HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Sumavel DosePro (sumatriptan injection) for subcutaneous use

Initial U.S. Approval: 1992

----------INDICATIONS AND USAGE----------

Sumavel® DosePro® is a 5-$HT_{1B/1D}$ receptor agonist (triptan) indicated for:

- the acute treatment of migraine attacks, with or without aura (1.1)
- the acute treatment of cluster headache episodes (1.1)

Important limitations:

- Use only after a clear diagnosis of migraine or cluster headache has been established (1.2)
- Not intended for the prophylactic therapy of migraine (1.2)

----------DOSAGE AND ADMINISTRATION----------

- For subcutaneous use only (2)
- Single 6 mg dose administered to the abdomen or thigh (2)
- Do not administer to the arm or other areas of the body (2)
- The maximum recommended dose that may be given in 24 hours is two doses separated by at least 1 hour (2)
- Benefit of a second dose in patients who have failed to respond to a first dose has not been established (2)
- Do not use Sumavel DosePro if the tip of the device is tilted or broken off upon removal from packaging (2)

----------DOSAGE FORMS AND STRENGTHS----------

Sumavel DosePro is a prefilled, single-dose, needle-free subcutaneous delivery system delivering 0.5 mL of sterile solution containing 6 mg sumatriptan (as the succinate salt). (3)

----------CONTRAINDICATIONS----------

- Do not administer intravenously as this may cause coronary vasospasm (4.1)
- Ischemic heart disease, coronary artery vasospasm, or other significant underlying cardiovascular disease (4.2)
- Cerebrovascular syndromes (e.g. history of stroke or TIA) (4.3)
- Peripheral Vascular Disease (including Ischemic Bowel Disease) (4.4)
- Uncontrolled hypertension (4.5)
- Do not use Sumavel DosePro within 24 hours of any ergotamine-containing or ergot-type medication or another 5-HT_1 agonist, e.g. another triptan (4.6)
- Hemiplegic or basilar migraine (4.7)
- Known hypersensitivity to sumatriptan (4.8)

----------WARNINGS AND PRECAUTIONS----------

- Serious adverse cardiac events, including acute myocardial infarction, and life-threatening disturbances of cardiac rhythm (5.1)
- It is strongly recommended that Sumavel DosePro not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors. In very rare cases, serious cardiovascular events have been reported in association with sumatriptan use in the absence of known cardiovascular disease. If Sumavel DosePro is considered, patients should first have a cardiovascular evaluation. If the evaluation is satisfactory, the first dose should take place in a physician's office setting (5.1)
- Sensations of pain, tightness, pressure and heaviness in the chest, throat, neck and jaw: generally not associated with myocardial ischemia, but patients with signs or symptoms suggestive of angina should be evaluated for the presence of CAD (5.2)
- Cerebrovascular events, some fatal (5.3)
- Gastrointestinal ischemic events and peripheral vasospastic reactions (e.g. Raynaud's syndrome) (5.4)
- Potentially life-threatening serotonin syndrome, particularly in combination with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). Monitor patients for neurologic changes and gastrointestinal symptoms if concomitant treatment is clinically warranted (5.5, 7.4)
- Increase in blood pressure, associated with significant clinical events (4.5, 5.6)
- Hypersensitivity, life-threatening or fatal (5.8)
- Seizures (5.9)

----------ADVERSE REACTIONS----------

In controlled studies with sumatriptan injection, the most common adverse reactions (≥ 2% and > placebo) were injection site reactions, tingling, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, feeling of tightness, numbness, feeling strange, tight feeling in head, flushing, tightness in chest, discomfort in nasal cavity/sinuses, jaw discomfort, dizziness/vertigo, drowsiness/sedation, and headache (6.1).

In active-controlled studies, bleeding, swelling, erythema and bruising were observed more frequently with Sumavel DosePro than with sumatriptan needle-based injection with most resolving spontaneously. (6.5)

To report SUSPECTED ADVERSE REACTIONS, contact Zogenix, Inc. at 1-866-ZOGENIX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- MAO-A inhibitors: sumatriptan plasma levels nearly doubled; concurrent use ordinarily not recommended (5.7, 7.1)
- Do not use Sumavel DosePro and ergotamine-containing or ergot-type medications within 24 hours of each other (4.6, 7.2)
- Do not use Sumavel DosePro and other 5HT_1 agonists (e.g. triptans) within 24 hours of each other (4.6, 7.3)
- SSRI/SNRI: life-threatening serotonin syndrome reported during combined use with triptans (5.5, 7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (5.10, 8.1)
- Nursing Mothers: Caution should be excercised when administered to a nursing woman (8.3)
- Pediatric Use: The safety and effectiveness in pediatric patients under 18 years of age have not been established (8.4)
- Geriatric Use: Not recommended (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2011

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Treatment of Migraine Attacks and Cluster Headache

Sumavel DosePro (sumatriptan injection) is indicated for the acute treatment of migraine attacks, with or without aura, and the acute treatment of cluster headache episodes.

1.2 Important Limitations

Sumavel DosePro should only be used where a clear diagnosis of migraine or cluster headache has been established. Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or cluster headache or who experience a headache that is atypical for them.

For a given attack, if a patient does not respond to the first dose of Sumavel DosePro, the diagnosis of migraine or cluster headache should be reconsidered before administration of a second dose.

Sumavel DosePro is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. *[see Contraindications (4.7)]*

2 DOSAGE AND ADMINISTRATION

Sumavel DosePro is for subcutaneous use only and is designed for patient self-administration to the abdomen or thigh. Sumavel DosePro is not to be administered to other areas of the body, including the arm. Sumavel DosePro is not to be administered intramuscularly or intravenously.

Administer one Sumavel DosePro to the abdomen or thigh to deliver subcutaneously 6 mg of sumatriptan (as the succinate salt) per 0.5 mL dose. One Sumavel DosePro is the maximum single recommended adult dose. The maximum recommended dose that may be given in 24 hours is two doses of Sumavel DosePro (or one dose of Sumavel DosePro and one dose of another sumatriptan product) separated by at least 1 hour. Controlled clinical trials with sumatriptan injection have failed to show that clear benefit is associated with the administration of a second 6 mg dose in patients who have failed to respond to a first dose.

Patients should be instructed to use administration sites on the abdomen or the thigh with an adequate subcutaneous thickness to accommodate penetration of sumatriptan injection into the subcutaneous space. Administration should not be made within 2 inches of the navel. Patients should be instructed not to use Sumavel DosePro if the tip of the device is tilted or broken off upon removal from packaging. *[see Patient Counseling Information (17.5)]*

Sumavel DosePro is for single use only. Discard after use.

3 DOSAGE FORMS AND STRENGTHS

Sumavel DosePro is a prefilled, single-dose, needle-free subcutaneous delivery system delivering 0.5 mL of sterile solution containing 6 mg sumatriptan (as the succinate salt).

