

## Sumatriptan for Treatment of Migraines: Focus on Onzetra Xsail® (sumatriptan intranasal powder)

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**M**igraine is a chronic neurologic disorder that has a prevalence of roughly 28 million people in the United States as of 2001.<sup>1</sup> Migraines usually present with a combination of photophobia, phonophobia, nausea, or vomiting associated with the episodic attacks. Evidence suggests that 49.5% of patients with migraine headaches experience migraine-related nausea with at least half of their attacks.<sup>2</sup>

Triptans, 5-HT<sub>1B/1D</sub> receptor agonists, are considered first-line abortive therapy for moderate-to-severe migraine headaches. Oral administration is the most commonly used route for triptans; however, variability in gastric emptying resulting in delayed absorption can affect the magnitude of migraine relief using oral sumatriptan.<sup>3</sup> Patients that experience inconsistent results with oral agents or have migraine associated with nausea and vomiting may benefit from an alternative route of administration. Of the commercially-available triptans, sumatriptan is the most widely prescribed for migraine headaches and it is available in various dosage forms including oral, subcutaneous, intranasal, and rectal.<sup>4</sup> Recently, a new breath-powered intranasal formulation (Onzetra Xsail®; Avanir Pharmaceuticals, Inc.; Aliso Viejo, CA) has received FDA-approved indications for the acute treatment of migraine with or without aura in adults.

The purpose of this article is to review the commercially available sumatriptan dosage forms, their pharmacokinetic profiles, clinical trial efficacy, side effects, dosing, and costs. The article will also summarize the clinical trials used for the FDA approval of Onzetra Xsail® for the acute treatment of migraine with or without aura in adults and evaluate the possible benefits of each of the available sumatriptan dosage forms in the treatment of migraines.

### CLINICAL PHARMACOLOGY

#### *Mechanism of Action*

The etiology of migraine headache has been associated with the activation of the sensory trigeminovascular system and the subsequent release of vasoactive peptides. The vasoactive neuropeptides calcitonin gene-related peptide (CGRP), substance P, and neurokinin A released from trigeminal neurons innervate intracranial blood vessels. The vasoactive peptides have potent vasodilatory effects and cause neurogenic inflammation within the meninges. Both mechanisms have been suggested as models to explain the source of migraine pain.

Sumatriptan is an agonist for 5-hydroxytryptamine receptor subtype-1 (5-HT<sub>1</sub>) with higher affinity at the 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> subtypes. Sumatriptan has 3 known mechanisms that may have antimigraine effects by modifying the suspected pathophysiology of migraine headaches. First, activation of 5-HT<sub>1</sub> receptors has direct effects on the vascular smooth muscle through vasoconstriction of distended intracranial extracerebral vessels. Second, the release of vasoactive neuropeptides are decreased by inhibition of trigeminal terminals that innervate the intracranial vessels and dura matter. Third, nociceptive neurotransmission is inhibited at the trigeminocervical complex in the brainstem and upper spinal cord.<sup>5</sup>

#### *Pharmacokinetics*

The pharmacokinetic properties of the available sumatriptan dosage forms are summarized in **Table 1**. Oral sumatriptan is mainly renally excreted (60%) and the rest eliminated in the feces (40%). The inactive metabolite indole acetic acid (IAA) is the major compound excreted in the urine (>97%). Unchanged sumatriptan, when administered orally, is only 3% of the sumatriptan compounds excreted in the urine.

The absorption rate of sumatriptan may be an important factor in the efficacy of the medication, and the level of exposure (both peak and total) likely contributes to reduced tolerability of the medication.<sup>6</sup> The advantages of the Onzetra Xsail® dosage form have been demonstrated to have greater and earlier bioavailability compared with traditional sumatriptan nasal spray (delivered 20 mg sumatriptan) and decreased systemic drug exposure compared with oral (100 mg) and subcutaneous sumatriptan injection (6 mg) (Imitrex® Nasal Spray, Imitrex® Tablet, and Imitrex® Injection; GlaxoSmithKline, Research Triangle Park, NC, USA).<sup>7</sup> Additionally, the intranasal Onzetra Xsail® device has advantages over traditional sumatriptan nasal sprays as it has significantly reduced sumatriptan deposition in the oropharynx and lungs which leads to improved consistency of drug dosing.<sup>8,9</sup> The reduced systemic exposure may help explain decreased incidences of triptan-related side effects for Onzetra Xsail® when compared with the oral and subcutaneous dosage forms (see Adverse Events section).



