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 serotonin (5-$HT_{1B/1D}$) receptor agonist (triptan) indicated for:

- Acute treatment of migraine with or without aura in adults (1)
- Acute treatment of cluster headache in adults (1)

Limitations of Use:

- Use only if a clear diagnosis of migraine or cluster headache has been established. (1)
- Not indicated for the prevention of migraine attacks. (1)

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

- For subcutaneous use only. (2.1, 2.2)
- Acute treatment of migraine: 4 mg or 6 mg single dose. (2.1)
- Acute treatment of cluster headache: 6 mg single dose. (2.1)
- Maximum dose in a 24-hour period: 12 mg. Separate doses by at least 1 hour. (2.1)
- Administer dose only to the abdomen or thigh. (2.2)

DO NOT USE SUMAVEL DOSEPRO IF THE TIP OF THE DEVICE IS TILTED OR BROKEN OFF UPON REMOVAL FROM PACKAGING. (2.2)

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

- Sumavel DosePro: 4 mg or 6 mg prefilled, single-dose, needle-free subcutaneous delivery systems.

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

- History of coronary artery disease 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-HT_1 agonist (e.g., another triptan) or of an ergotamine-containing medication (4)
- Current or recent (past 2 weeks) use of monoamine oxidase-A inhibitor (4)
- Hypersensitivity to Sumavel DosePro (angioedema and anaphylaxis seen) (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 Sumavel DosePro if occurs. (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk. (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, or stroke: Discontinue Sumavel DosePro if occurs. (5.4)
- Gastrointestinal ischemia or infarction events, or peripheral vasospastic reactions: Discontinue Sumavel DosePro if occurs. (5.5)
- Medication overuse headache: Detoxification may be necessary. (5.6)
- Serotonin syndrome: Discontinue Sumavel DosePro if occurs. (5.7)
- Seizures: Use with caution in patients with epilepsy or a lowered seizure threshold. (5.10)

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

Most common adverse reactions (≥5% and > placebo) were injection site reactions, tingling, dizziness/vertigo, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, flushing, feeling of tightness, and numbness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals at 1-800-462-3636 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 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sumavel DosePro is indicated in adults for (1) the acute treatment of migraine, with or without aura, and (2) the acute treatment of cluster headache.

Limitations of Use:

- Use only if a clear diagnosis of migraine or cluster headache has been established.
- If a patient has no response to the first migraine attack treated with Sumavel DosePro, reconsider the diagnosis of migraine before Sumavel DosePro is administered to treat any subsequent attacks.
- Sumavel DosePro is not indicated for the prevention of migraine attacks.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The maximum single recommended dose of Sumavel DosePro for the acute treatment of migraine or cluster headache is 6 mg given subcutaneously. For the treatment of migraine, if side effects are dose limiting, a lower dose (4 mg) may be used *[see Clinical Studies (14.1)]*. For the treatment of cluster headache, the efficacy of a lower dose has not been established.

The maximum cumulative injected dose that may be given in 24 hours is 12 mg, with doses of Sumavel DosePro separated by at least 1 hour. Sumavel DosePro may be given at least 1 hour following a dose of another sumatriptan product. A second dose should only be considered if some response to a first dose was observed.

2.2 Administration Using Sumavel® DosePro®

Sumavel DosePro is available for use as 4 mg or 6 mg needle-free delivery systems. It is intended to be given subcutaneously only. Sumavel DosePro is designed for patient self-administration to 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 naval. Sumavel DosePro is not to be administered to other areas of the body, including the arm.

Instruct patients on the proper use of Sumavel DosePro and direct them to use proper injection sites. Instruct patients to not use Sumavel DosePro if the tip of the device is tilted or broken off upon removal from packaging *[see Patient counseling Information (17) and Instructions for Use]*.

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 4 mg or 6 mg sumatriptan (as the succinate salt).

4 CONTRAINDICATIONS

Sumavel DosePro is contraindicated in patients with:

- Ischemic coronary artery disease (CAD) (angina pectoris, history of myocardial infarction, or documented silent ischemia) or coronary artery vasospasm, including Prinzmetal's angina *[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 or transient ischemic attack (TIA) because these patients are at a higher risk of stroke *[see Warnings and Precautions (5.4)]*
- History of hemiplegic or basilar migraine
- 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 (i.e., within 24 hours) use of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine1 (5-HT_1) agonist *[see Drug Interactions (7.1, 7.3)]*
- Concurrent administration of a monamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*
- Hypersensitivity to Sumavel DosePro (angioedema and anaphylaxis seen) *[see Warnings and Precautions (5.9) and Adverse Reactions (6)]*

5 WARNINGS AND PRECAUTIONS

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

Sumavel DosePro 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 Sumavel DosePro. Some of these reactions occurred in patients without known CAD. Sumavel DosePro may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

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

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 Sumavel DosePro if these disturbances occur. Sumavel DosePro 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 precordium, throat, neck, and jaw commonly occur after treatment with Sumavel DosePro and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of Sumavel DosePro is contraindicated in patients shown to have CAD and those with Prinzmetal's variant angina.

5.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT_1 agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Also, patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). Discontinue Sumavel DosePro 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. Sumavel DosePro is contraindicated in patients with a history of stroke or TIA.

5.5 Other Vasospasm Reactions

Sumavel DosePro, 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 non-coronary vasospasm reaction following the use of any 5-HT_1 agonist, rule out a vasospastic reaction before receiving additional doses of Sumavel DosePro.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT_1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT_1 agonists have not been clearly established.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or combination 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 Sumavel DosePro, 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 aberrations (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 Sumavel DosePro 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-HT_1 agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with Sumavel DosePro. Sumavel DosePro is contraindicated in patients with uncontrolled hypertension.

5.9 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients receiving Sumavel DosePro. 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. Sumavel DosePro is contraindicated in patients with a history of hypersensitivity reaction to Sumavel DosePro.

5.10 Seizures

Seizures have been reported following administration of Sumavel DosePro. 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. Sumavel DosePro 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 adverse reactions are discussed in more detail in other sections of the labeling:

- 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Migraine Headache: Table 1 lists adverse reactions that occurred in 2 US placebo-controlled clinical trials in migraine subjects *[see Clinical Studies (14.1)]* following either a single 6 mg dose of sumatriptan injection or placebo. Only reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection 6 mg 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 Subjects and at a Greater Frequency Than Placebo in 2 Placebo-Controlled Migraine Clinical Trials[a]

Adverse Reaction	Percent of Subjects Reporting	
	Sumatriptan Injection 6 mg Subcutaneous (n = 547)	Placebo (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[b]	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
Skin		
Sweating	2	1

[a] The sum of percentages cited is greater than 100% because subjects may have experienced more than 1 type of adverse reaction. Only reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection and occurred at a frequency greater than that of the placebo group are included.

[b] Includes injection site pain, stinging/burning, swelling, erythema, bruising, bleeding.

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

Cluster Headache: In the controlled clinical trials assessing the efficacy of sumatriptan injection as a treatment for cluster headache *[see Clinical Studies (14.2)]*, no new significant adverse reactions were detected that had not already been identified in trials of sumatriptan in subjects with migraine.

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

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 Sumavel DosePro within 24 hours of each other is contraindicated.

7.2 Monoamine Oxidase-A Inhibitors

MAO-A inhibitors increase systemic exposure by 2-fold. Therefore, the use of Sumavel DosePro in patients receiving MAO-A inhibitors is contraindicated *[see Clinical Pharmacology (12.3)]*.