4 CONTRAINDICATIONS

4.1 Intravenous Administration

Sumavel DosePro is not designed to administer sumatriptan injection intravenously. Do not administer intravenously since sumatriptan may cause coronary vasospasm.

4.2 Ischemic or Vasospastic Coronary Artery Disease

Do not use Sumavel DosePro in patients with ischemic heart disease (e.g. angina pectoris, history of myocardial infarction, or documented silent ischemia), or in patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina or other significant underlying cardiovascular disease. *[see Warnings and Precautions (5.1)]*

4.3 Cerebrovascular Syndromes

Do not use Sumavel DosePro in patients with cerebrovascular syndromes including (but not limited to) strokes of any type as well as transient ischemic attacks. *[see Warnings and Precautions (5.3)]*

4.4 Peripheral Vascular Disease

Do not use Sumavel DosePro in patients with peripheral vascular disease including (but is not limited to) ischemic bowel disease. *[see Warnings and Precautions (5.4)]*

4.5 Uncontrolled Hypertension

Because Sumavel DosePro may increase blood pressure, do not use in patients with uncontrolled hypertension. *[see Warnings and Precautions (5.6)]*

4.6 Do not use within 24 hours of treatment with Ergotamine-Containing or Ergot-Type Medications or Other 5-HT$_1$ Agonists (e.g. triptans)

Do not use Sumavel DosePro and any ergotamine-containing or ergot-type medication (such as dihydroergotamine or methysergide) within 24 hours of each other; do not use Sumavel DosePro and another 5-HT$_1$ agonist (e.g. triptan) within 24 hours of each other (with the exception of a single dose of another sumatriptan product, provided the doses are separated by at least 1 hour). *[see Drug Interactions (7.3)]*

4.7 Hemiplegic or Basilar Migraine

Do not use Sumavel DosePro in patients with hemiplegic or basilar migraine.

4.8 Hypersensitivity

Sumavel DosePro is contraindicated in patients with known hypersensitivity to sumatriptan.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Myocardial Ischemia and Infarction and Other Adverse Cardiac Events

Cardiac Events and Fatalities with 5-HT$_1$ Agonists

Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of sumatriptan. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low.

Sumatriptan can cause coronary vasospasm. Some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD with close proximity of the events to sumatriptan use. Because Sumavel DosePro may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following Sumavel DosePro administration should be evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of sumatriptan and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur.

Premarketing Experience with Sumatriptan

Among the more than 1,900 patients with migraine who participated in reported premarketing controlled clinical trials of subcutaneous sumatriptan, there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six of these 8 patients had ECG changes consistent with transient ischemia, without accompanying clinical symptoms or signs. Of these 8 patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Of 6,348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, 2 experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Post-marketing Experience with Sumatriptan

Serious cardiovascular events, some resulting in death, have been reported in association with the use of subcutaneous sumatriptan injection. The uncontrolled nature of post-marketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of sumatriptan and the onset of the clinical event, the less likely the association is to be causative. Interest has focused on events beginning within 1 hour of the administration of sumatriptan.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan administration include coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among reports of serious cardiac events within 1 hour of sumatriptan administration, the majority had risk factors predictive of CAD, and the presence of significant underlying CAD was established in most cases. *[see Contraindications (4.2)]*

Patients with documented coronary artery disease

Because of the potential of this class of compound (5-HT$_1$ agonists) to cause coronary vasospasm, Sumavel DosePro should not be given to patients with documented ischemic or vasospastic coronary artery disease. *[see Contraindications (4.2)]*

Patients with risk factors for CAD

It is strongly recommended that Sumavel DosePro not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, Sumavel DosePro should not be administered. *[see Contraindications (4.2)]*

For patients with risk factors predictive of CAD who have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of Sumavel DosePro take place in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining, on the first occasion of use, an electrocardiogram (ECG) during the interval immediately following use of Sumavel DosePro in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of Sumavel DosePro and who have or acquire risk factors predictive of CAD, as described above, undergo cardiovascular evaluation periodically as they continue to use sumatriptan. In considering this recommendation for periodic cardiovascular evaluation, it is noted that patients with cluster headache are predominantly male and over 40 years of age, which are risk factors for CAD.

5.2 Sensations of Pain, Tightness, Pressure in the Chest and/or Throat, Neck and Jaw

Sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw are relatively common after treatment with sumatriptan. Only rarely have these symptoms been associated with ischemic ECG changes.

However, because sumatriptan may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms occur. Patients shown to have CAD and those with Prinzmetal's variant angina should not receive 5-HT$_1$ agonists. *[see Contraindications (4.2) and Warnings and Precautions (5.1)]*

Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome, following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm. *[see Contraindications (4.4) and Warnings and Precautions (5.4)]*

5.3 Cerebrovascular Events and Fatalities

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with subcutaneous sumatriptan, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief the symptoms experienced were a consequence of migraine when they were not. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack). *[see Contraindications (4.3)]*

5.4 Other Vasospasm-Related Events, Including Peripheral Vascular Ischemia and Colonic Ischemia

5-HT$_1$ agonists, including Sumavel DosePro, may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported.

Very rare reports of transient and permanent blindness and significant partial vision loss have been reported with the use of sumatriptan. Visual disorders may also be part of a migraine attack.

Patients who experience other symptoms or signs suggestive of decreased arterial flow following the use of any 5-HT$_1$ agonist, such as ischemic bowel syndrome or Raynaud's syndrome, are candidates for further evaluation *[see Contraindications (4.4)]*

5.5 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with triptans, including Sumavel DosePro, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRI (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). *[see Drug Interactions (7.4)]*

5.6 Increase in Blood Pressure

Sumavel DosePro is contraindicated in patients with uncontrolled hypertension. Sumatriptan should be administered with caution to patients with controlled hypertension, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients. Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. *[see Contraindications (4.5)]*

5.7 Concomitant MAO-A Inhibitors

The co-administration of Sumavel DosePro and an MAO-A inhibitor is not generally recommended. In patients taking MAO-A inhibitors, sumatriptan plasma levels are nearly doubled. If such therapy is clinically warranted, however, do not use Sumavel DosePro to administer sumatriptan, as Sumavel DosePro only exists as a 6 mg fixed-dose needle-free delivery system and dose adjustments are not possible. *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*

5.8 Hypersensitivity

Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. *[see Contraindications (4.8)]*

5.9 Seizures

There have been rare reports of seizure following administration of sumatriptan. Sumatriptan should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

5.10 Corneal Opacities

Sumatriptan causes corneal opacities and defects in the corneal epithelium in dogs; this raises the possibility that these changes may occur in humans. While patients were not systematically evaluated for these changes in clinical trials, and no specific recommendations for monitoring are being offered, prescribers should be aware of the possibility of these changes. *[see Nonclinical Toxicology (13.2)]*

6 ADVERSE REACTIONS

This section provides a summary of adverse reactions reported in subjects in clinical studies conducted with Sumavel DosePro and sumatriptan injection.

