

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ONZETRA Xsail safely and effectively. See full prescribing information for ONZETRA Xsail.

ONZETRA™ Xsail™ (sumatriptan nasal powder)

Initial U.S. Approval: 1992

INDICATIONS AND USAGE

ONZETRA Xsail is a serotonin 5-HT_{1B/1D} receptor agonist (triptan) indicated for the acute treatment of migraine with or without aura in adults (1).

Limitations of Use

- Use only if a clear diagnosis of migraine headache has been established (1)
- Not indicated for the prophylactic therapy of migraine attacks (1)
- Not indicated for the treatment of cluster headache (1)

DOSAGE AND ADMINISTRATION

- Recommended dose: 22 mg, administered by use of one nosepiece (11 mg) in each nostril (2.1)
- Maximum dose in a 24-hour period should not exceed two doses (44 mg) separated by at least 2 hours (2.1)

DOSAGE FORMS AND STRENGTHS

- Capsule in disposable nosepiece: 11 mg sumatriptan as the succinate salt.
- For use with the Xsail breath-powered delivery device only.

CONTRAINDICATIONS

- History of coronary artery disease (CAD) or coronary vasospasm (4)
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine (4)
- Peripheral vascular disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)

- Recent (within 24 hours) use of another 5-HT₁ agonist (e.g., another triptan) or of an ergotamine-containing medication (4)
- Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitor (4)
- Hypersensitivity to sumatriptan (angioedema and anaphylaxis seen) (4)
- Severe hepatic impairment (4)

WARNINGS AND PRECAUTIONS

- *Myocardial ischemia/infarction and Prinzmetal's angina*: Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.1)
- *Arrhythmias*: Discontinue ONZETRA Xsail if occurs (5.2)
- *Chest/throat/neck/jaw pain, tightness, pressure, or heaviness*: Generally not myocardial ischemia; evaluate high risk patients for CAD (5.3)
- *Cerebral hemorrhage, subarachnoid hemorrhage, and stroke*: Discontinue ONZETRA Xsail if occurs (5.4)
- *Gastrointestinal ischemia and infarction events, peripheral vasospastic reactions*: Discontinue ONZETRA Xsail if occurs (5.5)
- *Medication overuse headache*: Detoxification may be necessary (5.6)
- *Serotonin syndrome*: Discontinue ONZETRA Xsail if occurs (5.7)
- *Seizures*: Use with caution in patients with epilepsy or a lowered seizure threshold (5.10)

ADVERSE REACTIONS

In controlled studies with ONZETRA Xsail, the most common adverse reactions (incidence of $\geq 2\%$ and greater than placebo) were abnormal taste, nasal discomfort, rhinorrhea, and rhinitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Avanir Pharmaceuticals at 1-844-ONZETRA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- **Pregnancy**: Based on animal data, may cause fetal harm (8.1)

See 0 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

1/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ONZETRA™ Xsail™ is indicated for the acute treatment of migraine with or without aura in adults.

Limitations of Use

- Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with ONZETRA Xsail, reconsider the diagnosis of migraine before treatment of subsequent attacks with ONZETRA Xsail.
- ONZETRA Xsail is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of ONZETRA Xsail have not been established for the treatment of cluster headache.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dosage of ONZETRA is 22 mg of sumatriptan nasal powder (2 nosepieces), administered using the Xsail breath-powered delivery device. If the migraine has not resolved by 2 hours after taking ONZETRA Xsail, or returns after a transient improvement, a second dose of 22 mg may be administered at least 2 hours after the first dose. The maximum recommended dose that may be given in 24 hours is two doses of ONZETRA Xsail (44 mg/4 nosepieces) or one dose of ONZETRA Xsail and one dose of another sumatriptan product, separated by at least 2 hours. The safety of treating an average of more than 4 headaches in a 30 day period has not been established.

2.2 Administration Instructions

The recommended dose of 22 mg is administered by using one 11 mg nosepiece in each nostril [*see Patient Counseling Information (17)*]. For administration of ONZETRA Xsail, the patient removes the clear device cap from the reusable delivery device, then removes a disposable nosepiece from its foil pouch and clicks the nosepiece into the device body. The patient then fully presses and promptly releases the white piercing button on the device body to pierce the capsule inside the nosepiece. The white piercing button should only be pressed once and released prior to administration to each nostril. The nosepiece is then inserted into the nostril so that it makes a tight seal. Keeping the nosepiece in the nose, the device is rotated to place the mouthpiece into the mouth. The patient blows forcefully through the mouthpiece to deliver the sumatriptan powder into the nasal cavity. Vibration (e.g., a rattling noise) may occur, and indicates that the patient is blowing forcefully, as directed. Once the medication in the first nosepiece has been administered, the patient removes and discards the nosepiece. The same process must then be repeated using a second 11 mg nosepiece into the other nostril to administer the remainder of the total recommended 22 mg dose [*see Patient Counseling Information (0)*].

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

ONZETRA Xsail is contraindicated in patients with:

- Ischemic coronary artery disease (CAD) (e.g., angina pectoris, history of myocardial infarction, or silent ischemia) or coronary artery vasospasm, including Prinzmetal's angina or in patients with other significant underlying cardiovascular diseases [*see Warnings and Precautions (5.1)*].
- Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders [*see Warnings and Precautions (5.2)*].
- History of stroke, transient ischemic attack (TIA), or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke [*see Warnings and Precautions (5.4)*].
- Peripheral vascular disease [*see Warnings and Precautions (5.5)*].
- Ischemic bowel disease [*see Warnings and Precautions (5.5)*].