7.3 Other 5-HT_1 Agonists

Because their vasospastic effects may be additive, co-administration of Sumavel DosePro and other 5-HT_1 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, or SNRIs, SNRIs, TCAs, and MAO inhibitors *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Data from a prospective pregnancy exposure registry and epidemiological studies of pregnant women have not detected an increased frequency of birth defects or a consistent pattern of birth defects among women exposed to sumatriptan compared with the general population *(see Data)*. 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 *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The reported rate of major birth defects among deliveries to women with migraine ranged from 2.2 to 2.9% and the reported rate of miscarriage was 17%, which were similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Several studies have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

Human Data

The Sumatriptan/Naratriptan/Treximet (sumatriptan and naproxen sodium) Pregnancy Registry, a population-based international prospective study, collected data for sumatriptan from January 1996 to September 2012. The Registry documented outcomes of 626 infants and fetuses exposed to sumatriptan during pregnancy (528 with earliest exposure during the first trimester, 78 during the second trimester, 16 during the third trimester, and 4 unknown). The occurrence of major birth defects (excluding fetal deaths and induced abortions without reported defects and all spontaneous pregnancy losses) during first-trimester exposure to sumatriptan was 4.2% (20/478 [95% CI: 2.6% to 6.5%]) and during any trimester of exposure was 4.2% (24/576 [95% CI: 2.7% to 6.2%]). The sample size in this study had 80% power to detect at least a 1.73- to 1.91-fold increase in the rate of major malformations. The number of exposed pregnancy outcomes accumulated during the registry was insufficient to support definitive conclusions about overall malformation risk or to support comparisons of the frequencies of specific birth defects. Of the 20 infants with reported birth defects after exposure to sumatriptan in the first trimester, 4 infants had ventricular septal defects, including one infant who was exposed to both sumatriptan and naratriptan, and 3 infants had pyloric stenosis. No other birth defect was reported for more than 2 infants in this

group.

In a study using data from the Swedish Medical Birth Register, live births to women who reported using triptans or ergots during pregnancy were compared with those of women who did not. Of the 2,257 births with first-trimester exposure to sumatriptan, 107 infants were born with malformations (relative risk 0.99 [95% CI: 0.91 to 1.21]). A study using linked data from the Medical Birth Registry of Norway to the Norwegian Prescription Database compared pregnancy outcomes in women who redeemed prescriptions for triptans during pregnancy, as well as a migraine disease comparison group who redeemed prescriptions for sumatriptan before pregnancy only, compared with a population control group. Of the 415 women who redeemed prescriptions for sumatriptan during the first trimester, 15 had infants with major congenital malformations (OR 1.16 [95% CI: 0.69 to 1.94]) while for the 364 women who redeemed prescriptions for sumatriptan before, but not during, pregnancy, 20 had infants with major congenital malformations (OR 1.83 [95% CI: 1.17 to 2.88]), each compared with the population comparison group. Additional smaller observational studies evaluating use of sumatriptan during pregnancy have not suggested an increased risk of teratogenicity.

Animal Data

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.

8.2 Lactation

Risk Summary

Sumatriptan is excreted in human milk following subcutaneous administration *(see Data)*. There are no data on the effects of sumatriptan on the breastfed infant or the effects of sumatriptan on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sumavel DosePro and any potential adverse effects on the breastfed infant from sumatriptan or from the underlying maternal condition.

Clinical Considerations

Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with Sumavel DosePro.

Data

Following subcutaneous administration of a 6-mg dose of sumatriptan succinate injection in 5 lactating volunteers, sumatriptan was present in milk.

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 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 trials, 3 multiple-attack trials) evaluating oral sumatriptan (25 to 100 mg) in pediatric subjects aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These trials did not establish the efficacy of oral sumatriptan 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. The frequency of all adverse reactions in these subjects appeared to

be both dose- and age-dependent, with younger subjects 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. Since clinical data to determine the frequency of serious adverse reactions in pediatric patients who might receive subcutaneous, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients under 18 years of age is not recommended.

8.5 Geriatric Use

Clinical trials of sumatriptan injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of 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 Sumavel DosePro *[see Warnings and Precautions (5.1)]*.

8.6 Hepatic Impairment

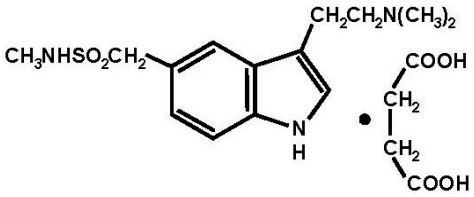
The effect of severe hepatic impairment on Sumavel DosePro metabolism has not been evaluated. Sumavel DosePro is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The elimination half-life of sumatriptan is about 2 hours *[see Clinical Pharmacology (12.3)]*, and therefore monitoring of patients after overdose with subcutaneous sumatriptan should continue for at least 10 hours or while symptoms or signs persist. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

11 DESCRIPTION

Sumavel DosePro contains sumatriptan succinate, a selective 5-$HT_{1B/1D}$ receptor agonist. 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.

Sumatriptan solution is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for subcutaneous delivery. Each 0.5 mL of Sumavel DosePro 8 mg/mL solution contains 4 mg of sumatriptan (base) as the succinate salt and 3.8 mg of sodium chloride, USP in Water for Injection, USP. Each 0.5 mL of Sumavel DosePro 12 mg/mL 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 both solutions is approximately 4.2 to 5.3. The osmolality of both solutions 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 lavender (4 mg) or green (6 mg) lever, and a glass medication chamber that is pre-filled with 4 mg or 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 binds with high affinity to human cloned 5-$HT_{1B/1D}$ receptors. Sumatriptan presumably exerts its therapeutic effects in the treatment of migraine headache by binding to 5-$HT_{1B/1D}$ receptors located on intracranial blood vessels and sensory nerves of the trigeminal system.

Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (including substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of sumatriptan for the treatment of migraine and cluster headaches is thought to be due to the agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) 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 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 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 subjects in clinical trials carried out during sumatriptan's development as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

12.3 Pharmacokinetics

Absorption and Bioavailability: 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 (C_{max}) (mean ± standard deviation) was 71.9 ± 14.4 ng/mL; the time to peak concentration (T_{max}) 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 (C_{max}) (mean ± standard deviation) was 78.6 ± 17.3 ng/mL; the time to peak concentration (T_{max}) was 12 minutes after dosing (range, 6 to 20 minutes); and the terminal half-life was 102 ± 12 minutes.

Distribution: 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.

Metabolism: In vitro studies with human microsomes suggest that sumatriptan is metabolized by MAO, predominantly the 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: After a single 6 mg subcutaneous dose, 22% ± 4% was excreted in the urine as unchanged sumatriptan and 38% ± 7% as the IAA metabolite.

Special Populations: *Age*: The pharmacokinetics of sumatriptan in the elderly (mean age: 72 years, 2 males and 4 females) and in subjects with migraine (mean age: 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age: 30 years).

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

Hepatic Impairment: The effect of mild to moderate hepatic disease on the pharmacokinetics of subcutaneously administered sumatriptan has been evaluated. There were no significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in moderately hepatically impaired subjects compared with healthy controls. The pharmacokinetics of subcutaneously administered sumatriptan in patients with severe hepatic impairment has not been studied. The use of Sumavel DosePro in this population is not recommended *[see Use in Specific Populations (8.6)]*.

Race: The systemic clearance and C_{max} of sumatriptan were similar in Black (n = 34) and Caucasian (n = 38) healthy male subjects.

Drug Interaction Studies: *Monoamine Oxidase-A Inhibitors*: In a trial of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage. Mice were dosed for 78 weeks and rats were dosed for 104 weeks. Average exposures achieved in mice receiving the highest dose were approximately 110 times the

exposure attained in humans after the maximum recommended single dose of 6 mg. The highest dose to rats was approximately 260 times the maximum single dose of 6 mg on a mg/m^2 basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration.

Mutagenesis: Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay). It was not clastogenic in 2 cytogenetics assays (the in vitro human lymphocyte assay and the in vivo rat micronucleus assay).

Impairment of Fertility:

When sumatriptan (5, 50, 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.

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 up to 60 mg/kg/day.

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; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100 mg oral dose or 3 times the human exposure after a 6 mg subcutaneous dose.