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.

Serious cardiac reactions, including myocardial infarction, have occurred following the use of sumatriptan. These reactions are extremely rare and most have been reported in patients with risk factors predictive of CAD. Reactions reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. *[see Contraindications (4.2) and Warnings and Precautions (5.1)]*

Significant hypertensive episodes, including hypertensive crises, have been reported on rare occasions in patients with or without a history of hypertension. *[see Warnings and Precautions (5.6)]*

The following other adverse reactions are discussed in more detail in other sections of the labeling:

Sensations of Chest Pain and Tightness *[see Warnings and Precautions (5.2)]*

Cerebrovascular Events and Fatalities *[see Warnings and Precautions (5.3)]*

Other Vasospasm related Events including Peripheral Vascular Ischemia and Colonic Ischemia *[see Warnings and Precautions (5.4)]*

Serotonin Syndrome *[see Warnings and Precautions (5.5)]*

Among patients in clinical trials of subcutaneous sumatriptan succinate injection (n = 6,218), up to 3.5% of patients withdrew for reasons related to adverse reactions.

6.1 Controlled Clinical Trials in Patients with Migraine Headache

Table 1 lists adverse reactions that occurred in 2 large placebo-controlled clinical trials in migraine patients following either a single 6 mg sumatriptan injection or placebo. Only adverse reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection 6 mg and occurred at a frequency greater than in the placebo group are included in Table 1.

Table 1. Treatment-Emergent Adverse Reactions Incidence in 2 Large, Placebo-Controlled Clinical Trials in Patients with Migraine: Events Reported by at Least 2% of Patients Treated with Sumatriptan Injection 6 mg*

	Percent of Patients Reporting	
Adverse Reactions	Sumatriptan Injection, 6 mg SC (n = 547)	Placebo Injection, SC (n = 370)
Atypical sensations	42	9
Tingling	14	3
Warm/hot sensation	11	4
Burning sensation	7	<1
Feeling of heaviness	7	1
Pressure sensation	7	2
Feeling of tightness	5	<1
Numbness	5	2
Feeling strange	2	<1
Tight feeling in head	2	<1
Cardiovascular		
Flushing	7	2
Chest discomfort	5	1
Tightness in chest	3	<1
Discomfort: nasal cavity/sinuses	2	<1
Injection site reaction	59	24
Miscellaneous		
Jaw Discomfort	2	0
Musculoskeletal		
Weakness	5	<1
Neck pain/stiffness	5	<1
Myalgia	2	<1
Neurological		
Dizziness/vertigo	12	4
Drowsiness/sedation	3	2
Headache	2	<1

* The sum of the percentages cited is greater than 100% because patients could have experienced more than 1 type of adverse event. Only events that occurred at a frequency of 2% or more in groups treated with sumatriptan injection and that occurred at a frequency greater than that in the placebo group are included.

The incidence of adverse reactions in controlled clinical trials was not affected by gender or age of the patients. There were insufficient data to assess the impact of race on the incidence of adverse events.

6.2 Controlled Clinical Trials in Patients with Cluster Headache

In the controlled clinical trials assessing sumatriptan injection as a treatment for cluster headache, no new significant adverse reactions associated with the use of sumatriptan were detected that had not already been identified in association with the drug's use in migraine.

Overall, the frequency of adverse events reported in studies of cluster headache was generally lower. Exceptions include reports of paresthesia (5% sumatriptan, 0% placebo), nausea and vomiting (4% sumatriptan, 0% placebo), and bronchospasm (1% sumatriptan, 0% placebo).

6.3 Other Adverse Reactions Observed in Association with the Administration of Sumatriptan Injection

The frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan injection in their causation cannot be reliably determined. Furthermore, variability associated with adverse reactions reporting, the terminology used to describe adverse reactions limits the value of the quantitative frequency estimates provided.

Adverse reactions frequencies are calculated as the number of patients reporting an event divided by the total number of patients (N = 6,218) exposed to subcutaneous sumatriptan. All reported adverse reactions are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Adverse reactions are further classified within body system categories and

enumerated in order of decreasing frequency using the following definitions: frequent adverse reactions are defined as those occurring in at least 1/100 patients, infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients, and rare adverse reactions are those occurring in fewer than 1/1,000 patients.

Cardiovascular: Infrequent were hypertension, hypotension, bradycardia, tachycardia, palpitations, pulsating sensations, various transient ECG changes (nonspecific ST or T-wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, non-sustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle), and syncope. Rare were pallor, arrhythmia, abnormal pulse, vasodilation, and Raynaud's syndrome.

Endocrine and Metabolic: Infrequent was thirst. Rare were polydipsia and dehydration.

Eye: Frequent were vision alterations. Infrequent was irritation of the eye.

Gastrointestinal: Frequent were abdominal discomfort and dysphagia. Infrequent were gastroesophageal reflux and diarrhea. Rare were peptic ulcer, retching, flatulence/eructation, and gallstones.

Musculoskeletal: Frequent were muscle cramps. Infrequent were various joint disturbances (pain, stiffness, swelling, ache). Rare were muscle stiffness, need to flex calf muscles, backache, muscle tiredness, and swelling of the extremities.

Neurological: Frequent was anxiety. Infrequent were mental confusion, euphoria, agitation, relaxation, chills, sensation of lightness, tremor, shivering, disturbances of taste, prickling sensations, paresthesia, stinging sensations, facial pain, photophobia, and lacrimation. Rare were transient hemiplegia, hysteria, globus hystericus, intoxication, depression, myoclonia, monoplegia/diplegia, sleep disturbance, difficulties in concentration, disturbances of smell, hyperesthesia, dysesthesia, simultaneous hot and cold sensations, tickling sensations, dysarthria, yawning, reduced appetite, hunger, and dystonia.

Respiratory: Infrequent was dyspnea. Rare were influenza, diseases of the lower respiratory tract, and hiccoughs.

Skin: Infrequent were erythema, pruritus, and skin rashes and eruptions. Rare was skin tenderness.

Urogenital: Rare were dysuria, frequency, dysmenorrhea, and renal calculus.

Miscellaneous: Infrequent were miscellaneous laboratory abnormalities, including minor disturbances in liver function tests, "serotonin agonist effect," and hypersensitivity to various agents. Rare was fever.

6.4 Other Adverse Reactions Observed in the Clinical Development of Sumatriptan

The following adverse reactions occurred in clinical trials with sumatriptan tablets and sumatriptan nasal spray. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan in their causation cannot be reliably determined. All reported events are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug.