- Uncontrolled hypertension [*see Warnings and Precautions (5.8)*].
- Recent use (i.e., within 24 hours) of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine₁ (5-HT₁) agonist [*see Drug Interactions (7.1 and 7.3)*].
- Concurrent administration of an MAO-A inhibitor or recent use (within 2 weeks) of a MAO-A inhibitor [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*].
- Hypersensitivity to sumatriptan (angioedema and anaphylaxis seen) [*see Warnings and Precautions (5.9)*].
- Severe hepatic impairment [*see Clinical Pharmacology (12.3)*]

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina

The use of ONZETRA Xsail is contraindicated in patients with ischemic or vasospastic CAD. There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of sumatriptan. Some of these reactions occurred in patients without known CAD. 5-HT₁ agonists, including ONZETRA Xsail, may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naïve patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving ONZETRA Xsail. If there is evidence of CAD or coronary artery vasospasm, ONZETRA Xsail is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of ONZETRA Xsail in a medically supervised setting and performing an electrocardiogram (ECG) immediately following administration of ONZETRA Xsail. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of ONZETRA Xsail.

5.2 Arrhythmias

Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours following the administration of 5-HT₁ agonists. Discontinue ONZETRA Xsail if these disturbances occur. ONZETRA Xsail is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.

5.3 Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure

Sensations of tightness, pain, pressure, and heaviness in the chest, throat, neck, and jaw commonly occur after treatment with 5-HT₁ agonists including other products containing sumatriptan and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of ONZETRA Xsail is contraindicated in patients with known CAD and those with Prinzmetal's variant angina.

5.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have occurred in patients treated with 5-HT₁ agonists including other products containing sumatriptan, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT₁ agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). ONZETRA Xsail is contraindicated in patients with a history of stroke or TIA. Discontinue ONZETRA Xsail if a cerebrovascular event occurs.

Before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, exclude other potentially serious neurological conditions.

5.5 Other Vasospasm Reactions

5-HT₁ agonists, including ONZETRA Xsail, may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic

infarction, and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of a non-coronary vasospastic reaction following the use of any 5-HT₁ agonist, rule out a vasospastic reaction before using ONZETRA Xsail.

Transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT₁ agonists including sumatriptan. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT₁ agonists have not been clearly established.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, nonsteroidal anti-inflammatory drugs or combinations of these drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.7 Serotonin Syndrome

Serotonin syndrome may occur with triptans, including ONZETRA Xsail, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors [see *Drug Interactions* (7.4)]. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue ONZETRA Xsail if serotonin syndrome is suspected.

5.8 Increase in Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT₁ agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with ONZETRA Xsail. ONZETRA Xsail is contraindicated in patients with uncontrolled hypertension.

5.9 Anaphylactic Reactions

Anaphylactic reactions have occurred in patients receiving sumatriptan. Such reactions can be life-threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. ONZETRA Xsail is contraindicated in patients with a history of hypersensitivity reaction to sumatriptan.

5.10 Seizures

Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent. ONZETRA Xsail should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections of the prescribing information:

- Myocardial ischemia, myocardial infarction, and Prinzmetal's angina [see *Warnings and Precautions* (5.1)]
- Arrhythmias [see *Warnings and Precautions* (5.2)]
- Chest, throat, neck and/or jaw pain/tightness/pressure [see *Warnings and Precautions* (5.3)]
- Cerebrovascular events [see *Warnings and Precautions* (5.4)]
- Other vasospasm reactions [see *Warnings and Precautions* (5.5)]
- Medication overuse headache [see *Warnings and Precautions* (5.6)]
- Serotonin syndrome [see *Warnings and Precautions* (5.7)]
- Increase in blood pressure [see *Warnings and Precautions* (5.8)]

- Hypersensitivity reactions [*see Contraindications (4) and Warnings and Precautions (5.9)*]
- Seizures [*see Warnings and Precautions (5.10)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

Table 1 lists adverse reactions that occurred in 2 placebo-controlled clinical trials in 301 patients with migraine who took at least 1 dose of ONZETRA Xsail or placebo. Only adverse reactions that occurred at a frequency of 2% or more with ONZETRA Xsail and that occurred at a frequency greater than the placebo group are included in Table 1.

Table 1: Adverse Reactions Reported by at Least 2% of Patients in 2 Controlled Migraine Trials

Adverse Reaction	Percent of Patients Reporting	
	ONZETRA N=151	Placebo N=150
Abnormal Taste	20	3
Nasal Discomfort	11 ^a	1
Rhinorrhea	5	2
Rhinitis	2	0

^a Limited examinations of the nose and throat did not reveal any clinically noticeable injury in these patients.

There is insufficient data with ONZETRA Xsail to assess the impact of age, gender, and race on adverse effects.

7 DRUG INTERACTIONS

7.1 Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine containing or ergot-type medications (like dihydroergotamine or methysergide) and ONZETRA Xsail within 24 hours of each other is contraindicated.

7.2 Monoamine Oxidase Inhibitors

MAO-A inhibitors increase systemic exposure by up to 7-fold. Therefore, the use of ONZETRA Xsail in patients receiving MAO-A inhibitors is contraindicated [*see Clinical Pharmacology (12.3)*].