Melanin Binding: In rats with a single subcutaneous dose (0.5 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this binding is unknown.

14 CLINICAL STUDIES

14.1 Migraine

In controlled clinical trials enrolling more than 1,000 subjects during migraine attacks who were experiencing moderate or severe pain and 1 or more of the symptoms enumerated in Table 3, onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Lower doses of sumatriptan injection may also prove effective, although the proportion of subjects obtaining adequate relief was decreased and the latency to that relief is greater with lower doses. In one well-controlled study, 6 different doses of sumatriptan injection (n = 30 each group) were compared with placebo (n = 62), in a single-attack, parallel-group design, the dose response relationship was found to be as shown in Table 2.

Table 2. Proportion of Subjects with Migraine Relief and Incidence of Adverse Events by Time and by Sumatriptan Dose

Dose of Sumatriptan Injection	Percent Subjects with Relief[a]				Adverse Events Incidence (%)
	at 10 Minutes	at 30 Minutes	at 1 Hour	at 2 Hours	
Placebo	5	15	24	21	55
1 mg	10	40	43	40	63
2 mg	7	23	57	43	63
3 mg	17	47	57	60	77
4 mg	13	37	50	57	80
6 mg	10	63	73	70	83
8 mg	23	57	80	83	93

[a] 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 2 randomized, placebo-controlled clinical trials of sumatriptan injection 6 mg in 1,104 subjects with moderate or severe migraine pain, the onset of relief was less than 10 minutes. Headache relief, as defined by a reduction in pain from severe or moderately severe to mild or no headache, was achieved in 70% of the subjects within 1 hour of a single 6 mg subcutaneous dose of sumatriptan injection. Approximately 82% and 65% of subjects treated with sumatriptan 6 mg had headache relief and were pain free within 2 hours, respectively.

Table 3 shows the 1- and 2-hour efficacy results for sumatriptan injection 6 mg.

Table 3. Proportion of Subjects with Pain Relief and Relief of Migraine Symptoms After 1 and 2 Hours of Treatment

	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)
Subjects with pain relief (grade 0/1)	18%	70%[a]	26%	70%[a]
Subjects with no pain	5%	48%[a]	13%	49%[a]
Subjects without nausea	48%	73%[a]	50%	73%[a]
Subjects without photophobia	23%	56%[a]	25%	58%[a]
Subjects with little or no clinical disability[b]	34%	76%[a]	34%	76%[a]
2-Hour Data[c]				
Subjects with pain relief (grade 0/1)	31%	81%[a]	39%	82%[a]
Subjects with no pain	11%	63%[a]	19%	65%[a]
Subjects without nausea	56%	82%[a]	63%	81%[a]
Subjects without photophobia	31%	72%[a]	35%	71%[a]
Subjects with little or no clinical disability[b]	42%	85%[a]	49%	84%[a]

[a] $P<0.05$ versus placebo.
[b] A successful outcome in terms of clinical disability was defined prospectively as ability to work mildly impaired or ability to work and function normally.
[c] 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 sumatriptan injection was unaffected by whether or not the migraine was associated with aura, duration of attack, gender or age of the subject, 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. Subjects aged 21 to 65 years 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 subjects receiving 6 mg of sumatriptan injection compared with those who received placebo (see Table 4).

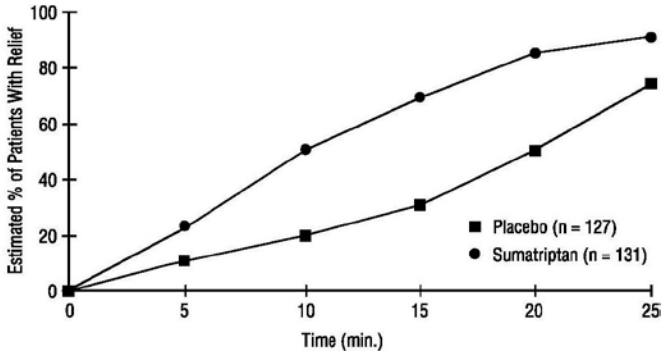
Table 4. Proportion of Subjects with Cluster Headache Relief by Time

	Study 1		Study 2	
	Placebo (n = 39)	Sumatriptan Injection 6 mg (n = 39)	Placebo (n = 88)	Sumatriptan Injection 6 mg (n = 92)
Subjects with pain relief (no/mild)				
5 Minutes post-injection	8%	21%	7%	23%[a]
10 Minutes post-injection	10%	49%[a]	25%	49%[a]
15 Minutes post-injection	26%	74%[a]	35%	75%[a]

[a] $P<0.05$.
(n = Number of headaches treated.)

An estimate of the cumulative probability of a subject with a cluster headache obtaining relief after being treated with either sumatriptan or placebo is presented in Figure 1.

Figure 1. Time to Relief of Cluster Headache from Time of Injection[a]



[a] The figure uses Kaplan-Meier (product limit) Survivorship Plot. Subjects taking rescue medication were censored at 15 minutes.

The plot was constructed with data from subjects 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 headaches treated with sumatriptan injection).

Other data suggest that treatment with sumatriptan injection is not associated with an increase in early recurrence of headache and 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 contains sumatriptan (base) in 0.5 mL, in a sterile, nonpyrogenic solution and is supplied as follows:

- Sumavel DosePro, 4 mg in a package of six prefilled, single-dose units (NDC 63481-229-06).
- Sumavel DosePro, 6 mg in a package of six prefilled, single-dose units (NDC 63481-367-06).

Store at 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 freeze. Protect from light.

17 PATIENT COUNSELING INFORMATION

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

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

Inform patients that Sumavel DosePro may cause serious cardiovascular side effects such as myocardial infarction or stroke. 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 when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.5, 5.8]* .

Hypersensitivity Reactions

Inform patients that anaphylactic reactions have occurred in patients receiving Sumavel DosePro. 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)]*.

Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the use of Sumavel DosePro 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

Advise patients to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed *[see Use in Specific Populations (8.2)]*.

Ability to Perform Complex Tasks

Since migraines or treatment with Sumavel DosePro may cause somnolence and dizziness, instruct patients to evaluate their ability to perform complex tasks during migraine attacks and after administration of Sumavel DosePro.

How to Use Sumavel DosePro

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.

Advise patients that they will hear a click and feel a burst of air. Inform the patients that they will feel the dose being delivered. Instruct patients not to use a device if the tip of the device is tilted or broken off upon removal from packaging *[see Instructions for Use]*.

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.

Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355

Manufactured by:
Patheon UK, Limited
Swindon, United Kingdom

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DosePro® is a registered trademark of Zogenix, Inc.

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PATIENT INFORMATION

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

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

Sumavel DosePro can cause serious side effects, including:

- Heart attack and other heart problems. Heart problems may lead to death. Stop taking Sumavel DosePro 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

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

What is Sumavel DosePro?

Sumavel DosePro is a prescription medicine used to treat acute migraine headaches with or without aura and acute cluster headaches in adults who have been diagnosed with migraine or cluster headaches.

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

Sumavel DosePro is not used to prevent or decrease the number of migraine or cluster headaches you have.

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

Do not take Sumavel DosePro:

- heart problems or a history of heart problems
- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
- uncontrolled high blood pressure
- 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®)
  - dihydroergotamine (D.H.E. 45®, MIGRANAL®)
  - ergotamines (CAFERGOT®, ERGOMAR®, MIGERGOT®)

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

- are allergic to sumatriptan or any of the ingredients in Sumavel DosePro. See the end of this leaflet for a complete list of ingredients in Sumavel DosePro.

Before taking Sumavel DosePro, 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 family history of heart problems or stroke
- have liver problems
- have had epilepsy or seizures
- are not using effective birth control
- are pregnant or plan to become pregnant. It is not known if Sumavel can harm your unborn baby.
- are breastfeeding or plan to breastfeed. Sumavel DosePro passes into your breast milk. It is not known if this can harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take Sumavel DosePro.