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**Table 1 | Pharmacokinetic profiles of the different sumatriptan dosage forms<sup>7,10</sup>**

Dosage Form	Oral (Imitrex®)	Intranasal (Onzetra Xsail®)	Subcutaneous (Imitrex®)	Nasal Spray (Imitrex® Nasal Spray)
Dose	100 mg	22 mg	6 mg	20 mg
C <sub>max</sub> (ng/mL)	70.2 ± 25.3	20.8 ± 12.2	111.6 ± 21.6	16.4 ± 5.7
AUC <sub>0-∞</sub> (ng·hour/mL)	308.8 ± 92.4	64.9 ± 20.6	128.2 ± 17.4	61.1 ± 17.8
AUC <sub>0-30min</sub> (ng·hour/mL)	8.1 ± 5.0	5.8 ± 4.1	39.7 ± 7.1	3.6 ± 1.9
t <sub>1/2</sub> (hour)	3.8 ± 1.8	3.1 ± 0.6	2.3 ± 0.4	3.3 ± 0.9
Urinary Excretion (% Dose)	3% unchanged 97% IAA	3% unchanged 42% IAA	22% unchanged 38% IAA	3% unchanged 42% IAA

Data represent mean ± standard deviation unless specified otherwise.

C<sub>max</sub> = Maximum observed drug concentration; AUC = Area under the drug concentration time curve; t<sub>1/2</sub> = terminal elimination half-life; IAA = indole acetic acid, (major metabolite of sumatriptan metabolized by MAO).

### Drug Interactions

The concomitant use of ergot-containing drugs and sumatriptan has been reported to prolong vasospastic reactions, and use within 24 hours of each other is contraindicated. The use of other 5-HT<sub>1</sub> agonists may have additive effects that include significant blood pressure elevation or serotonin syndrome. Therefore the use of other 5-HT<sub>1</sub> agonists with sumatriptan within 24 hours is contraindicated. Monoamine oxidase (MAO-A) inhibitors may increase the systemic exposure of sumatriptan up to 7-fold and are contraindicated in patients using sumatriptan. Co-administration of triptans with selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and MAO-A inhibitors has been reported to cause serotonin syndrome and therefore their use together should be cautioned.<sup>11</sup>

## CLINICAL TRIALS

Two phase III trials were conducted for the approval of Onzetra Xsail®: the placebo-controlled TARGET study and the COMPASS study, using oral sumatriptan as an active control.

### The TARGET Study

The TARGET study was a randomized, double-blind, parallel-group (1:1 allocation) comparison of Onzetra Xsail® to placebo.<sup>12</sup> A total of 230 subjects from 15 U.S. centers were randomly assigned to treatment with 22 mg intranasal sumatriptan powder (11 mg per nostril) or matching intranasal placebo. Subjects were men and women aged 18-65 years, with migraines diagnosed at least 1 year prior to screening. Subjects were required to have at least one migraine headaches/month in the previous year before screening. Exclusions to the study included hemiplegic or basilar migraines, history of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, or a history of headache for ≥15 days/month.

The assigned treatment was administered within 1 hour of headache onset that the patient would classify as moderate or severe (2 or 3) on a 4-point Headache Severity scale. The 4-point Headache Severity scale classifies headache associated pain as none = 0, mild = 1, moderate = 2, and severe = 3. Only 1 qualifying migraine headache was treated per subject. The study par-

ticipants were not allowed to use other triptans, ergots, opioids, MAO inhibitors, or antipsychotics from 48 hours prior to 2 hours after study drug administration; however, a rescue medication was allowed 2 hours after administration of the study drug dose. Headache severity was recorded serially using the 4-point scale at baseline and at designated time points (10, 15, 30, 45, 60, 90, and 120 minutes, and 24 and 48 hours) after study drug or placebo administration. The participants also documented the presence of nausea, phonophobia, photophobia, and vomiting at the same time points as above.