7.3 Other 5-HT₁ Agonists

Because their vasospastic effects may be additive, co-administration of ONZETRA Xsail and other 5-HT₁ agonists (e.g., triptans) within 24 hours of each other is contraindicated.

7.4 Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of serotonin syndrome have been reported during co-administration of triptans and SSRIs, SNRIs, TCAs, and MAO inhibitors [*see Warnings and Precautions (5.7)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled trials in pregnant women. In developmental toxicity studies in rats and rabbits, oral administration of sumatriptan to pregnant animals was associated with embryolethality, fetal abnormalities, and pup mortality. When administered by the intravenous route to pregnant rabbits, sumatriptan was embryolethal.

Developmental toxicity studies of sumatriptan by the intranasal route have not been conducted. ONZETRA Xsail should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral administration of sumatriptan to pregnant rats during the period of organogenesis resulted in an increased incidence of fetal blood vessel (cervicothoracic and umbilical) abnormalities. The highest no-effect dose for embryofetal developmental toxicity in rats was 60 mg/kg/day. Oral administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in increased incidences of embryolethality and fetal cervicothoracic vascular and skeletal abnormalities. Intravenous administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in an increased incidence of embryolethality. The highest oral and intravenous no-effect doses for developmental toxicity in rabbits were 15 and 0.75 mg/kg/day, respectively.

Oral administration of sumatriptan to rats prior to and throughout gestation resulted in embryofetal toxicity (decreased body weight, decreased ossification, increased incidence of skeletal abnormalities). The highest no-effect dose was 50 mg/kg/day. In offspring of pregnant rats treated orally with sumatriptan during organogenesis, there was a decrease in pup survival. The highest no-effect dose for this effect was 60 mg/kg/day. Oral treatment of pregnant rats with sumatriptan during the latter part of gestation and throughout lactation resulted in a decrease in pup survival. The highest no-effect dose for this finding was 100 mg/kg/day.

8.3 Nursing Mothers

Sumatriptan is excreted in human milk following subcutaneous administration. Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with ONZETRA Xsail.

8.4 Pediatric Use

Safety and effectiveness has not been established in pediatric patients younger than 18 years of age.

Two controlled clinical trials evaluated sumatriptan nasal spray (5 to 20 mg) in 1,248 adolescent migraineurs aged 12 to 17 years who treated a single attack. The trials did not establish the efficacy of sumatriptan nasal spray compared with placebo in the treatment of migraine in adolescents. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults.

Five controlled clinical trials (2 single-attack studies, 3 multiple-attack studies) evaluating oral sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse reactions in these patients appeared to be both dose- and age-dependent, with younger patients reporting reactions more commonly than older adolescents.

Postmarketing experience documents that serious adverse reactions have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include reactions similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Clinical data to determine the frequency of serious adverse reactions in pediatric patients who might receive subcutaneous, oral, or nasal sumatriptan are not presently available.

8.5 Geriatric Use

Clinical trials of ONZETRA Xsail did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience with subcutaneous, oral, and liquid nasal spray sumatriptan has not identified differences in responses between the elderly and younger patients. In general, treatment for an elderly patient should be cautious, reflecting the greater frequency of decreased or abnormal hepatic function, renal function, or cardiac function, more pronounced blood pressure increases, higher risks for unrecognized CAD, and/or concomitant disease or other drug therapy.

A cardiovascular evaluation is recommended for geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving ONZETRA Xsail [see *Warnings and Precautions* (5.1)].

8.6 Hepatic Impairment

The clearance of oral sumatriptan was reduced in patients with moderate hepatic impairment [see *Clinical Pharmacology* (12.3)]. Similar changes can be expected following intranasal administration. The effect of severe hepatic impairment was NOT evaluated using oral formulation. The use of ONZETRA Xsail in patients with severe hepatic impairment is contraindicated [see *Contraindications* (4)].

10 OVERDOSAGE

In clinical trials, the highest single doses of sumatriptan nasal spray administered without significant reactions were 40 mg to 12 volunteers and 40 mg to 85 subjects with migraine, which is twice the highest single recommended dose. In addition, 12 volunteers were administered a total daily dose of 60 mg (20 mg 3 times daily) for 3.5 days without significant adverse reactions.

Overdose in animals has been fatal and has been heralded by convulsions, tremor, paralysis, inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.

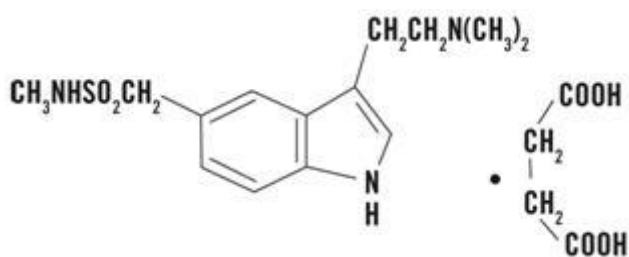
The elimination half-life of ONZETRA Xsail is about 3 hours [see *Clinical Pharmacology* (12.3)], and therefore monitoring of patients after overdose with ONZETRA Xsail should continue for at least 15 hours or while symptoms persist.

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

11 DESCRIPTION

ONZETRA Xsail (sumatriptan nasal powder) uses a disposable, single use nosepiece which is attached by the patient to a delivery device body which has a mouthpiece and a piercing mechanism. The nosepiece contains a hypromellose capsule filled with 11 mg sumatriptan base (as 15.4 mg of sumatriptan succinate) in a dry powder form. Two nosepieces comprise a single 22 mg dose. ONZETRA is for nasal administration with the Xsail device only.