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

Using Sumavel DosePro with 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 take Sumavel DosePro?

- See the Instructions for Use at the end of this leaflet for complete information on how to use Sumavel DosePro.
- Certain people should take their first dose of Sumavel DosePro in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should take your first dose in a medical setting.
- Use Sumavel DosePro exactly as your healthcare provider tells you to use it.
- Before you try to inject Sumavel DosePro yourself, a healthcare provider should teach you how to use the Sumavel DosePro Needle-free Delivery System.
- Your healthcare provider may change your dose. Do not change your dose without first talking to your healthcare provider.
- You should use Sumavel DosePro as soon as the symptoms of your headache start, but it may be given at any time during a migraine attack.
- If you did not get any relief after the first dose, do not give a second dose without first talking with your healthcare provider.
- You may use a second dose of Sumavel DosePro or 1 dose of another sumatriptan medicine separated by at least 1 hour, but not sooner, if your headache came back after your first dose.
- Do not use more than 2 doses of 6 mg or 3 doses of 4 mg Sumavel DosePro in a 24-hour period.
- If you use too much Sumavel DosePro, 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 Sumavel DosePro so you can talk with your healthcare provider about how Sumavel DosePro is working for you.

What should I avoid while taking Sumavel DosePro?

Sumavel DosePro 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 Sumavel DosePro?

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

- **stroke**
- **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
  - weight loss
  - constipation or diarrhea
  - fever
  - stomach pain after meals
  - nausea or vomiting
  - bloody diarrhea
- **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
- **medication overuse headaches**. Some people who use too many Sumavel DosePro injections may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with Sumavel DosePro.
- **serotonin syndrome.** Serotonin syndrome is a rare but serious problem that can happen in people using Sumavel DosePro, especially if Sumavel DosePro is used with anti-depressant medicines 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 Sumavel DosePro who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take Sumavel DosePro.

The most common side effects of Sumavel DosePro include:

- pain or redness at your injection site
- tingling or numbness in your fingers or toes
- dizziness
- warm, hot, burning feeling to your face (flushing)
- discomfort or stiffness in your neck
- feeling weak, drowsy, or tired

These are not all the possible side effects of Sumavel DosePro. 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 68 °F to 77 °F (20 °C to 25 °C).
- Do not freeze.
- Protect from light.

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

General information about the safe and effective use of Sumavel DosePro.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. 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. You can ask your pharmacist or healthcare provider for information about Sumavel DosePro that is written for health professionals.

What are the ingredients in Sumavel DosePro?

Active ingredient: sumatriptan succinate

Inactive ingredients: sodium chloride, water for injection

For more information, go to www.SumavelDosePro.com or call Endo Pharmaceuticals at 1-800-462-3636

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 12/2019

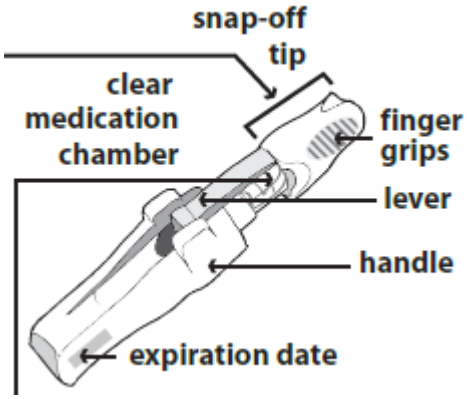
Instructions for Use

Sumavel® DosePro® (SUE-muh-vell DOSE-pro)

(sumatriptan injection), for subcutaneous use

Needle-free Delivery System

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:

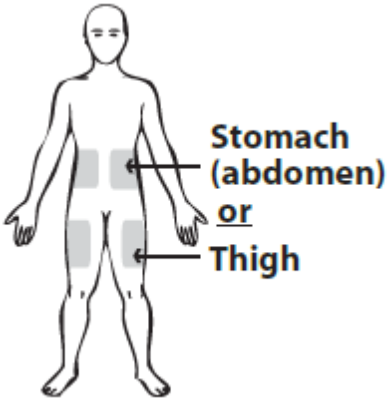
The snap-off tip should sit firmly on the end of the clear medication chamber. Do not use Sumavel DosePro if the snap-off tip is tilted or broken off.

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.

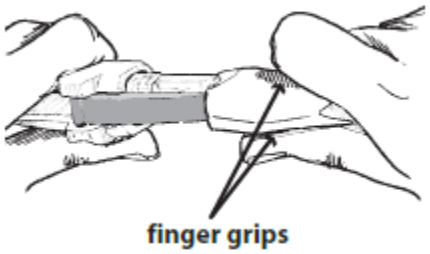


Shaded areas show all possible areas of delivery.

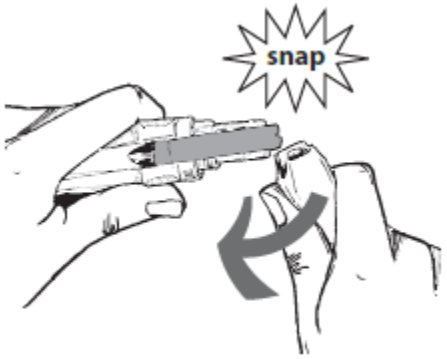
1. Snap: In this step, you will learn how to correctly remove the snap-off tip.

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.



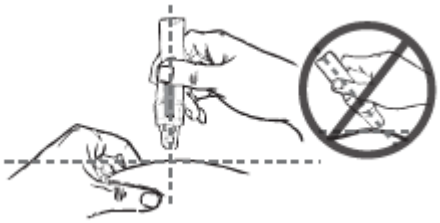
2. Flip: In this step, you will learn how to prepare Sumavel DosePro for delivery of the medicine.
Firmly press the lavender (4 mg) or green (6 mg) lever **all the way down** (away from the clear plastic end), until it **clicks and locks into the handle**. You may feel some resistance – this is normal.
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. Pinch and 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.

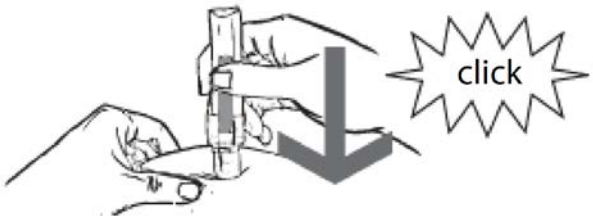
Place Sumavel DosePro straight out from the delivery site with the end of the **clear medication chamber against your skin.**

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



During the next step, **you will hear a click and feel a burst of air.** Do not be alarmed. This means that the medicine has been delivered.

Steadily press Sumavel DosePro straight down against your skin until you hear a click and feel a burst of air. You will feel the dose being delivered. There is no button to push. After you hear the click and feel the burst of air, 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.

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

Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355

Manufactured by:
Patheon UK, Limited
Swindon, United Kingdom

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SIE 90030

Appendix B

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 serotonin (5-$HT_{1B/1D}$) receptor agonist (triptan) indicated for:

- Acute treatment of migraine with or without aura in adults (1)
- Acute treatment of cluster headache in adults (1)

Limitations of Use:

- Use only if a clear diagnosis of migraine or cluster headache has been established. (1)
- Not indicated for the preventive~~on~~ treatement of migraine or cluster headache attacks. (1)

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

- For subcutaneous use only. (2.1, 2.2)
- Acute treatment of migraine: 4 mg or 6 mg single dose. (2.1)
- Acute treatment of cluster headache: 6 mg single dose. (2.1)
- Maximum dose in a 24-hour period: 12 mg. Separate doses by at least 1 hour. (2.1)
- Administer dose only to the abdomen or thigh. (2.2)

DO NOT USE SUMAVEL DOSEPRO IF THE TIP OF THE DEVICE IS TILTED OR BROKEN OFF UPON REMOVAL FROM PACKAGING. (2.2)

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

- Sumavel DosePro: 4 mg or 6 mg prefilled, single-dose, needle-free subcutaneous delivery systems.

