals received a challenge patch of the appropriate test article extract and the vehicle control. All sites were scored for dermal reactions at 24 and 48 hours after patch removal.

The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test.

Conclusions: The submission contains adequate biocompatibility information to show that the patient contacting materials in the device are biocompatible during the intended use of this device.

Reviewer Sign-Off:	Vasant G. Malshet -S 2014.03.10 11:09:53 -04'00'
Branch Chief Sign-Off:	Srinivas Nandkumar -S 2014.10.23 11:21:58 -04'00'

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/s/

VANDNA N KISHORE

10/24/2014

entered in DARRTS for CDRH reviewer

**Memorandum to File
Pharmacology/Toxicology, Division of Neurology Products (HFD-120)**

NDA: 206-099	Sponsor: Avanir Pharmaceuticals
Drug: Onzetra (sumatriptan nasal powder)	Indication: Acute migraine

Subject: Nonclinical Data Requirements for NDABackground

NDA 206-099 was received on January 27, 2014, following development under IND 110,090 (May Proceed Letter, February 22, 2012). The application was filed as a 505(b)(2) NDA, relying on previous findings of sumatriptan safety and efficacy under NDA 20-626 (Imitrex Nasal Spray), NDA 20-132 (Imitrex Oral Tablets), and NDA 20-080 (Imitrex Injection). A Pre-NDA meeting was held with then Sponsor, OptiNose US, Inc., on July 22, 2013 (Meeting Minutes, August 21, 2013).

At the time of the original IND 110,090 submission, the Sponsor had addressed certain questions to the Division, including a question regarding nonclinical data requirements for an NDA. The Division responded in the MP Letter as follows:

“If your NDA includes compelling evidence that contact with the nasal epithelium is no higher (in extent and/or duration) with your product than with Imitrex Nasal Spray, then no additional nonclinical data would be required. This assumes that there are no CMC issues (e.g., excipient, impurities) that would require safety assessment.”

Subsequently, based on internal evaluation by the Clinical Review Team of human clinical data submitted by the Sponsor to address the relative nasal epithelium exposure between Imitrex Nasal Spray and Onzetra Nasal Powder, it was concluded that “No additional nonclinical studies will be needed to support an NDA, provided there are no safety concerns (e.g., impurities, leachables/extractables) that would require nonclinical assessment” (Pre-NDA Meeting Minutes, August 21, 2013).

Submission Contents

NDA 206-099 contains no nonclinical data.

Evaluation and Recommendations

The ONDQA Reviewer, Dr. Thomas Wong, has identified no drug product quality issues that raise safety concerns requiring nonclinical assessment (T.M. Wong, Quality Review, September 17, 2014). Therefore, no nonclinical data are required to support approval of the NDA.

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/s/

DONALD C THOMPSON
10/10/2014

LOIS M FREED
10/10/2014
I concur.