The active component of ONZETRA Xsail is sumatriptan, a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT₁) agonist (triptan), as the succinate salt. Sumatriptan succinate 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 $C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$, 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 ONZETRA Xsail breath-powered delivery device is used to deliver the dry powder contained in the disposable nosepiece (in a capsule) into the nostril using breath exhaled into the device. The Xsail delivery 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sumatriptan binds with high affinity to human cloned 5-HT_{1B/1D} receptors. Sumatriptan presumably exerts its therapeutic effects in the treatment of migraine headache through agonist effects at the 5-HT_{1B/1D} receptors on intracranial blood vessels and sensory nerves of the trigeminal system, which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

12.2 Pharmacodynamics

Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis, has been reported in patients treated with sumatriptan, with and without a history of hypertension [*see Warnings and Precautions (5.8)*].

Peripheral (Small) Arteries

In healthy volunteers (N = 18), a trial evaluating the effects of sumatriptan injection on peripheral (small vessel) arterial reactivity failed to detect a clinically significant increase in peripheral resistance.

Heart Rate

Transient increases in blood pressure observed in some patients in clinical studies carried out during development of sumatriptan as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

12.3 Pharmacokinetics

Absorption and Bioavailability

The mean maximum concentration (C_{max}) following a 22 mg nasal dose of ONZETRA Xsail was 21 ng/mL (range: 9 to 61 ng/mL), and the $AUC_{0-\infty}$ was 65 ng•hr/mL (range: 40 to 107 ng/mL). Peak plasma concentration (T_{max}) was achieved on average 45 minutes (range: 10 minutes to 2 hours) following ONZETRA Xsail administration. The bioavailability of ONZETRA relative to subcutaneous injection was approximately 19%, primarily due to pre-systemic metabolism and partly due to incomplete absorption. Sumatriptan bioavailability following liquid nasal spray administration is 14%, similar to that after oral administration (15%).

Distribution

Protein binding of sumatriptan, determined by equilibrium dialysis over the concentration range of 10 to 1000 ng/mL, is approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated. The apparent volume of distribution is 2.7 L/kg.

Metabolism

In vitro studies with human microsomes suggest that sumatriptan is metabolized by MAO (predominately A isoenzyme). Most of a radiolabeled dose of sumatriptan excreted in the urine is the major metabolite indole acetic acid (IAA) or the IAA glucuronide, both of which are inactive.

Elimination

The elimination half-life of sumatriptan administered as a nasal powder by the Xsail device is approximately 3 hours, similar to the half-life seen with sumatriptan nasal spray. Only 3% of a nasal spray dose is excreted in the urine as unchanged sumatriptan; 42% of a nasal spray dose is excreted as the major metabolite, the indole acetic acid analogue of sumatriptan. The total plasma clearance of the nasal spray is approximately 1200 mL/min.

Specific Populations

Age

The pharmacokinetics of oral sumatriptan in the elderly (mean age: 72 years, 2 males and 4 females) and in patients with migraine (mean age: 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age: 30 years). Intranasal sumatriptan has not been evaluated for age differences.

Race

The systemic clearance and C_{\max} of subcutaneous sumatriptan were similar in black (n=34) and Caucasian (n=38) healthy male subjects. Intranasal sumatriptan has not been evaluated for race differences.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined.

Hepatic Impairment

The effect of mild hepatic disease on the pharmacokinetics of sumatriptan has not been evaluated. Following oral administration, an approximately 70% increase in C_{\max} and AUC was observed in one small trial of patients with moderate liver impairment (n=8) matched for sex, age, and weight with healthy subjects (n=8). Similar changes can be expected following intranasal administration.

The pharmacokinetics of sumatriptan in patients with severe hepatic impairment has not been studied [see *Contraindications* (4)].

Drug Interaction Studies

Monoamine Oxidase-A Inhibitors

Treatment with MAO-A inhibitors generally leads to an increase of sumatriptan plasma levels [see *Contraindications* (4) and *Drug Interactions* (7.2)]. MAO inhibitors interaction studies have not been performed with intranasal sumatriptan.

Due to gut and hepatic metabolic first-pass effects, the increase of systemic exposure after co-administration of an MAO-A inhibitor with oral sumatriptan is greater than after co-administration of the MAO inhibitors with subcutaneous sumatriptan. The effects of an MAO inhibitor on systemic exposure after intranasal sumatriptan would be expected to be greater than the effect after subcutaneous sumatriptan but smaller than the effect after oral sumatriptan because only swallowed drug would be subject to first-pass effects.

In a trial of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of subcutaneous sumatriptan, resulting in a 2-fold increase in the area under the sumatriptan plasma concentration-time curve (AUC), corresponding to a 40% increase in elimination half-life.

A small study evaluating the effect of pretreatment with an MAO-A inhibitor on the bioavailability from a 25 mg oral sumatriptan tablet resulted in an approximately 7-fold increase in systemic exposure.

Xylometazoline

An in vivo drug interaction trial indicated that 3 drops of xylometazoline (0.1% w/v), a decongestant, administered 15 minutes prior to a 20 mg nasal spray dose of sumatriptan did not alter the pharmacokinetics of sumatriptan.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In carcinogenicity studies in mouse and rat in which sumatriptan was administered orally for 78 weeks and 104 weeks, respectively, there was no evidence in either species of an increase in tumors related to sumatriptan administration.