Breasts: Breast swelling, cysts, disorder of breasts, lumps, masses of breasts, nipple discharge, primary malignant breast neoplasm, and tenderness.

Cardiovascular: Abdominal aortic aneurysm, angina, atherosclerosis, cerebral ischemia, cerebrovascular lesion, heart block, peripheral cyanosis, phlebitis, thrombosis, and transient myocardial ischemia.

Ear, Nose, and Throat: Allergic rhinitis; disorder of nasal cavity/sinuses; ear, nose, and throat hemorrhage; ear infection; external otitis; feeling of fullness in the ear(s); hearing disturbances; hearing loss; Meniere's disease; nasal inflammation; otalgia; sensitivity to noise; sinusitis; tinnitus; and upper respiratory inflammation.

Endocrine and Metabolic: Elevated thyrotropin stimulating hormone (TSH) levels; endocrine cysts, lumps, and masses; fluid disturbances; galactorrhea; hyperglycemia; hypoglycemia; hypothyroidism; weight gain; and weight loss.

Eye: Accommodation disorders, blindness and low vision, conjunctivitis, disorders of sclera, external ocular muscle disorders, eye edema and swelling, eye hemorrhage, eye itching, eye pain, keratitis, mydriasis, and visual disturbances.

Gastrointestinal: Abdominal distention, colitis, constipation, dental pain, dyspeptic symptoms, feelings of gastrointestinal pressure, gastric symptoms, gastritis, gastroenteritis, gastrointestinal bleeding, gastrointestinal pain, hematemesis, hypersalivation, hyposalivation, intestinal obstruction, melena, nausea and/or vomiting, oral itching and irritation, pancreatitis, salivary gland swelling, and swallowing disorders.

Hematological Disorders: Anemia.

Mouth and Teeth: Disorder of mouth and tongue (e.g., burning of tongue, numbness of tongue, dry mouth).

Musculoskeletal: Acquired musculoskeletal deformity, arthralgia and articular rheumatitis, arthritis, intervertebral disc disorder, muscle atrophy, muscle tightness and rigidity, musculoskeletal inflammation, and tetany.

Neurological: Apathy, aggressiveness, bad/unusual taste, bradylogia, cluster headache, convulsions, depressive disorders, detachment, disturbance of emotions, drug abuse, facial paralysis, hallucinations, heat sensitivity, incoordination, increased alertness, memory disturbance, migraine, motor dysfunction, neoplasm of pituitary, neuralgia, neurotic disorders, paralysis, personality change, phobia, phonophobia, psychomotor disorders, radiculopathy, raised intracranial pressure, rigidity, stress, syncope, suicide, and twitching.

Respiratory: Asthma, breathing disorders, bronchitis, cough, and lower respiratory tract infection.

Skin: Dry/scaly skin, eczema, herpes, seborrheic dermatitis, skin nodules, tightness of skin, and wrinkling of skin.

Urogenital: Abnormal menstrual cycle, abortion, bladder inflammation, endometriosis, hematuria, increased urination, inflammation of fallopian tubes, intermenstrual bleeding, menstruation symptoms, micturition disorders, urethritis, and urinary infections.

Miscellaneous: Contusions, difficulty in walking, edema, hematoma, hypersensitivity, fever, fluid retention, lymphadenopathy, overdose, speech disturbance, swelling of extremities, swelling of face, and voice disturbances.

Pain and Other Pressure Sensations: Chest pain and/or heaviness, neck/throat/jaw pain/tightness/pressure, and pain (location specified).

6.5 Clinical Studies Using Sumavel DosePro

Four clinical trials compared the safety and tolerability of Sumavel DosePro (n = 243 administrations) and sumatriptan injection (n = 217 injections) in 120 adult healthy subjects. Local site reactions were prospectively recorded in these trials. There was a higher incidence of bleeding, swelling, erythema, and bruising initially with Sumavel DosePro than with sumatriptan needle based injection (see Table 2). Bleeding was considered minor in all cases, and did not require medical intervention. Most injection site reactions resolved spontaneously, with no apparent difference between Sumavel DosePro and sumatriptan needle injection for bleeding and bruising at 8-hrs post dose, and for swelling and erythema at 24-hrs post dose. No injection site reactions were reported as adverse reactions, and no subject discontinued the studies due to an injection site reaction or adverse reaction in these trials.

Table 2: Incidence of Local Site Reactions in Sumavel DosePro Active-Controlled Studies

	Sumavel DosePro (n = 243 injections)	Sumatriptan Injection (n = 217 injections)
Bleeding		
Immediately after	42%	22%
1 hour post-injection	7%	0%
8 hours post-injection	0%	0%
24 hours post-injection	0%	0%
Swelling		
Immediately after	86%	1%
1 hour post-injection	72%	15%
8 hours post-injection	6%	0%
24 hours post-injection	1%	1%
Erythema		
Immediately after	18%	4%
1 hour post-injection	53%	25%
8 hours post-injection	20%	4%
24 hours post-injection	9%	3%
Bruising		
Immediately after	11%	1%
1 hour post-injection	3%	3%
8 hours post-injection	3%	5%
24 hours post-injection	5%	6%

Administration site pain was reported as an adverse event in 2% of administrations in patients after delivery of Sumavel DosePro, compared to 1% after administration of sumatriptan needle injection.

6.6 Post-marketing Experience

Reports for Subcutaneous or Oral Sumatriptan

The following adverse reactions have been identified during post-approval use of sumatriptan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. However, systemic reactions following sumatriptan use are likely to be similar regardless of route of administration.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Cardiovascular: Atrial fibrillation, cardiomyopathy, colonic ischemia *[see Warnings and Precautions (5.5)]*, Prinzmetal's variant angina, pulmonary embolism, shock, thrombophlebitis.

Ear, Nose, and Throat: Deafness.

Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis, loss of vision.

Gastrointestinal: Ischemic colitis with rectal bleeding *[see Warnings and Precautions (5.5)]*, xerostomia.

Hepatic: Elevated liver function tests.

Neurological: Central nervous system vasculitis, cerebrovascular accident, dysphasia, serotonin syndrome, subarachnoid hemorrhage.

Non-Site Specific: Angioneurotic edema, cyanosis, death *[see Warnings and Precautions (5.3)]*, temporal arteritis.

Psychiatry: Panic disorder.

Respiratory: Bronchospasm in patients with and without a history of asthma.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid reactions have been reported *[see Warnings and Precautions (5.8)]*), photosensitivity. Following subcutaneous administration of sumatriptan, pain, redness, stinging, induration, swelling, contusion, subcutaneous bleeding, and, on rare occasions, lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) has been reported.

Urogenital: Acute renal failure.