The primary outcome was the percentage of patients in each group with headache relief, defined as a reduction in the headache intensity from moderate/severe (2 or 3 points) to none or mild (0 or 1 points) after 2 hours. The secondary outcomes included multiple time point evaluations of pain freedom, relief of migraine associated symptoms, clinical disability score, patient self-assessment of pain relief, rescue medication use, and migraine maintenance response at 24 to 48 hours. Of the original 230 randomized subjects, 7 did not receive any treatment after randomization because they did not have a qualifying migraine headache within the time-frame of the trial. Among the 223 subjects who received the study medication, headache relief at 2 hours after treatment was significantly greater for Onzetra Xsail® (67.6% of patients) compared to placebo (45.2% of patients), with an odds ratio (OR) of 2.53 (95% CI, 1.45, 4.42; p=0.002) favoring intranasal sumatriptan administration. Significant differences in headache relief were first observed at 30 minutes post-dose with 41.7% of patients experiencing relief after administering Onzetra Xsail® versus 26.9% of patients experiencing relief following placebo administration (p=0.03). Significant differences in headache relief were maintained at 48 hours in the Onzetra Xsail® group compared to placebo (34.3% vs 20.2%, p=0.01). At the 2-hour endpoint 34.3% of Onzetra Xsail® patients were pain-free compared with 17.3% of placebo patients (p=0.008). No difference was observed between groups in the incidence of nausea during the 2-hour post-dose period. Likewise, no significant differences were seen at any time point for phonophobia. Phonophobia decreased from 64.8% at baseline to 32.4% at 2 hours following Onzetra Xsail® treatment and from 64.4% to 44.2% following placebo treatment. Photophobia significant differences were seen at 90 minutes with reductions from 77.8% at baseline to 50.0% for

**Table 2 | Efficacy profile of sumatriptan dosage forms**<sup>10,13,18,19,20</sup>

Characteristic or Endpoint	Oral (Imitrex®) (n=228)	Subcutaneous (Imitrex®) (n=734)	Intranasal (Onzetra Xsail®) (n=108)	Nasal Spray (Imitrex® Nasal Spray) (n=1,098)	Placebo <sup>a</sup>
Headache Relief (%) <sup>b</sup>	77	81-82	68	55-64	31-45
No Headache (%)	56	63-65	34	26-42	11-17
No Nausea (%)	NR	81-82	82	42-53	20-79
No Photophobia (%)	NR	71-72	52	65-75	31-40
No Phonophobia (%)	NR	NR	68	57-65	44-56

<sup>a</sup>Data gathered from oral tablets, subcutaneous, transdermal, and intranasal placebo devices.

<sup>b</sup>Headache relief defined as reduction of Headache Severity 4-point pain score from moderate or severe (3 or 4) to none or mild (0 or 1).

Onzetra Xsail®-treated patients and from 78.8% to 64.4% for placebo-treated patients ( $p=0.048$ ).

#### The COMPASS Study

The COMPASS trial was a phase III trial comparing the efficacy, tolerability and safety of Onzetra Xsail® (22 mg sumatriptan nasal powder) to 100 mg of oral sumatriptan.<sup>13</sup> A 100-mg dose of oral sumatriptan was used on the basis of previous meta-analysis findings that this dose is more effective than a 50-mg dose at providing migraine relief 2 hours post-dose.<sup>14</sup> The COMPASS study was a randomized, double-blind, double-dummy, active-comparator, cross-over study conducted in 13 centers in the U.S. Subjects were eligible if they were aged 18 to 65 years, with a diagnosis of episodic migraine, with or without aura, and if they experienced between 2 and 8 migraines/month in the 12 months prior to screening. The migraines were required to meet at least the International Headache Society mild (grade 1) intensity definition. Exclusion criteria included the following: headache of any kind  $\geq 15$  days/month, hemiplegic or basilar-type migraine, a history or signs/symptoms of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, uncontrolled hypertension, severe hepatic impairment, or a history of epilepsy. Subjects were also excluded if they were unable to distinguish migraines from other headache types, any systemic disease, or a neurologic or psychiatric condition.