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

- C~~History of c~~oronary artery disease or coronary artery 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-HT_1 agonist (e.g., another triptan) or of an ergotamine-containing medication (4)
- Current or recent (past 2 weeks) use of monoamine oxidase-A inhibitor (4)
- Hypersensitivity to Sumavel DosePro (angioedema and anaphylaxis seen) (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 Sumavel DosePro if occurs. (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk. (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, or stroke: Discontinue Sumavel DosePro if occurs. (5.4)
- Gastrointestinal ischemic~~a~~ reactions ~~or infarction events, or~~and peripheral vasospastic reactions: Discontinue Sumavel DosePro if occurs. (5.5)
- Medication overuse headache: Detoxification may be necessary. (5.6)
- Serotonin syndrome: Discontinue Sumavel DosePro if occurs. (5.7)
- Seizures: Use with caution in patients with epilepsy or a lowered seizure threshold. (5.10)

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

Most common adverse reactions (≥5% and > placebo) were injection site reactions, tingling, dizziness/vertigo, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, flushing, feeling of tightness, and numbness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals at 1-800-462-3636 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 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: XX/20XX

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sumavel DosePro is indicated in adults for (1) the acute treatment of migraine, with or without aura, and (2) the acute treatment of cluster headache.

Limitations of Use:

- Use only if a clear diagnosis of migraine or cluster headache has been established.
- If a patient has no response to the first migraine or cluster headache attack treated with Sumavel DosePro, reconsider the diagnosis ~~of migraine~~ before Sumavel DosePro is administered to treat any subsequent attacks.
- Sumavel DosePro is not indicated for the preventive~~on~~ treatment of migraine or cluster headache attacks.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The maximum single recommended dose of Sumavel DosePro for the acute treatment of migraine or cluster headache is 6 mg given subcutaneously. For the treatment of migraine, if side effects are dose limiting, a lower dose (4 mg) may be used *[see Clinical Studies (14.1)]*. For the treatment of cluster headache, the efficacy of a lower dose has not been established.

The maximum cumulative injected dose that may be given in 24 hours is 12 mg, with doses of Sumavel DosePro separated by at least 1 hour. Sumavel DosePro may be given at least 1 hour following a dose of another sumatriptan product. A second dose should only be considered if some response to a first dose was observed.

2.2 Administration Using Sumavel® DosePro®

Sumavel DosePro is available for use as 4 mg or 6 mg needle-free delivery systems. It is intended to be given subcutaneously only. Sumavel DosePro is designed for patient self-administration to 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 naval. Sumavel DosePro is not to be administered to other areas of the body, including the arm.

Instruct patients on the proper use of Sumavel DosePro and direct them to use proper injection sites. Instruct patients to not use Sumavel DosePro if the tip of the device is tilted or broken off upon removal from packaging *[see Patient counseling Information (17) and Instructions for Use]*.

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 4 mg or 6 mg sumatriptan (as the succinate salt).

4 CONTRAINDICATIONS

Sumavel DosePro is contraindicated in patients with:

- Ischemic coronary artery disease (CAD) (angina pectoris, history of myocardial infarction, or documented silent ischemia) or coronary artery vasospasm, including Prinzmetal's angina *[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 or 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)]*
- ~~History of hemiplegic or basilar migraine~~
- 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 (i.e., within 24 hours) use of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine1 (5-HT_1) agonist *[see Drug Interactions (7.1, 7.3)]*
- Concurrent administration of a monamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*
- Hypersensitivity to Sumavel DosePro (angioedema and anaphylaxis seen) *[see Warnings and Precautions (5.9) and Adverse Reactions (6)]*

5 WARNINGS AND PRECAUTIONS

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

Sumavel DosePro 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 Sumavel DosePro. Some of these reactions occurred in patients without known CAD. Sumavel DosePro may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

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

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 Sumavel DosePro if these disturbances occur. Sumavel DosePro 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 precordium, throat, neck, and jaw commonly occur after treatment with Sumavel DosePro and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of Sumavel DosePro is contraindicated in patients ~~shown to have~~with CAD and those with Prinzmetal's variant angina.

5.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT_1 agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Also, patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). Discontinue Sumavel DosePro if a cerebrovascular event occurs.

Before treating headaches in patients not previously diagnosed with migraine or cluster headache or ~~as migraineurs, and~~ in ~~migraineurs~~ patients who present with atypical symptoms, exclude other potentially serious neurological conditions. Sumavel DosePro is contraindicated in patients with a history of stroke or TIA.

5.5 Other Vasospasm Reactions

Sumavel DosePro~~,~~ 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 non-coronary vasospasm reaction following the use of any 5-HT_1 agonist, rule out a vasospastic reaction before receiving additional doses of Sumavel DosePro.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT_1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT_1 agonists have not been clearly established.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or combination 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 Sumavel DosePro, 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 aberrations (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 Sumavel DosePro 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-HT_1 agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with Sumavel DosePro. Sumavel DosePro is contraindicated in patients with uncontrolled hypertension.

5.9 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients receiving Sumavel DosePro. 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. Sumavel DosePro is contraindicated in patients with a history of hypersensitivity reaction to Sumavel DosePro.

5.10 Seizures

Seizures have been reported following administration of Sumavel DosePro. 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. Sumavel DosePro 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 adverse reactions are discussed in more detail in other sections of the labeling:

- 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Migraine Headache: Table 1 lists adverse reactions that occurred in 2 US placebo-controlled clinical trials in patients with migraine ~~subjects~~ *[see Clinical Studies (14.1)]* following either a single 6 mg dose of sumatriptan injection or placebo. Only reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection 6 mg 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 ~~Subjects~~ Patients and at a Greater Frequency Than Placebo in 2 Placebo-Controlled Migraine Clinical Trials[a]

Adverse Reaction	~~Percent of Subjects Reporting~~ Sumatriptan Injection 6 mg Subcutaneous (n = 547) %	Placebo (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[b]	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
Skin		
Sweating	2	1

[a] The sum of percentages cited is greater than 100% because subjects may have experienced more than 1 type of adverse reaction. Only reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection and occurred at a frequency greater than that of the placebo group are included.

[b] Includes injection site pain, stinging/burning, swelling, erythema, bruising, bleeding.

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

Cluster Headache: In the controlled clinical trials assessing the efficacy of sumatriptan injection as a treatment for cluster headache *[see Clinical Studies (14.2)]*, no new significant adverse reactions were detected that had not already been identified in trials of sumatriptan in ~~subjects~~ patients with migraine.

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sumatriptan tablets, sumatriptan nasal spray, or sumatriptan injection. 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.

Cardiovascular
Hypotension, palpitations.

Neurological
Dystonia, tremor.

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 Sumavel DosePro within 24 hours of each other is contraindicated.

7.2 Monoamine Oxidase-A Inhibitors

MAO-A inhibitors increase systemic exposure by 2-fold. Therefore, the use of Sumavel DosePro in patients receiving MAO-A inhibitors is contraindicated *[see Clinical Pharmacology (12.3)]*.