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors

MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of sumatriptan in patients receiving MAO-A inhibitors is not ordinarily recommended. If the clinical situation warrants the combined use of sumatriptan and an MAOI, the dose of sumatriptan employed should be reduced. *[see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)]*

7.2 5-$HT_{1B/1D}$ Agonists (e.g. triptans)

Concomitant use of other 5-$HT_{1B/1D}$ agonists (e.g. triptans) within 24 hours of sumatriptan treatment is not recommended. *[see Contraindications (4.6) and Clinical Pharmacology (12.3)]*

7.3 Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Since these effects may be additive, use of ergotamine containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided. *[see Contraindications (4.6)]*

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

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with sumatriptan injection is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. *[see Warnings and Precautions (5.5)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Sumatriptan produced evidence of developmental toxicity (embryolethality and increased incidences of fetal abnormalities) in rabbits. Embryolethality was observed at a dose less than the maximum recommended human dose (MRHD) of 12 mg/day on a body surface area (mg/m^2) basis. There are no adequate and well-controlled studies of Sumavel DosePro in pregnant women. Sumavel DosePro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When sumatriptan was administered intravenously to pregnant rabbits daily throughout the period of organogenesis, embryolethality was observed at doses at or close to those producing maternal toxicity. These doses were less than the MRHD of 12 mg/day on a mg/m^2 basis. Oral administration of sumatriptan to rabbits during organogenesis was associated with increased incidences of fetal vascular and skeletal abnormalities. The highest no-effect dose for these effects was 15 mg/kg/day. The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at doses that are approximately 10 times the MRHD on a mg/m^2 basis, did not produce evidence of embryolethality. The subcutaneous administration of sumatriptan to pregnant rats prior to and throughout pregnancy did not produce evidence of embryolethality or teratogenicity.

8.3 Nursing Mothers

Sumatriptan is excreted in human milk following subcutaneous administration. Therefore, caution should be exercised when considering the administration of Sumavel DosePro to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of sumatriptan injection in pediatric patients under 18 years of age have not been established; therefore, sumatriptan injection is not recommended for use in patients under 18 years of age.

Two controlled clinical trials evaluating sumatriptan nasal spray (5 to 20 mg) in pediatric patients aged 12 to 17 years enrolled a total of 1,248 adolescent migraineurs who treated a single attack. The studies did not establish the efficacy of sumatriptan nasal spray compared to placebo in the treatment of migraine in adolescents. Adverse events 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 events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents.

Post-marketing experience documents that serious adverse events have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include events 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.

8.5 Geriatric Use

The use of Sumavel DosePro in elderly patients is not recommended because they are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly. *[see Warnings and Precautions (5.1, 5.6)]*

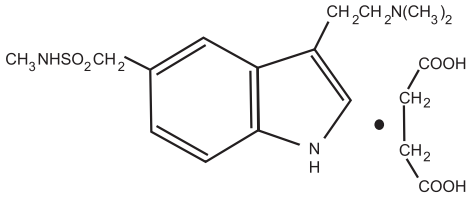
10 OVERDOSAGE

Patients (N = 269) have received single injections of 8 to 12 mg sumatriptan without significant adverse effects. Volunteers (N = 47) have received single subcutaneous doses of up to 16 mg without serious adverse events.

No gross overdoses in clinical practice have been reported. The half-life of elimination of sumatriptan is about 2 hours *[see Clinical Pharmacology (12.3)]*, and therefore monitoring of patients after overdose with subcutaneous sumatriptan should continue while symptoms or signs persist, and for at least 10 hours. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

11 DESCRIPTION

Sumatriptan, the active component of Sumavel DosePro, is a selective 5-hydroxytryptamine receptor subtype 1 (5-HT_1) 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 $C_{14}H_{21}N_3O_2S \bullet C_4H_6O_4$, 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. Sumatriptan solution is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for subcutaneous delivery. Each 0.5 mL of solution contains 6 mg of sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride, USP, in water for injection, USP. The pH range of the solution is approximately 4.2 to 5.3. The osmolality of the solution is 291 mOsmol.

Sumavel DosePro is a pre-filled, single-use, disposable, needle-free subcutaneous delivery system delivering sterile sumatriptan injection. Sumavel DosePro consists of the following components: a gray plastic handle and snap-off tip, a green lever, and a glass medication chamber that is pre-filled with 6 mg per 0.5 mL sumatriptan injection. Utilizing pressure from a compressed nitrogen gas source in the handle, Sumavel DosePro delivers the medication by pushing it through a small, precise hole in the glass medication chamber. The resulting stream of medication is propelled through the skin and is delivered subcutaneously without a needle, following a biphasic pressure profile.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sumatriptan is the active component of Sumavel DosePro. Sumatriptan is a selective agonist for the 5-HT_{1B} and 5-HT_{1D} receptors. Sumatriptan presumably exerts its antimigrainous effect through binding to vascular 5-HT_1-type receptors, which have been shown to be present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of the isolated dura mater of humans. In these tissues, sumatriptan activates this receptor to cause vasoconstriction, an action in humans correlating with the relief of migraine and cluster headache.

12.2 Pharmacodynamics

Blood Pressure: Sumavel DosePro is contraindicated in patients with uncontrolled hypertension *[see Contraindications (4.5)]*. It should be administered with caution to patients with controlled hypertension. *[see Warnings and Precautions (5.6)]*

Peripheral (Small) Arteries: In healthy volunteers (N = 18), a study evaluating the effects of sumatriptan 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 sumatriptan's development as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

Respiratory Rate: Experience gained during the clinical development of sumatriptan as a treatment for migraine failed to detect an effect of the drug on respiratory rate.

12.3 Pharmacokinetics

Absorption and Elimination

Sumavel DosePro is bioequivalent to sumatriptan needle-based injection via autoinjector at the thigh and abdomen administration sites. A sub-optimal dose may be delivered when administered to the arm and therefore, the arm is not recommended as a site of administration.

Pharmacokinetic parameters following a 6 mg subcutaneous dose of Sumavel DosePro into the thigh were determined in 32 subjects (males and females). The maximum serum concentration (Cmax) (mean ± standard deviation) was 71.9 ± 14.4 ng/mL; the time to peak concentration (Tmax) was 12 minutes after dosing (range, 4 to 20 minutes); and the terminal half-life was 103 ± 22 minutes.

Pharmacokinetic parameters following a 6 mg subcutaneous dose of Sumavel DosePro into the abdomen were determined in 35 subjects (males and females). The maximum serum concentration (Cmax) (mean ± standard deviation) was 78.6 ± 17.3 ng/mL; the time to peak concentration (Tmax) was 12 minutes after dosing (range, 6 to 20 minutes); and the terminal half-life was 102 ± 12 minutes.

Protein Binding

The bioavailability of sumatriptan via subcutaneous site injection to 18 healthy male subjects was 97% ± 16% of that obtained following intravenous injection. Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated.