The trial consisted of two study periods that lasted for 12 weeks or until subjects treated up to 5 migraines with a study drug, whichever came first. After the initial period, the participants crossed over to receive the alternative treatment. Subjects were withdrawn from the study for failure to treat any migraines within either of the 12-week study periods. Efficacy was evaluated using the Sum of Pain Intensity Differences from baseline through 30 minutes post-dose (SPID-30) as the primary endpoint.<sup>15</sup> The SPID-30 is defined as the mean value of the 4-point pain scale values at recorded by subjects at baseline, 10 minutes, 15 minutes, and 30 minutes post-dose (maximum SPID-30 value: 12). Headache severity was measured using a 4-point pain scale at 10, 15, 30, 45, 60, 90, and 120 minutes post-dose. The efficacy data was gathered from 185 participants who had at least 1 treated migraine.

At study end, Onzetra Xsail® was found to be superior to 100 mg of oral sumatriptan over the first 30 minutes post-dose using the SPID-30 pain scale. Specifically, the adjusted mean difference in SPID-30 score was 3.39 (10.80 vs 7.41, 95% CI, 1.76, 5.01), favoring Onzetra Xsail®. A difference of 3.39 between groups on the SPID-30 score indicates that patients in the Onzetra Xsail® scored, on average, 0.848 points less on the 4-point pain

scale at each of the 4 time points from baseline through 30 minutes. However, the SPID-30 score difference assumes that a change from severe to moderate (3 to 2) headache is equivalent to a change from moderate to mild headaches (2 to 1) on the 4-point pain scale and is not currently validated to be a primary outcome measurement.

The pain relief (defined as pain level reduced from moderate or severe to none or mild on the 4-point pain scale) and pain freedom statistics were reported as secondary outcomes for comparison to other migraine trials. Pain relief and pain freedom favored Onzetra Xsail® from time points 15 through 90 minutes post-dose. The 15 minute pain relief was reported as 27.9% of Onzetra Xsail® treated attacks vs. 20.9% of treated attacks for oral sumatriptan ( $p=0.007$ ) and the 90 minute pain relief was reported as 77.4% vs. 72.0%, respectively ( $p=0.03$ ). However, similar proportions of patients reported pain relief at 2 hours (79.6% for Onzetra Xsail® vs. 76.9% for oral sumatriptan;  $p=0.21$ ), 24 hours (61.9% vs. 65.4%, respectively;  $p=0.27$ ), and 48 hours (61.3% vs. 62.6%, respectively;  $p=0.81$ ). Pain freedom was significant at 15 minutes (7.2% for Onzetra Xsail® vs. 3.7% for oral sumatriptan;  $p=0.008$ ) through 90 minutes (52.8% vs. 44.9%, respectively;  $p=0.006$ ). Freedom from migraine pain was not significantly different between the groups at 2 hours (60.4% for Onzetra Xsail® vs. 56.3% for oral sumatriptan;  $p=0.27$ ), 24 hours (50.3% vs. 48.2%, respectively;  $p=0.006$ ), or 48 hours (49.2% vs. 46.5%, respectively;  $p=0.53$ ). Sustained pain relief for the two therapies were similar with Onzetra Xsail® only demonstrating a more rapid onset of action compared with oral sumatriptan.

### COMPARING DOSAGE FORMS

The International Headache Society has published guideline criteria for investigators that develop trials for migraine treatment so that comparisons can be made between treatments.<sup>17</sup> The recommended measurement of treatment efficacy is the percentage of patients that are pain-free 2 hours after antimigraine drug administration. A summary of the common 2-hour post-dose efficacy of the different dosage forms is presented in **Table 2**. A limitation in the data presented in **Table 2** is the initial proportion of patients that experience nausea, photophobia, and phonophobia vary between each of the studies.