Carcinogenicity studies of sumatriptan using the nasal route have not been conducted.

Mutagenesis

Sumatriptan was negative in in vitro (bacterial reverse mutation [Ames], gene cell mutation in Chinese hamster V79/HGPRT, chromosomal aberration in human lymphocytes) and in vivo (rat micronucleus) assays.

Impairment of Fertility

When sumatriptan was administered by subcutaneous injection to male and female rats prior to and throughout the mating period, there was no evidence of impaired fertility at doses of up to 60 mg/kg/day. When sumatriptan (5, 50, or 500 mg/kg/day) was administered orally to male and female rats prior to and throughout the mating period, there was a treatment-related decrease in fertility secondary to a decrease in mating in animals treated with doses greater than 5 mg/kg/day. It is not clear whether this finding was due to an effect on males or females or both.

Fertility studies of sumatriptan using the intranasal route have not been conducted.

13.2 Animal Toxicology and/or Pharmacology

Corneal Opacities

Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dose tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60-week study. Earlier examinations for these toxicities were not conducted, and no-effect doses were not established.

14 CLINICAL STUDIES

The efficacy of ONZETRA Xsail for the acute treatment of migraine with or without aura was established in a multicenter, randomized, double-blind, placebo-controlled study (Study 1).

Migraineurs enrolled in Study 1 were primarily female (84%) and Caucasian (86%), with a mean age of 42 years (range of 19 to 64). Patients were instructed to treat a moderate to severe migraine headache. Additional medications were allowed as rescue therapy beginning 2 hours after the initial treatment.

In Study 1, the proportion of patients who had headache relief defined as a reduction from moderate or severe pain to mild or no pain was assessed at 15, 30, 60, 90 minutes and 2, 24 and 48 hours after treatment with study drug. Associated symptoms of nausea, photophobia, and phonophobia were assessed as secondary endpoints. The proportion of patients who had no headache at 2 hours (120 minutes) was also assessed.

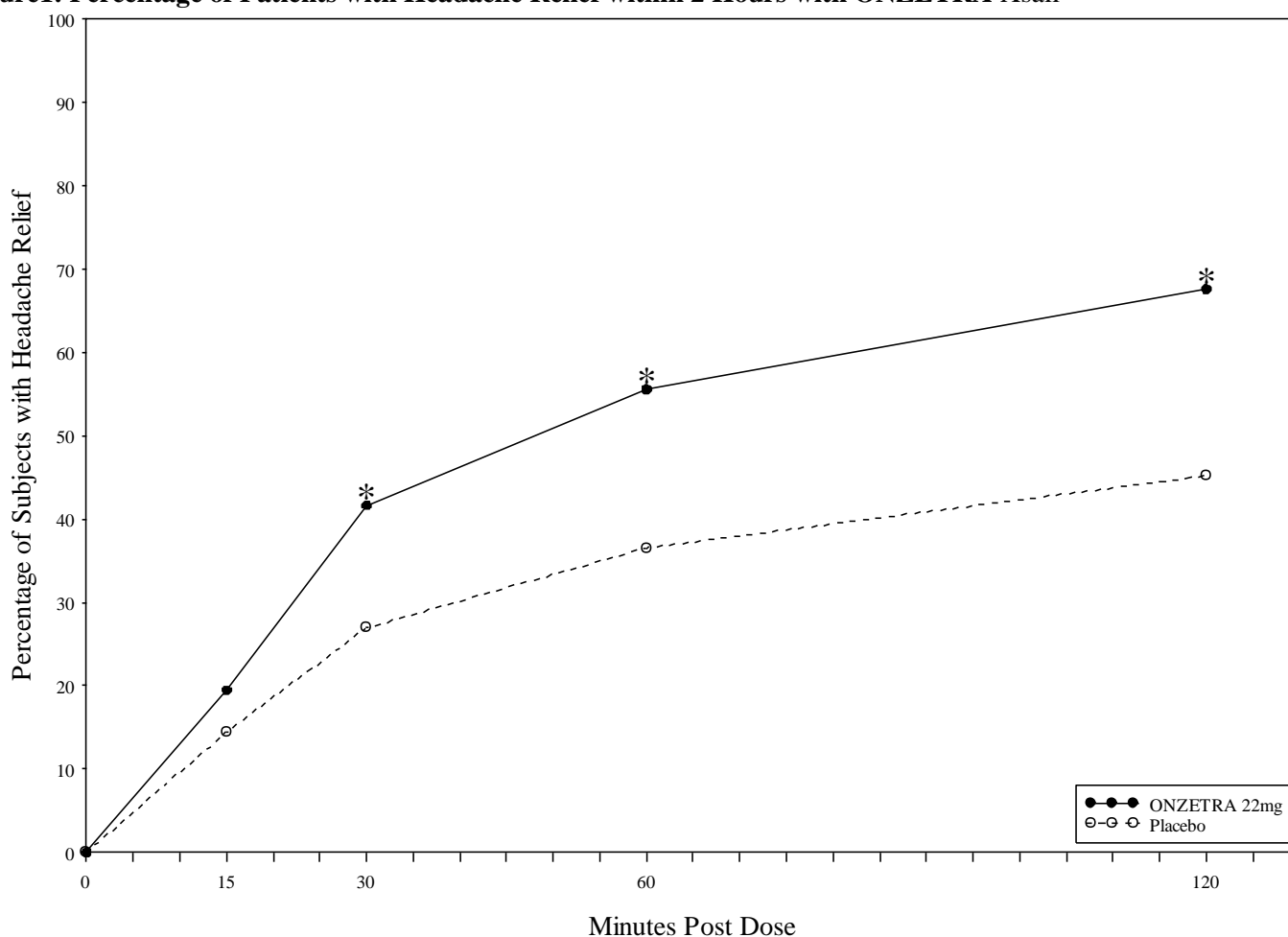
The percentage of patients achieving headache relief 2 hours after treatment was significantly greater in the ONZETRA Xsail 22 mg group compared to those who received placebo (see Table 2 and Figure 1). For patients with migraine-associated nausea, photophobia, and phonophobia at baseline, there was a lower incidence of these symptoms at 2 hours following administration of ONZETRA Xsail compared with placebo.