Drug Interactions

Monoamine Oxidase Inhibitors

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme. In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of sumatriptan, resulting in a two-fold increase in the area under the sumatriptan plasma concentration-time curve (AUC), corresponding to a 40% increase in elimination half-life.

Migraine Prophylactic Medications

There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy of sumatriptan. In 2 clinical trials in the United States, a retrospective analysis of 282 patients who had been using prophylactic drugs (verapamil, n = 63; amitriptyline, n = 57; propranolol, n = 94; for 45 other drugs, n = 123) were compared to those who had not used prophylaxis (n = 452). There were no differences in relief rates at 60 minutes postdose for sumatriptan injection, whether or not prophylactic medications were used.

Special Populations

Renal Impairment: The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment: The effect of hepatic disease on the pharmacokinetics of subcutaneously administered sumatriptan has been evaluated. There were no statistically significant differences in the pharmacokinetics of subcutaneously delivered sumatriptan in hepatically impaired patients compared to healthy controls.

Age: The pharmacokinetics of 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 those in healthy male subjects (mean age, 30 years).

Race: The systemic clearance and Cmax of sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks) or drinking water (mice, 78 weeks). There was no evidence of an increase in tumors in either species related to sumatriptan administration.

Sumatriptan was not mutagenic when tested in the Ames test or the *in vitro* mammalian Chinese hamster V79/HGPRT assay. Sumatriptan was not clastogenic when tested in the *in vitro* human lymphocyte assay or the *in vivo* rat micronucleus assay.

Subcutaneous administration of sumatriptan to male and female rats prior to and throughout the mating period at doses approximately 50 times the maximum recommended human dose (MRHD) of 12 mg/day on a body surface area (mg/m^2) basis produced no evidence of adverse effects on fertility. However, following oral administration, a treatment-related decrease in fertility, secondary to a decrease in mating, was seen for rats treated with 50 and 500 mg/kg/day. It is not clear whether the problem is associated with the treatment of males or females or both.

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 dosage 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

14.1 Migraine

In US controlled clinical trials enrolling more than 1,000 patients during migraine attacks who were experiencing moderate or severe pain and 1 or more of the symptoms enumerated in Table 4, onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Smaller doses of sumatriptan may also prove effective, although the proportion of patients obtaining adequate relief is decreased and the latency to that relief is greater.

In one well-controlled study in which placebo (n = 62) was compared to 6 different doses of sumatriptan injection (n = 30 each group) in a single-attack, parallel-group design, the dose response relationship was found to be as shown in Table 3.

Table 3. Dose-Response Relationship for Efficacy

Sumatriptan Dose (mg)	% Patients with Relief*				Incidence of AEs (%)
	At 10 min	At 30 min	At 1 hr	At 2 hr	
Placebo	5	15	24	21	55
1	10	40	43	40	63
2	7	23	57	43	63
3	17	47	57	60	77
4	13	37	50	57	80
6	10	63	73	70	83
8	23	57	80	83	93

* Relief is defined as the reduction of moderate or severe pain to no pain or mild pain after dosing without use of rescue medication.

In two US well-controlled clinical trials in 1,104 migraine patients with moderate or severe migraine pain, the onset of relief was rapid (less than 10 minutes) with a 6 mg subcutaneous dose of sumatriptan injection. Headache relief, as evidenced by a reduction in pain from severe or moderately severe to mild or no headache, was achieved in 70% of the patients within 1 hour of a single 6 mg subcutaneous dose of sumatriptan injection. Headache relief was achieved in approximately 82% of patients within 2 hours, and 65% of all patients were pain-free within 2 hours. Table 4 shows the 1- and 2-hour efficacy results for subcutaneous sumatriptan 6 mg.

Table 4. Efficacy Data from US Clinical Efficacy Trials with Sumatriptan Injection in Patients with Migraine

	Study 1		Study 2	
1-Hour Data	Placebo (n = 190)	Sumatriptan Injection 6 mg (n = 384)	Placebo (n = 180)	Sumatriptan Injection 6 mg (n = 350)
Patients with pain relief (grade 0/1)	18%	70%*	26%	70%*
Patients with no pain	5%	48%*	13%	49%*
Patients without nausea	48%	73%*	50%	73%*
Patients without photophobia	23%	56%*	25%	58%*
Patients with little or no clinical disability [a]	34%	76%*	34%	76%*
2-Hour Data [b]				
Patients with pain relief (grade 0/1)	31%	81%*	39%	82%*
Patients with no pain	11%	63%*	19%	65%*
Patients without nausea	56%	82%*	63%	81%*
Patients without photophobia	31%	72%*	35%	71%*
Patients with little or no clinical disability [a]	42%	85%*	49%	84%*

* $p<0.05$ versus placebo.

[a] A successful outcome in terms of clinical disability was defined prospectively as ability to work mildly impaired or ability to work and function normally.

[b] Includes patients who may have received an additional injection of the assigned treatment (placebo or sumatriptan 6 mg) 1 hour after the initial injection.

Subcutaneous sumatriptan also relieved photophobia, phonophobia (sound sensitivity), nausea, and vomiting associated with migraine attacks.

The efficacy of subcutaneous sumatriptan injection is unaffected by whether or not migraine is associated with aura, duration of attack, gender or age of the patient, or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers).

14.2 Cluster Headache

The efficacy of sumatriptan injection in the acute treatment of cluster headache was demonstrated in 2 randomized, double-blind, placebo-controlled, 2-period crossover trials. Patients age 21 to 65 were enrolled and were instructed to treat a moderate to very severe headache within 10 minutes of onset. Headache relief was defined as a reduction in headache severity to mild or no pain. In both trials, the proportion of individuals gaining relief at 10 or 15 minutes was significantly greater among patients receiving 6 mg of sumatriptan injection compared to those who received placebo (see Table 5). One study evaluated a 12 mg dose; there was no statistically significant difference in outcome between patients randomized to the 6 and 12 mg doses.

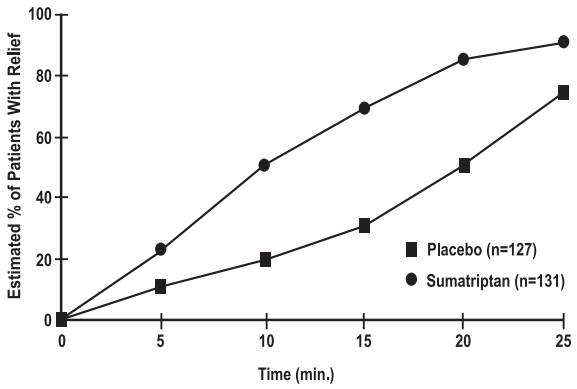
Table 5. Efficacy Data from the Cluster Headache Efficacy Trials with Sumatriptan Injection

	Study 1		Study 2	
	Placebo (n = 39)	Sumatriptan Injection 6 mg (n = 39)	Placebo (n = 88)	Sumatriptan Injection 6 mg (n = 92)
Patients with pain relief				
5 minutes post injection	8%	21%	7%	23%*
10 minutes post injection	10%	49%*	25%	49%*
15 minutes post injection	26%	74%*	35%	75%*

* $p<0.05$ (n = Number of headaches treated)

The Kaplan-Meier (product limit) Survivorship Plot (Figure 1) provides an estimate of the cumulative probability of a patient with a cluster headache obtaining relief after being treated with either sumatriptan or placebo.