On the basis of this outcome comparison – and recognizing the limitations of comparing outcomes across heterogeneous trials – the most effective dosage form appears to be subcutaneous sumatriptan with 81-82% of patients reporting headache relief 2 hours post dose.<sup>18</sup> This result is to be expected as the pharmacokinetic profile for the subcutaneous route has the greatest concen-

tration at any time point except for overall exposure for sumatriptan. The large initial systemic concentration of sumatriptan may also explain why it has the most frequent and severe triptan-related side effects as well, as discussed below.

## ADVERSE EVENTS

A comparison of the adverse events (AEs) of different sumatriptan dosage forms is limited by the fact that not all studies report the same AE profile and because different dosage forms may prompt varying AE profiles. Commonly reported AEs for each dosage form are any treatment-emergent adverse event (TEAE), categorized according to severity, but without specifying particular AEs, as well as administration reactions with the non-oral drug routes. A summary AEs according to different dosage forms is presented in **Table 3**. Common TEAEs include classical triptan-associated AEs such as pain and pressure in the chest, symptoms of the arms, hands or feet, warm/hot sensations, burning sensations, feeling of heaviness, feeling of tightness, numbness, or feeling strange. Significant blood pressure elevation, including hypertensive crisis, has been known to occur in patients with or without a history of hypertension but was not reported in any of these studies. Likewise, no significant elevations in heart rate were reported during these trials.<sup>18</sup>

Compared with the oral and subcutaneous dosage forms, Onzetra Xsail® users report more mild symptoms, with most TEAEs related to application-site irritation. In the COMPASS study, safety and tolerability were analyzed using 262 subjects (used at least 1 dose of Onzetra Xsail®).<sup>13</sup> TEAEs were experienced by 53.9% of Onzetra Xsail® subjects and 32% of oral sumatriptan subjects. The authors reported that no serious TEAEs occurred and <2% of participants withdrew from the trial due to adverse events. Most TEAEs were local and mild consisting of nasal discomfort and abnormal taste. Participants reported atypical sensations related to sumatriptan use which included the following: symptoms in the chest, arms, hands or feet that are described as warm/hot sensations, burning sensations, feeling of heaviness, pressure, feeling of tightness, numbness, or feeling strange. TEAEs were reported significantly less often with Onzetra Xsail® compared with oral sumatriptan at 120 min post-

dose (2% of 512 attacks vs 5% of 512 attacks; OR 0.40 [95% CI 0.19, 0.85];  $p=0.02$ ). However, data regarding the percentage of atypical sensations post 120 min were not reported. Because patients in the COMPASS study received a placebo nasal powder along with oral sumatriptan, the report of TEAEs associated with the oral dosage form provided in **Table 3** may not apply to standalone oral therapy.

Similarly, the safety and tolerability profile for Onzetra Xsail® was shown to have mild adverse effects in the TARGET study.<sup>12</sup> Most of the adverse events associated with Onzetra Xsail® were local abnormal taste, nasal discomfort, rhinorrhea, and rhinitis. Subjects in the TARGET study that received either Onzetra Xsail® or placebo did not report any signs of chest pain or pressure and TEAEs were reported as mild or moderate intensity only. The patients in the Onzetra Xsail® group did report 4 instances of severe intensity AE including rhinitis, sinus headache, and abnormal product taste.

Aversion to nasal spray products may deter patients from choosing Onzetra Xsail® as their primary treatment dosage form. Nonetheless, Onzetra Xsail® is associated with low incidence of triptan-related AEs. While subcutaneous sumatriptan may be the most effective route of administration, it also is associated with the highest amount of atypical sensations. According to the package labeling, 42% of subcutaneous sumatriptan-treated patients experience atypical sensations associated with triptans. Subcutaneous sumatriptan is also associated with application-site reactions in up to 59% of patients. Tolerance between oral sumatriptan and Onzetra Xsail® appears to be similar, and subcutaneous sumatriptan is associated with more frequent and severe TEAEs.