Table 2: Percentage of Patients With Headache Relief (Primary Efficacy Endpoint), with No Headache, No Nausea, No Photophobia, and No Phonophobia 2 hours Post Treatment with ONZETRA Xsail (Study 1)

2 hours post treatment	ONZETRA 22 mg (n=108)	Placebo (n=104)
Headache Relief	68% ^a	45%
No Headache	34% ^a	17%
No Nausea	82%	79%
No Photophobia	52%	40%
No Phonophobia	68%	56%

^a $p < 0.05$ versus placebo

Figure1: Percentage of Patients with Headache Relief within 2 Hours with ONZETRA Xsail



* $p < 0.05$

The efficacy of ONZETRA Xsail was unaffected by presence of aura; duration of headache prior to treatment; gender, age, or weight of the subject; or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium

channel blockers, tricyclic antidepressants). There was insufficient data to assess the impact of race on efficacy.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ONZETRA Xsail is supplied as a disposable nosepiece containing a capsule and a reusable breath-powered delivery device body. Each capsule contains 11 mg sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder) in a clear, hypromellose capsule with 825 printed on one side.

ONZETRA Xsail is available in kits containing 8 doses.

The following table provides a description of the packaging configurations:

Description	Contents	NDC Code
8 Dose Kit	8 pouches containing 2 nosepieces (22 mg sumatriptan) per pouch. Each nosepiece contains 11 mg sumatriptan 2 breath-powered delivery system bodies	64597-311-08

16.2 Storage and Handling

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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Only patients who are able to understand and follow the instructions should use ONZETRA Xsail.

Instructions on the proper use of ONZETRA Xsail from a physician or healthcare professional prior to administration for the first time may be helpful. For support, healthcare professionals and patients can call 1-844-ONZETRA or see www.ONZETRA.com.

Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other Vasospasm-Related Events, Arrhythmias, and Cerebrovascular Events

Inform patients that triptan medications, including ONZETRA Xsail, may cause serious cardiovascular side effects such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious cardiovascular events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, irregular heartbeat, significant rise in blood pressure, weakness, and slurring of speech and should ask for medical advice if any indicative signs or symptoms are observed. Apprise patients of the importance of this follow-up [see *Warnings and Precautions* (5.1, 5.2, 5.3, 5.4, and 5.5)].

Anaphylactic Reactions

Inform patients that anaphylactic reactions have occurred in patients receiving sumatriptan. Such reactions can be life-threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens [see *Warnings and Precautions* (5.9)].

Concomitant Use with Other Triptans and Ergot Medications

Inform patients that use of ONZETRA Xsail within 24 hours of another triptan or an ergot-type medication (including dihydroergotamine or methysergide) is contraindicated [see *Contraindications* (4) and *Drug Interactions* (7.1, 7.3)].

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with the use of ONZETRA Xsail or other triptans, particularly during combined use with SSRIs, SNRIs, TCAs, and MAO inhibitors [see *Warnings and Precautions (5.7)* and *Drug Interactions (7.4)*].

Medication Overuse Headache

Inform patients that use of acute migraine drugs for 10 or more days per month may lead to an exacerbation of headache and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) [see *Warnings and Precautions (5.6)*].

Pregnancy

Inform patients that ONZETRA Xsail should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus [see *Use in Specific Populations (8.1)*].

Nursing Mothers

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed [see *Use in Specific Populations (8.3)*].

Ability To Perform Complex Tasks

Treatment with sumatriptan may cause somnolence and dizziness; instruct patients to evaluate their ability to perform complex tasks during migraine attacks and after administration of ONZETRA Xsail.

Local Irritation

Inform patients that they may experience local irritation of their nose and throat. The symptoms will generally resolve in less than 2 hours.

How to Use ONZETRA Xsail with the breath powered device

Provide patients with instructions on the proper use of ONZETRA Xsail with the breath powered device.

Advise patients that use of the breath powered device is for ONZETRA Xsail only. No other product or substance is approved for use in the breath powered device.

Advise patients to remove a disposable nosepiece from the foil pouch, remove the clear device cap from the reusable device, and click the nosepiece into the device body.

Advise the patient to fully press and release the white piercing button on the device body to pierce the capsule inside the nosepiece. Instruct the patient to press the white piercing button only once.

Advise the patient to insert the nosepiece into the nostril so that it makes a tight seal. The device is then rotated and the mouthpiece inserted between the lips.

Instruct the patient to blow forcefully through the mouthpiece to deliver the sumatriptan powder into the nasal cavity. Vibration (e.g., a rattling noise) may occur, and indicates that the patient is blowing forcefully, as directed.