Figure 1. Time to Relief from Time of Injection*



*Patients taking rescue medication were censored at 15 minutes.

The plot was constructed with data from patients who either experienced relief or did not require (request) rescue medication within a period of 2 hours following treatment. As a consequence, the data in the plot are derived from only a subset of the 258 headaches treated (rescue medication was required in 52 of the 127 placebo-treated headaches and 18 of the 131 sumatriptan-treated headaches).

Other data suggest that sumatriptan treatment is not associated with an increase in early recurrence of headache, and that treatment with sumatriptan has little effect on the incidence of later-occurring headaches (i.e., those occurring after 2, but before 18 or 24 hours).

16 HOW SUPPLIED/STORAGE AND HANDLING

Each Sumavel DosePro needle-free delivery system delivers 6 mg sumatriptan (base) in 0.5 mL, in a sterile, nonpyrogenic solution. Sumavel DosePro is supplied in a package of six prefilled, single-dose units (NDC 43376-106-06).

Store at 20–25ºC (68–77ºF), with excursions permitted between 15–30ºC (59–86ºF). Do not freeze.

17 PATIENT COUNSELING INFORMATION

[see FDA-Approved Patient Labeling]

17.1 Risk of Myocardial Ischemia and/or Infarction, Other Adverse Cardiac Events, Other Vasospasm-related Events, and Cerebrovascular Events

Inform patients that Sumavel DosePro 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, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Apprise patients of the importance of this follow-up. *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4)]*

17.2 Serotonin Syndrome

Caution patients about the risk of serotonin syndrome with the use of Sumavel DosePro or other triptans, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). *[see Warnings and Precautions (5.5)]*

17.3 Pregnancy

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

17.4 Nursing Mothers

Advise patients to notify their physician if they are breast-feeding or plan to breast-feed. *[see Use in Specific Populations (8.3)]*

17.5 Importance of Training

Patients who are to self-administer Sumavel DosePro in medically unsupervised situations should receive instruction on the proper use of Sumavel DosePro from the physician or healthcare professional prior to administering for the first time.

Patients should be made aware that a loud burst of air will be heard and a sensation felt at the time the dose is delivered via Sumavel DosePro. Patients should be advised not to use a device if the tip of the device is tilted or broken off upon removal from packaging.

17.6 Choosing Administration Sites

Sumavel DosePro delivers the medication to the subcutaneous space in a manner similar to a subcutaneous injection. Since delivery is to be given subcutaneously, patients should be instructed to use administration sites on the abdomen or the thigh with adequate subcutaneous thickness to accommodate penetration of the drug into the subcutaneous space. Administration should not be made within 2 inches of the navel. Instruct patients not to administer Sumavel DosePro to the arms or other areas of the body. Inform patients that Sumavel DosePro is for subcutaneous use only and is not designed for intramuscular or intravenous use.

PATIENT INFORMATION

Sumavel® DosePro® (SUE-muh-vell DOSE-pro) (sumatriptan injection) Needle-free Delivery System

Read this Patient Information before you start to take Sumavel DosePro. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment. You and your doctor should talk about Sumavel DosePro when you start taking it and at regular checkups.

What is the most important information I should know about Sumavel DosePro?

In very rare cases, people taking triptans, such as Sumavel DosePro, may experience serious side effects, including heart attacks. Call your doctor right away if you have:

- severe chest pain
- shortness of breath

Sumavel DosePro 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
- are a female who has gone through menopause
- are a male over age 40

"Serotonin syndrome" is a serious and life-threatening problem that can happen with Sumavel DosePro, especially if used with anti-depressant medicines called selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs).

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

Call your doctor if you have any of these symptoms of serotonin syndrome:

- mental changes (hallucinations, agitation, coma)
- fast heartbeat
- changes in blood pressure
- high body temperature
- tight muscles
- trouble walking
- nausea, vomiting, diarrhea

What is Sumavel DosePro?

Sumavel DosePro is a prescription medicine given with a needle-free delivery system to treat people who have been diagnosed with migraine or cluster headaches.

Sumavel DosePro is not used to prevent or lessen the number of migraine or cluster headache attacks you have.

Sumavel DosePro is not used to treat other types of headaches.

It is not known if Sumavel DosePro is safe or effective in people younger than 18 years of age.

Who should not take Sumavel DosePro?

Do not take Sumavel DosePro if you have:

- narrowing of blood vessels to the legs, arms, stomach or kidney (peripheral vascular disease)
- heart disease or a history of heart disease
- uncontrolled high blood pressure
- migraines that cause temporary paralysis (unable to move) on one side of your body or basilar migraine. If you are not sure about this, ask your doctor.
- 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)
- sumatriptan and naproxen (Treximet)
- ergotamines like Bellergal-S, Cafergot, Ergomar
- dihydroergotamine (D.H.E. 45) or (Migranal)

- an allergy to sumatriptan
- expired medication

What should I tell my doctor before taking Sumavel DosePro?

Before taking Sumavel DosePro, tell your doctor about all of your medical conditions, including if you:

- have high cholesterol
- have diabetes
- smoke
- are overweight
- have gone through menopause
- have heart disease or a family history of heart disease or stroke
- are pregnant or plan to become pregnant. It is not known if Sumavel DosePro will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breast feeding or plan to breast feed. Sumavel DosePro passes into your breast milk and may harm your baby. Talk to your doctor about the best way to feed your baby if you take Sumavel DosePro.
- are not using effective birth control
- have had epilepsy or seizures

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

Using Sumavel DosePro with certain other medicines can affect each other causing serious side effects.

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

- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- Monoamine Oxidase Inhibitors (MAO-A)

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

How should I take Sumavel DosePro?

- Use Sumavel DosePro exactly as your doctor tells you to
- Read the detailed Instructions for Use at the end of this leaflet
- Deliver Sumavel DosePro into your stomach area (abdomen), or thigh
- Do not deliver Sumavel DosePro into the arm or other body parts.
- Do not deliver Sumavel DosePro into a vein or a muscle
- Do not deliver Sumavel DosePro within 2 inches of your belly button (navel)
- You may deliver a second dose of Sumavel DosePro or 1 dose of another sumatriptan medicine separated by at least 1 hour
- Do not deliver more than two doses of Sumavel DosePro in a 24-hour period.