7.3 Other 5-HT_1 Agonists

Because their vasospastic effects may be additive, co-administration of Sumavel DosePro and other 5-HT_1 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, ~~or~~ SNRIs, SNRIs, TCAs, and MAO inhibitors *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Data from a prospective pregnancy exposure registry and epidemiological studies of pregnant women have not detected an increased frequency of birth defects or a consistent pattern of birth defects among women exposed to sumatriptan compared with the general population *(see Data)*. 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 *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The reported rate of major birth defects among deliveries to women with migraine ranged from 2.2 to 2.9% and the reported rate of miscarriage was 17%, which were similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Several studies have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

Human Data

The Sumatriptan/Naratriptan/Treximet (sumatriptan and naproxen sodium) Pregnancy Registry, a population-based international

prospective study, collected data for sumatriptan from January 1996 to September 2012. The Registry documented outcomes of 626 infants and fetuses exposed to sumatriptan during pregnancy (528 with earliest exposure during the first trimester, 78 during the second trimester, 16 during the third trimester, and 4 unknown). The occurrence of major birth defects (excluding fetal deaths and induced abortions without reported defects and all spontaneous pregnancy losses) during first-trimester exposure to sumatriptan was 4.2% (20/478 [95% CI: 2.6% to 6.5%]) and during any trimester of exposure was 4.2% (24/576 [95% CI: 2.7% to 6.2%]). The sample size in this study had 80% power to detect at least a 1.73- to 1.91-fold increase in the rate of major malformations. The number of exposed pregnancy outcomes accumulated during the registry was insufficient to support definitive conclusions about overall malformation risk or to support comparisons of the frequencies of specific birth defects. Of the 20 infants with reported birth defects after exposure to sumatriptan in the first trimester, 4 infants had ventricular septal defects, including one infant who was exposed to both sumatriptan and naratriptan, and 3 infants had pyloric stenosis. No other birth defect was reported for more than 2 infants in this group.

In a study using data from the Swedish Medical Birth Register, live births to women who reported using triptans or ergots during pregnancy were compared with those of women who did not. Of the 2,257 births with first-trimester exposure to sumatriptan, 107 infants were born with malformations (relative risk 0.99 [95% CI: 0.91 to 1.21]). A study using linked data from the Medical Birth Registry of Norway to the Norwegian Prescription Database compared pregnancy outcomes in women who redeemed prescriptions for triptans during pregnancy, as well as a migraine disease comparison group who redeemed prescriptions for sumatriptan before pregnancy only, compared with a population control group. Of the 415 women who redeemed prescriptions for sumatriptan during the first trimester, 15 had infants with major congenital malformations (OR 1.16 [95% CI: 0.69 to 1.94]) while for the 364 women who redeemed prescriptions for sumatriptan before, but not during, pregnancy, 20 had infants with major congenital malformations (OR 1.83 [95% CI: 1.17 to 2.88]), each compared with the population comparison group. Additional smaller observational studies evaluating use of sumatriptan during pregnancy have not suggested an increased risk of teratogenicity.

Animal Data

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.

8.2 Lactation

Risk Summary

Sumatriptan is excreted in human milk following subcutaneous administration *(see Data)*. There are no data on the effects of sumatriptan on the breastfed infant or the effects of sumatriptan on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sumavel DosePro and any potential adverse effects on the breastfed infant from sumatriptan or from the underlying maternal condition.

Clinical Considerations

Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with Sumavel DosePro.

Data

Following subcutaneous administration of a 6-mg dose of sumatriptan succinate injection in 5 lactating volunteers, sumatriptan was present in milk.

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~~SUMAVEL is not recommended for use in patients ~~under~~ 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 trials, 3 multiple-attack trials) evaluating oral sumatriptan (25 to 100 mg) in pediatric subjects aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These trials did not establish the efficacy of oral sumatriptan 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. The frequency of all adverse reactions in these subjects appeared to be both dose- and age-dependent, with younger subjects 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. Since clinical data to determine the frequency of serious adverse reactions in pediatric patients who might receive subcutaneous, oral, or intranasal sumatriptan are not presently available~~, the use of sumatriptan in patients under 18 years of age is not recommended.~~

8.5 Geriatric Use

Clinical trials of sumatriptan injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of 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 Sumavel DosePro *[see Warnings and Precautions (5.1)]*.

8.6 Hepatic Impairment

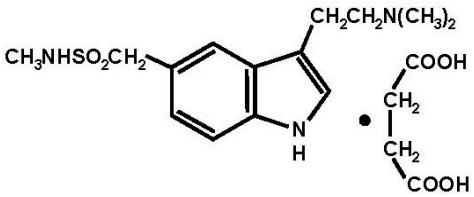
The effect of severe hepatic impairment on Sumavel DosePro metabolism has not been evaluated. Sumavel DosePro is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The elimination half-life of sumatriptan is about 2 hours *[see Clinical Pharmacology (12.3)]*, and therefore monitoring of patients after overdose with subcutaneous sumatriptan should continue for at least 10 hours or while symptoms or signs persist. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

11 DESCRIPTION

Sumavel DosePro contains sumatriptan succinate, a selective 5-$HT_{1B/1D}$ receptor agonist. 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.

Sumatriptan solution is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for subcutaneous delivery. Each 0.5 mL of Sumavel DosePro 8 mg/mL solution contains 4 mg of sumatriptan (base) as the succinate salt and 3.8 mg of sodium chloride, USP in Water for Injection, USP. Each 0.5 mL of Sumavel DosePro 12 mg/mL 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 both solutions is approximately 4.2 to 5.3. The osmolality of both solutions 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 lavender (4 mg) or green (6 mg) lever, and a glass medication chamber that is pre-filled with 4 mg or 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 binds with high affinity to human cloned 5-$HT_{1B/1D}$ receptors. Sumatriptan presumably exerts its therapeutic effects in the treatment of migraine and cluster headaches ~~by binding to~~through agonist effects at the 5-$HT_{1B/1D}$ receptors ~~located~~ on intracranial blood vessels and sensory nerves of the trigeminal system~~.~~

~~Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (including substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of sumatriptan for the treatment of migraine and cluster headaches is thought to be due to the agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) 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 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 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 subjects in clinical trials carried out during sumatriptan's development as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

12.3 Pharmacokinetics

Absorption and Bioavailability: 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 (C_{max}) (mean ± standard deviation) was 71.9 ± 14.4 ng/mL; the time to peak concentration (T_{max}) 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 (C_{max}) (mean ± standard deviation) was 78.6 ± 17.3 ng/mL; the time to peak concentration (T_{max}) was 12 minutes after dosing (range, 6 to 20 minutes); and the terminal half-life was 102 ± 12 minutes.

Distribution: 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.

Metabolism: In vitro studies with human microsomes suggest that sumatriptan is metabolized by MAO, predominantly the 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: After a single 6 mg subcutaneous dose, 22% ± 4% was excreted in the urine as unchanged sumatriptan and 38% ± 7% as the IAA metabolite.

Special Populations: *Age*: The pharmacokinetics of sumatriptan in the elderly (mean age: 72 years, 2 males and 4 females) and in subjects with migraine (mean age: 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age: 30 years).

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

Hepatic Impairment: The effect of mild to moderate hepatic disease on the pharmacokinetics of subcutaneously administered sumatriptan has been evaluated. There were no significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in moderately hepatically impaired subjects compared with healthy controls. The pharmacokinetics of subcutaneously administered sumatriptan in patients with severe hepatic impairment has not been studied. The use of Sumavel DosePro in this population is not recommended *[see Use in Specific Populations (8.6)]*.

Race: The systemic clearance and C_{max} of sumatriptan were similar in Black (n = 34) and Caucasian (n = 38) healthy male subjects.

Drug Interaction Studies: *Monoamine Oxidase-A Inhibitors*: In a trial of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In carcinogenicity studies~~,~~ in mouse and rat,~~s~~ ~~and mice were given~~ sumatriptan was administered ~~by~~ orally ~~gavage. Mice were dosed~~ for 78 and ~~weeks and rats were dosed for~~ 104 weeks, respectively, at~~. Average exposures achieved in mice receiving the highest~~ doses up to 160 mg/kg/day (the high dose in rat was reduced from 360 mg/kg/day during Week 21). ~~were approximately 110 times the exposure attained in humans after the maximum recommended single dose of 6 mg.~~ The highest dose to mice and rats was approximately 130 and 260 times the ~~maximum~~ single MRHD ~~dose~~ of 6 mg administered subcutaneously on a mg/m^2 basis. There was no evidence in either species of an increase in tumors ~~in either species~~ related to sumatriptan administration.