Advise the patient to remove and discard the nosepiece once the medication has been administered.

Instruct the patient to follow the same process using a second nosepiece in the other nostril to administer the remainder of the total recommended dose.

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This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

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Aliso Viejo, CA 92656

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Patient Information
ONZETRA™ (On ze' trah) Xsail™ (Eks'-seil)
(sumatriptan nasal powder) 11 mg

Read this Patient Information before you start using ONZETRA Xsail and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ONZETRA Xsail?

ONZETRA Xsail can cause serious side effects, including:

Heart attack and other heart problems. Heart problems may lead to death.

Stop taking ONZETRA Xsail and get emergency medical help right away if you have any of the following symptoms of a heart attack:

- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

ONZETRA Xsail is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. You have a higher risk for heart disease if you:

- have high blood pressure
- have high cholesterol levels
- smoke
- are overweight
- have diabetes
- have a family history of heart disease

What is ONZETRA Xsail?

ONZETRA Xsail is a prescription medicine used to treat acute migraine headaches with or without aura in adults.

ONZETRA Xsail is not used to treat other types of headaches such as hemiplegic migraines (that make you unable to move on one side of your body) or basilar migraines (rare form of migraine with aura).

ONZETRA Xsail is not used to prevent or decrease the number of migraine headaches you have.

It is not known if ONZETRA Xsail is safe and effective to treat cluster headaches.

It is not known if ONZETRA Xsail is safe and effective in children under 18 years of age.

Who should not use ONZETRA Xsail?

Do not use ONZETRA Xsail if you have:

- an allergy to sumatriptan
- heart problems or history of heart problems

- narrowing of blood vessels to your legs, arms, stomach or kidney (peripheral vascular disease)
- uncontrolled high blood pressure
- severe liver problems
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- had a stroke, transient ischemic attacks (TIAs) or problems with your blood circulation
- taken any of the following medicines in the last 24 hours:
 - almotriptan (AXERT[®])
 - eletriptan (RELPAX[®])
 - frovatriptan (FROVA[®])
 - naratriptan (AMERGE[®])
 - rizatriptan (MAXALT[®], MAXALT-MLT[®])
 - zolmitriptan (ZOMIG[®], ZOMIG-ZMT[®], ZOMIG[®] NASAL SPRAY)
 - sumatriptan (IMITREX[®], IMITREX[®] NASAL SPRAY, IMITREX[®] INJECTION)
 - sumatriptan and naproxen (TREXIMET[®])
 - sumatriptan (SUMAVEL[®] DOSE PRO[®] INJECTION)
 - sumatriptan (ALSUMA[®])
 - sumatriptan (ZECUITY[®] TRANSDERMAL PATCH)
 - ergotamines (CAFERGOT[®], ERGOMAR[®], MIGERGOT[®])
 - dihydroergotamine (D.H.E. 45[®], MIGRANAL[®])

Ask your healthcare provider if you are not sure if your medicine is listed above.

What should I tell my healthcare provider before taking ONZETRA Xsail?

Before you use ONZETRA Xsail, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- have heart problems or a family history of heart problems or stroke
- have kidney problems
- have liver problems
- have had epilepsy or seizures
- are not using effective birth control
- become pregnant while taking ONZETRA Xsail
- are breastfeeding or plan to breastfeed. ONZETRA Xsail passes into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you use ONZETRA Xsail.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

ONZETRA Xsail and certain other medicines can affect each other, causing serious side effects.

Especially tell your healthcare provider if you take anti-depressant medicines called:

- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants (TCAs)

- monoamine oxidase inhibitors (MAOIs)

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I use ONZETRA Xsail?

Before using ONZETRA Xsail, read the Patient Instructions for Use.

- Certain people should use their first dose of ONZETRA Xsail in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should use your first dose in a medical setting.
- Use ONZETRA Xsail exactly as your healthcare provider tells you to use it.
- Use a full dose (2 nosepieces) to treat your headache.
- If you do not get any relief after your first full dose, do not use a second dose without first talking with your healthcare provider.
- If your headache comes back after the first full dose or you only get some relief from your headache, you can use a second full dose 2 hours after the first full dose.
- Do not take more than a total of 44 mg (two full doses) of ONZETRA Xsail in a 24-hour period.
- It is not known how using ONZETRA Xsail for a long time affects the nose and throat.
- If you use too much ONZETRA Xsail, call your healthcare provider or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take ONZETRA Xsail so you can talk with your healthcare provider about how ONZETRA Xsail is working for you.

What should I avoid while taking ONZETRA Xsail?

ONZETRA Xsail can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery or do anything where you need to be alert.

What are the possible side effects of ONZETRA Xsail?

ONZETRA Xsail may cause serious side effects. See "What is the most important information I should know about ONZETRA Xsail?"