## DOSING & ADMINISTRATION

Onzetra Xsail® is administered by a novel breath-powered intranasal delivery system. Patients should insert an 11 mg nose-piece into the intranasal delivery system. Administration of the drug involves patients placing the nose piece into their nostril and then inserting the mouthpiece into the mouth. The patient blows into the mouthpiece to deliver the medication to the nasal cavity. The nosepiece containing 11 mg sumatriptan is then discarded and a second nosepiece is inserted and the process repeated for

**Table 3 | Side-effects of different sumatriptan dosage forms from select clinical trials<sup>10,13,18,20</sup>**

Adverse Event	Oral (Imitrex®) (n=228)	Subcutaneous (Imitrex®) (n=547)	Intranasal (Onzetra Xsail®) (n=219)	Nasal Spray (Imitrex® Nasal Spray) (n=1,212)
<b>Any TEAE<sup>a</sup></b>	32%	50%	54%	NR
<b>Mild</b>	22.80%	NR	43.80%	NR
<b>Moderate</b>	6.10%	NR	7.80%	NR
<b>Severe</b>	3.10%	NR	2.30%	NR
<b>Pain and Pressure</b>	NR	4.50%	NR	NR
<b>Atypical Sensations<sup>b</sup></b>	5% of 512 migraines	42%	2% of 512 migraines	0.1-1.7%
<b>Application-site adverse event</b>	N/A	59%	Abnormal Taste: 26% Nasal Discomfort: 16%	Bad Taste: 24.5% Sinus Discomfort: 3.8% Throat Discomfort: 2.4%

TEAEs = treatment-emergent adverse events.

<sup>a</sup>Considered as all adverse effects including: application site reactions, symptoms in the chest, arms, hands, or feet; warm/hot sensation; burning sensation; feeling of heaviness; pressure; feeling of tightness; numbness; or feeling strange.

<sup>b</sup>Atypical sensations are defined as tingling, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, feeling of tightness, numbness, feeling strange, tight feeling in head.

**Table 4 | Cash prices for sumatriptan dosage forms in Gainesville, FL.<sup>21</sup>**

Drug	Quantity	Price
Sumatriptan tablet (generic)	9 tablets of 50 mg	\$15.00-54.00
Sumatriptan subcutaneous injection (generic)	2 cartridges of 6 mg	\$70.00-100.00
Sumatriptan nasal powder (Onzetra Xsail®)	16 nose-pieces of 11 mg	\$510.00-525.00 \$25 co-pay with private insurance

the other nostril.<sup>11</sup> Patients should administer a dose of 22 mg sumatriptan by using one 11 mg nose-piece in each nostril. A second dose of 22 mg (11 mg in each nostril) may be administered at least 2 hours after the first dose. Two dose administrations of Onzetra Xsail® is the maximum recommended dose (44 mg/4 nose-pieces).

### COST

The average retail prices for the available sumatriptan dosage forms are listed in **Table 4**. Avanir pharmaceuticals currently provides a savings coupon to reduce the copay of Onzetra Xsail® to \$25 per 16 nose-pieces of 11 mg (8 doses total) for patients with private insurance. A maximum benefit of \$100 per prescription is rewarded regardless of co-pay. Patients are not eligible for the savings coupon if they receive Medicare, Medicaid, or other public payment programs. Currently, oral sumatriptan tablets are the most reasonably priced.

### SUMMARY

Onzetra Xsail® is a reasonable alternative to the standard oral sumatriptan for patients that suffer from vomiting episodes or intolerance to the oral medication. Unless patients have an objection to nasal powders, Onzetra Xsail® may be a more effective alternative in patients that experience TEAEs with oral sumatriptan. If efficacy is the primary concern for patients and are willing to inject themselves, subcutaneous sumatriptan appears to be the most efficacious out of all the dosage forms. However, patients may experience more frequent and serious TEAEs with subcutaneous sumatriptan than with any of the other dosage forms. Additional research is needed to more clearly define the appropriate place in therapy for the newer sumatriptan dosage form in the treatment of migraine headaches.

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