Mutagenesis: Sumatriptan was negative~~ot mutagenic~~ in ~~the presence or absence of metabolic activation when tested in 2 gene mutation~~ in vitro ~~assays~~ (bacterial reverse mutation [~~the~~ Ames], gene cell mutation ~~test and the~~ in ~~vitro mammalian~~ Chinese hamster V79/HGPRT, chromosomal aberration in human lymphocytes ~~assay~~) and ~~. It was not clastogenic in 2 cytogenetics assays (the in vitro human lymphocyte assay and the~~ in vivo (rat micronucleus) assays~~)~~.

Impairment of Fertility:
When sumatriptan (5, 50, 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.

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 up to 60 mg/kg/day.

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; however, the relative plasma exposure at the lowest dose tested was approximately ~~5 times the human exposure after a 100 mg oral dose or~~ 3 times the human exposure after a 6 mg subcutaneous dose.

~~Melanin Binding: In rats with a single subcutaneous dose (0.5 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this binding is unknown.~~

14 CLINICAL STUDIES

14.1 Migraine

In controlled clinical trials enrolling more than 1,000 subjects during migraine attacks who were experiencing moderate or severe pain and 1 or more of the symptoms enumerated in Table 3, onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Lower doses of sumatriptan injection may also prove effective, although the proportion of subjects obtaining adequate relief was decreased and the latency to that relief is greater with lower doses. In one well-controlled study, 6 different doses of sumatriptan injection (n = 30 each group) were compared with placebo (n = 62), in a single-attack, parallel-group design, the dose response relationship was found to be as shown in Table 2.

Table 2. Proportion of ~~Subjects~~ Patients with Migraine Relief and Incidence of Adverse ~~Events~~ Reactions by Time and by Sumatriptan Dose

Dose of Sumatriptan Injection	Percent ~~Subjects~~ Patients with Relief[a]				Adverse ~~Events~~ Reactions Incidence (%)
	at 10 Minutes	at 30 Minutes	at 1 Hour	at 2 Hours	
Placebo	5	15	24	21	55
1 mg	10	40	43	40	63
2 mg	7	23	57	43	63
3 mg	17	47	57	60	77
4 mg	13	37	50	57	80

6 mg	10	63	73	70	83
8 mg	23	57	80	83	93

[a] 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 2 randomized, placebo-controlled clinical trials of sumatriptan injection 6 mg in 1,104 subjects with moderate or severe migraine pain, the onset of relief was less than 10 minutes. Headache relief, as defined by a reduction in pain from severe or moderately severe to mild or no headache, was achieved in 70% of the subjects within 1 hour of a single 6 mg subcutaneous dose of sumatriptan injection. Approximately 82% and 65% of subjects treated with sumatriptan 6 mg had headache relief and were pain free within 2 hours, respectively.

Table 3 shows the 1- and 2-hour efficacy results for sumatriptan injection 6 mg.

Table 3. Proportion of ~~Subjects~~ Patients with Pain Relief and Relief of Migraine Symptoms After 1 and 2 Hours of Treatment

	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)
Subjects with pain relief (grade 0/1)	18%	70%[a]	26%	70%[a]
Subjects with no pain	5%	48%[a]	13%	49%[a]
Subjects without nausea	48%	73%[a]	50%	73%[a]
Subjects without photophobia	23%	56%[a]	25%	58%[a]
Subjects with little or no clinical disability[b]	34%	76%[a]	34%	76%[a]
2-Hour Data[c]				
Subjects with pain relief (grade 0/1)	31%	81%[a]	39%	82%[a]
Subjects with no pain	11%	63%[a]	19%	65%[a]
Subjects without nausea	56%	82%[a]	63%	81%[a]
Subjects without photophobia	31%	72%[a]	35%	71%[a]
Subjects with little or no clinical disability[b]	42%	85%[a]	49%	84%[a]

[a] $P<0.05$ versus placebo.

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

[c] 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 sumatriptan injection was unaffected by whether or not the migraine was associated with aura, duration of attack, gender or age of the subject, 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. Subjects aged 21 to 65 years 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 subjects receiving 6 mg of sumatriptan injection compared with those who received placebo (see Table 4).

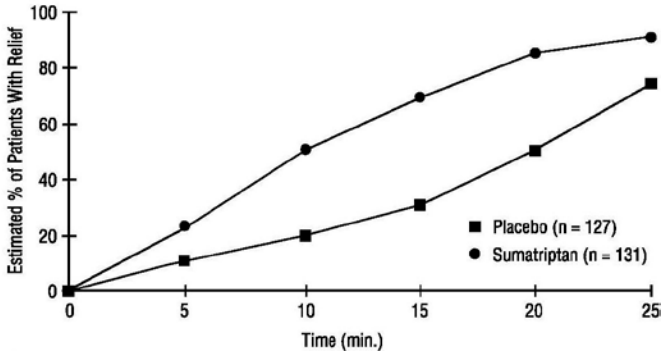
Table 4. Proportion of Subjects with Cluster Headache Relief by Time

	Study 1		Study 2	
	Placebo (n = 39)	Sumatriptan Injection 6 mg (n = 39)	Placebo (n = 88)	Sumatriptan Injection 6 mg (n = 92)
Subjects with pain relief (no/mild)				
5 Minutes post-injection	8%	21%	7%	23%[a]
10 Minutes post-injection	10%	49%[a]	25%	49%[a]
15 Minutes post-injection	26%	74%[a]	35%	75%[a]

[a] $P<0.05$.
(n = Number of headaches treated.)

An estimate of the cumulative probability of a subject with a cluster headache obtaining relief after being treated with either sumatriptan or placebo is presented in Figure 1.

Figure 1. Time to Relief of Cluster Headache from Time of Injection[a]



[a] The figure uses Kaplan-Meier (product limit) Survivorship Plot. Subjects taking rescue medication were censored at 15 minutes.

The plot was constructed with data from subjects 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 headaches treated with sumatriptan injection).

Other data suggest that treatment with sumatriptan injection is not associated with an increase in early recurrence of headache and 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 contains sumatriptan (base) in 0.5 mL, in a sterile, nonpyrogenic solution and is supplied as follows:

- Sumavel DosePro, 4 mg in a package of six prefilled, single-dose units (NDC 63481-229-06).
- Sumavel DosePro, 6 mg in a package of six prefilled, single-dose units (NDC 63481-367-06).

Store at 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 freeze. Protect from light.

17 PATIENT COUNSELING INFORMATION

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

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

Inform patients that Sumavel DosePro may cause serious cardiovascular side effects such as myocardial infarction or stroke. 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 ~~when observing~~if any indicative sign or symptoms are observed. A~~Patients should be a~~pprise~~d~~ patients of the importance of this follow-up *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.5, 5.8]* .

Hypersensitivity Reactions

Inform patients that anaphylactic reactions have occurred in patients receiving Sumavel DosePro. 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 or Ergot Medications

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

Serotonin Syndrome

~~Patients should be~~ C~~c~~aution~~ed~~ patients about the risk of serotonin syndrome with the use of Sumavel DosePro 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

Advise patients to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed *[see Use in Specific Populations (8.2)]*.

Ability to Perform Complex Tasks

Since migraines or treatment with Sumavel DosePro may cause somnolence and dizziness, instruct patients to evaluate their ability to perform complex tasks during migraine attacks and after administration of Sumavel DosePro.

How to Use Sumavel DosePro

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.

Advise patients that they will hear a click and feel a burst of air. Inform the patients that they will feel the dose being delivered. Instruct patients not to use a device if the tip of the device is tilted or broken off upon removal from packaging *[see Instructions for Use]*.

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.

Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355

Manufactured by:
Patheon UK, Limited
Swindon, United Kingdom

Sumavel® is a registered trademark of Endo Ventures Bermuda Limited.

DosePro® is a registered trademark of Zogenix, Inc.

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PATIENT INFORMATION

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

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

Sumavel DosePro can cause serious side effects, including:

- Heart attack and other heart problems. Heart problems may lead to death. Stop taking Sumavel DosePro 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

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

What is Sumavel DosePro?