These serious side effects include:

- changes in color or sensation in your fingers and toes (Raynaud's syndrome)
- stomach and intestinal problems (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
 - sudden or severe stomach pain
 - stomach pain after meals
 - weight loss
 - nausea or vomiting
 - constipation or diarrhea
 - bloody diarrhea
 - fever
- problems with blood circulation to your legs and feet (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
 - cramping and pain in your legs or hips
 - feeling of heaviness or tightness in your leg muscles
 - burning or aching pain in your feet or toes while resting

- numbness, tingling or weakness in your legs
- cold feeling or color changes in 1 or both legs or feet
- hives (itchy bumps); swelling of your tongue, mouth or throat
- medication overuse headaches. Some people who use too much sumatriptan may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with ONZETRA Xsail.
- serotonin syndrome. Serotonin syndrome is a rare but serious problem that can happen in people using ONZETRA Xsail, especially if ONZETRA Xsail is used with anti-depressant medications called SSRIs or SNRIs. Call your healthcare provider right away if you have any of the following symptoms of serotonin syndrome:
 - Mental changes such as seeing things that are not there (hallucinations), agitation, or coma
 - Fast heartbeat
 - Changes in blood pressure
 - High body temperature
 - Tight muscles
 - Trouble walking
- seizures. Seizures have happened in people taking sumatriptan who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take ONZETRA Xsail.

The most common side effects of ONZETRA Xsail include:

- unusual or bad taste in your mouth
- discomfort of your throat or nose
- runny nose, stuffy nose, and/or postnasal drip

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ONZETRA Xsail. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ONZETRA Xsail?

- Store at room temperature, between 68°F to 77°F (20°C to 25°C).
- Do not store in the refrigerator or freezer.

Keep ONZETRA Xsail and all medicines out of the reach of children.

General information about the safe and effective use of ONZETRA Xsail.

- ONZETRA Xsail is to be used only with the Xsail breath powered device.
- Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets.
- Do not use ONZETRA Xsail for a condition for which it was not prescribed.
- Do not give ONZETRA Xsail to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about ONZETRA Xsail. If you would like more information, talk with your healthcare provider. You can ask your healthcare

provider or pharmacist for information about ONZETRA Xsail that is written for healthcare professionals.

For more information, go to www.ONZETRA.com or call 1-844-ONZETRA.

What are the ingredients in ONZETRA Xsail?

- Active ingredient: sumatriptan succinate
- Inactive ingredient: hypromellose (capsule)

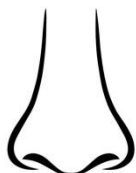
This Patient Information has been approved by the U.S. Food and Drug Administration.

Instructions for Use

Read these Instructions for Use which come with ONZETRA™ Xsail™ before you start using it and each time you get a refill. Follow these instructions each time you use ONZETRA Xsail.

HOW TO USE ONZETRA™ Xsail™

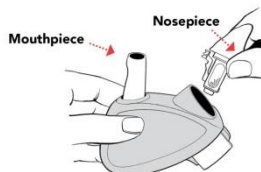
PART 1



1ST NOSEPIECE
in 1st nostril

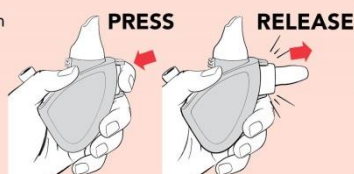
- 1** **OPEN** the pouch and remove the **first nosepiece**.

Remove device cover. **INSERT** the first nosepiece into the device until you hear it click into place.

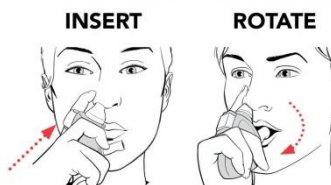


- 2** Fully **PRESS** and **RELEASE** white button to pierce the medication capsule.

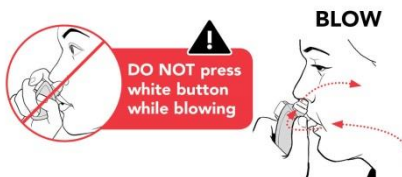
! If you skip this step, you will not get any medication



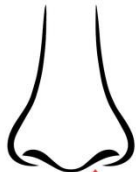
- 3** **INSERT** the nosepiece deeply into your nose. Keep the nosepiece in your nose while you rotate the device to place the mouthpiece into your mouth.



- 4** **BLOW WITH YOUR MOUTH** into the device for **2-3 seconds**, like you're blowing up a balloon, to deliver medication into your nose. (You may hear a rattling sound or feel a vibration.)

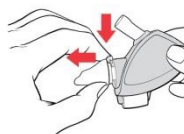


PART 2



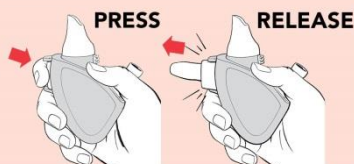
2ND NOSEPIECE
in 2nd nostril

- 5** Press the clear tab to remove the first nosepiece. **CHECK** the capsule to see if the medication is gone. **DISCARD** the used nosepiece in the trash. Insert **second nosepiece** into device.

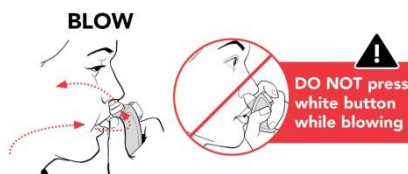


- 6** **DON'T FORGET TO PIERCE THE CAPSULE IN SECOND NOSEPIECE.**

! If you skip this step, you will not get any medication



- 7** Lastly, repeat steps 3-4 with **second nosepiece** in **second nostril**.



DID I DO IT RIGHT?

- ☒ **Checked the nosepieces.** It is normal to see a thin white residue after use. If one or both of the capsules appear unused, repeat steps 2-4 with the same nosepiece
- ☒ **Used both nosepieces—one in each nostril**
- ☒ **Pierced both capsules** before blowing
- ☒ **DID NOT** hold down white button while blowing



These Instructions for Use have been approved by the U.S. Food and Drug Administration.

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