What should I avoid while taking Sumavel DosePro?

You may feel drowsy or dizzy because of your migraine or your treatment with Sumavel DosePro. If you have these symptoms, do not drive a car, use machinery, or do anything that needs you to be alert.

What are the possible side effects of Sumavel DosePro?

Sumavel DosePro can cause serious side effects including death. See "What is the most important information I ∘should know about Sumavel DosePro?"

Serious side effects include:

- heart attack
- fast heartbeat
- increase in blood pressure
- stroke
- changes in mental status (agitation, hallucinations, coma)
- changes in color or sensation to your fingers and toes (Raynaud's syndrome)
- gastrointestinal ischemic events
- peripheral vascular ischemia and colonic ischemia

Get medical help right away, if you have:

- severe tightness, pain, pressure or heaviness in your chest, throat, neck, or jaw
- shortness of breath or wheezing
- sudden or severe stomach pain
- hives (itchy bumps), swelling of your tongue, mouth, or throat
- problems seeing
- unusual weakness or numbness
- nausea or vomiting
- bloody diarrhea
- stomach pain
- high temperature
- unusual sweating

The most common side effects of Sumavel DosePro include:

- bleeding, swelling, redness, bruising and pain at the administration site
- tingling or numbness in your fingers or toes
- dizziness
- warm, hot, burning feeling to your face (flushing)
- feeling of heaviness or pressure
- discomfort or tightness in the chest, neck, throat, nose, or jaw
- feeling weak, drowsy, or tired
- feeling strange
- muscle pain

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Sumavel DosePro. For more information, ask your doctor 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 Sumavel DosePro?

- Store Sumavel DosePro between 59ºF to 86ºF (15ºC to 30ºC).
- Do not freeze.

Keep Sumavel DosePro and all medicines out of the reach of children.

General information about Sumavel DosePro.

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflets. Do not use Sumavel DosePro for a condition for which it was not prescribed. Do not give Sumavel DosePro to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about Sumavel DosePro. If you would like more information about Sumavel DosePro, talk to your doctor. You can ask your doctor or pharmacist for information about Sumavel DosePro that is written for health professionals.

For more information, go to www.SumavelDosePro.com or call 1-866-ZOGENIX.

What are the Ingredients in Sumavel DosePro?

Active ingredient: sumatriptan

Inactive ingredient: sodium chloride

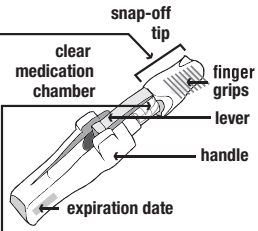
Instructions for Use

Read these Instructions for Use which come with Sumavel DosePro before you start using it and each time you get a refill. Follow these instructions each time you use Sumavel DosePro. Before you use Sumavel DosePro for the first time, make sure your doctor shows you the right way to use it.

A Check your device:

⚠ The snap-off tip should sit firmly on the end of the clear medication chamber.

Do not use Sumavel DosePro if the snap-off tip is tilted or broken off.



⚠ The medicine inside Sumavel DosePro should be clear and colorless or pale yellow.

Do not use Sumavel DosePro if the medicine looks dark-colored or cloudy.

⚠ The expiration date is printed on both the Sumavel DosePro label and carton.

Do not use Sumavel DosePro if the medicine is expired.

B Choose a delivery site:

Select a delivery site such as your stomach area (abdomen) **or** your thigh.

Do not deliver Sumavel DosePro in the arm.

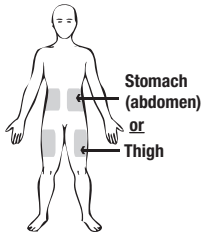
Your skin should be clean, dry, and free of clothing.

Do not deliver through your clothes.

Do not deliver into scars or moles, or within 2 inches of your belly button (navel).

Do not deliver into the same spot.

Change delivery sites with each use.

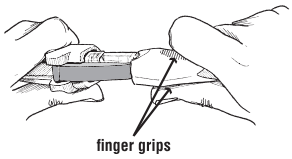


Shaded areas show all possible areas of delivery.

1 Snap: In this step, you will learn how to correctly remove the snap-off tip.

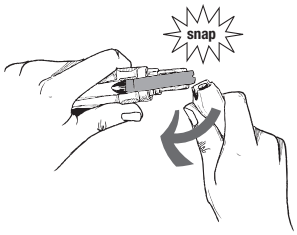
⚠ Do not begin these steps until you are ready to take your dose.

Firmly hold the handle of Sumavel DosePro in one hand. With the other hand, use your fingers to **grip the top and bottom of the snap-off tip**, where the finger grips are located.



To break off the snap-off tip, firmly snap it off in a downward motion. You may need to use some force.

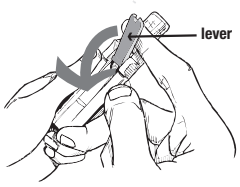
You do not need to twist or pull the snap-off tip; doing so will not work.



2 Flip: In this step, you will learn how to prepare Sumavel DosePro for delivery of the medicine.

Firmly press the green lever **all the way down** (away from the clear plastic end), until it **clicks and locks into the handle** . You may feel some resistance – this is normal.

⚠ Once you have flipped the lever, **do not touch the end of the clear medication chamber.** Keep the medication chamber pointed away from your face or eyes.



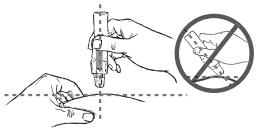
3 Press: In this step, you will learn how to deliver the medicine.

Deliver the dose exactly as shown to you by your healthcare provider.

Pinch about 2 inches of the skin of your stomach (abdomen) **or** thigh to create a firm section of skin.

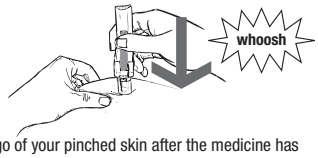
Place Sumavel DosePro straight out from the delivery site with the end of the **clear medication chamber against your skin.**

⚠ Do not hold Sumavel DosePro at an angle to your skin.



⚠ During the next step, **you will hear a loud burst of air**. Do not be alarmed – this indicates that the medicine has been delivered.

Steadily press Sumavel DosePro straight down against your skin until you hear and feel a burst of air. There is no button to push. After you hear the burst of air (whoosh), the medicine has been delivered and you can remove Sumavel DosePro from your skin.



Let go of your pinched skin after the medicine has been delivered.

After removing Sumavel DosePro from your skin, a small droplet of blood may be present. You can gently press a cotton ball or gauze over the injection site. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Manufactured by Patheon UK, Limited
Swindon, United Kingdom

Manufactured for:
Zogenix, Inc.
San Diego, CA 92130

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