Sumavel DosePro is a prescription medicine used to treat acute migraine headaches with or without aura and acute cluster headaches in adults who have been diagnosed with migraine or cluster headaches.

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

Sumavel DosePro is not used to prevent or decrease the number of migraine or cluster headaches you have.

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

Do not take Sumavel DosePro:

- heart problems or a 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®)
  - dihydroergotamine (D.H.E. 45®, MIGRANAL®)
  - ergotamines (CAFERGOT®, ERGOMAR®, MIGERGOT®)

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

- are allergic to sumatriptan or any of the ingredients in Sumavel DosePro. See the end of this leaflet for a complete list of ingredients in Sumavel DosePro.

Before taking Sumavel DosePro, 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 family history of heart problems or stroke
- have kidney problems
- have liver problems
- have had epilepsy or seizures
- are not using effective birth control
- are pregnant or plan to become pregnant. It is not known if Sumavel can harm your unborn baby.
- are breastfeeding or plan to breastfeed. Sumavel DosePro passes into your breast milk. It is not known if this can harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take Sumavel DosePro.

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

Using Sumavel DosePro with 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 take Sumavel DosePro?

- See the Instructions for Use at the end of this leaflet for complete information on how to use Sumavel DosePro.
- Certain people should take their first dose of Sumavel DosePro in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should take your first dose in a medical setting.
- Use Sumavel DosePro exactly as your healthcare provider tells you to use it.
- Before you try to inject Sumavel DosePro yourself, a healthcare provider should teach you how to use the Sumavel DosePro Needle-free Delivery System.
- Your healthcare provider may change your dose. Do not change your dose without first talking to your healthcare provider.
- You should use Sumavel DosePro as soon as the symptoms of your headache start, but it may be given at any time during a migraine or cluster headache attack.
- If you did not get any relief after the first dose, do not give a second dose without first talking with your healthcare provider.
- You may use a second dose of Sumavel DosePro or 1 dose of another sumatriptan medicine separated by at least 1 hour, but not sooner, if your headache came back or you only get some relief after your first dose.
- Do not use more than 2 doses of 6 mg or 3 doses of 4 mg Sumavel DosePro in a 24-hour period.
- If you use too much Sumavel DosePro, 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 Sumavel DosePro so you can talk with your healthcare provider about how Sumavel DosePro is working for you.

What should I avoid while taking Sumavel DosePro?

Sumavel DosePro 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 Sumavel DosePro?

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

- **stroke**
- **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
  - weight loss
  - constipation or diarrhea
  - fever
  - stomach pain after meals
  - nausea or vomiting
  - bloody diarrhea
- **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
- **medication overuse headaches**. Some people who use too many Sumavel DosePro injections may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with Sumavel DosePro.
- **serotonin syndrome.** Serotonin syndrome is a rare but serious problem that can happen in people using Sumavel DosePro, especially if Sumavel DosePro is used with anti-depressant medicines 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 Sumavel DosePro who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take Sumavel DosePro.

The most common side effects of Sumavel DosePro include:

- pain or redness at your injection site
- tingling or numbness in your fingers or toes
- dizziness
- warm, hot, burning feeling to your face (flushing)
- discomfort or stiffness in your neck
- feeling weak, drowsy, or tired

These are not all the possible side effects of Sumavel DosePro. 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 68 °F to 77 °F (20 °C to 25 °C).
- Do not freeze.
- Protect from light.

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

General information about the safe and effective use of Sumavel DosePro.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. 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. You can ask your pharmacist or healthcare provider for information about Sumavel DosePro that is written for health professionals.

What are the ingredients in Sumavel DosePro?

Active ingredient: sumatriptan succinate

Inactive ingredients: sodium chloride, water for injection

For more information, go to www.SumavelDosePro.com or call Endo Pharmaceuticals at 1-800-462-3636
This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: x/201x

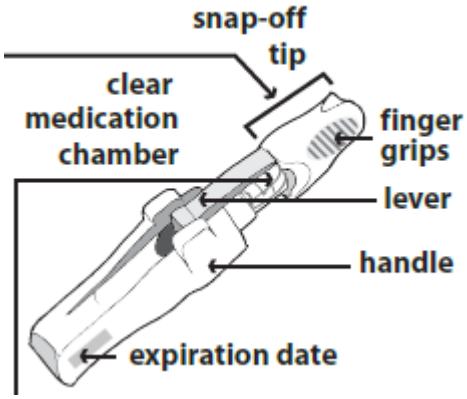
Instructions for Use

Sumavel® DosePro® (SUE-muh-vell DOSE-pro)

(sumatriptan injection), for subcutaneous use

Needle-free Delivery System

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:

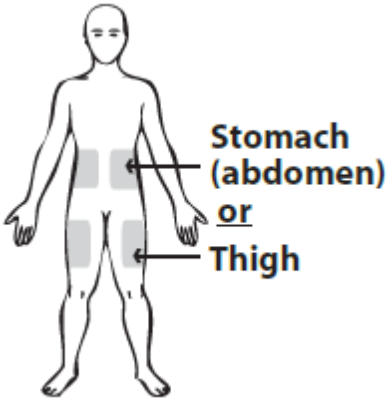
The snap-off tip should sit firmly on the end of the clear medication chamber. Do not use Sumavel DosePro if the snap-off tip is tilted or broken off.

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.

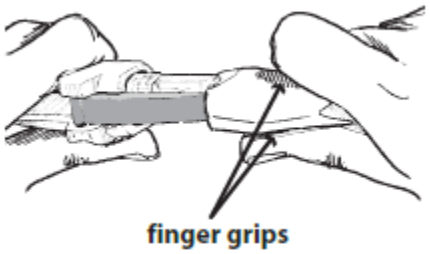


Shaded areas show all possible areas of delivery.

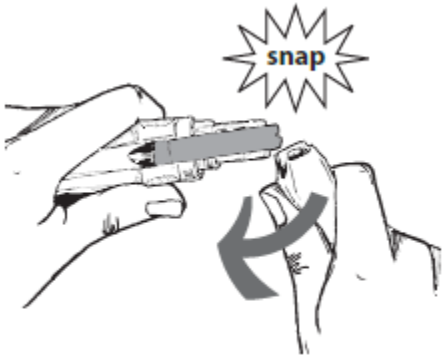
1. Snap: In this step, you will learn how to correctly remove the snap-off tip.

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.



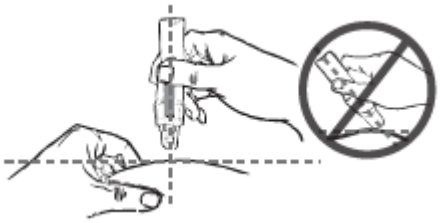
2. Flip: In this step, you will learn how to prepare Sumavel DosePro for delivery of the medicine.
Firmly press the lavender (4 mg) or green (6 mg) lever **all the way down** (away from the clear plastic end), until it **clicks and locks into the handle**. You may feel some resistance – this is normal.
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. Pinch and 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.

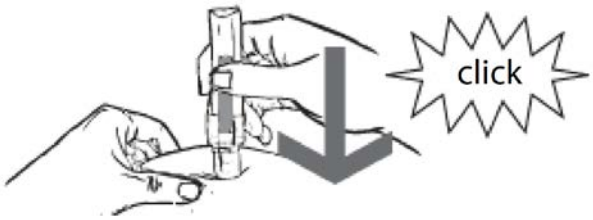
Place Sumavel DosePro straight out from the delivery site with the end of the **clear medication chamber against your skin.**

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



During the next step, **you will hear a click and feel a burst of air.** Do not be alarmed. This means that the medicine has been delivered.

Steadily press Sumavel DosePro straight down against your skin until you hear a click and feel a burst of air. You will feel the dose being delivered. There is no button to push. After you hear the click and feel the burst of air, 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.

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

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/s/

ALICE HUGHES
12/26/2019 09:47:51 PM