PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Sumatriptan Injection, USP

6 mg / 0.5 mL (as sumatriptan succinate)
Subcutaneous Injection and Autoinjector

5-HT_1 Receptor Agonist
Migraine Therapy

Manufactured by :
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Sections or subsections that are not applicable at the time of authorization are not listed.

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6 mg / 0.5 mL
Sumatriptan (as sumatriptan succinate)

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sumatriptan Injection, USP (sumatriptan succinate) is indicated for the acute treatment of migraine attacks with or without aura.

Sumatriptan Injection, USP is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine (see 2 CONTRAINDICATIONS). Safety and efficacy have not been established for cluster headache, which is present in an older, predominantly male population.

1.1 Pediatrics
Pediatrics (< 18 years of age): The safety and efficacy of sumatriptan in pediatrics patients have not been established and their use in this age group is not recommended (See 7.1.3 Pediatrics).

1.2 Geriatrics
Geriatrics (> 65 years of age): Experience of the use of sumatriptan in patients aged over 65 years is limited. Therefore, the use of Sumatriptan Injection, USP in patients over 65 years is not recommended (See 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Sumatriptan Injection, USP is contraindicated in:

- Patients with hypersensitivity to sumatriptan or to any of the ingredients of the formulations, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease) should not receive Sumatriptan Injection, USP. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
- Patients with uncontrolled or severe hypertension because Sumatriptan Injection, USP may increase blood pressure (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
- Concurrent administration of MAO inhibitors or use within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see 9.4 Drug-Drug Interactions, MAO Inhibitors and 10.3 Pharmacokinetics, Absorption/Metabolism).
- Within 24 hours before or after treatment with other 5-HT_1 receptor agonists, or ergotamine- containing drugs or their derivatives (e.g. dihydroergotamine, methysergide). Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because Sumatriptan Injectin, USP may also cause coronary

vasospasm, these effects may be additive (see 9.4 Drug- Drug Interactions, Ergot-Containing Drugs; Other 5-HT1 agonists).

- Patients with severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and 4.2 Recommended Dose and Dosage Adjustment, Hepatic Insufficiency).
- Patients with hemiplegic, basilar, or ophthalmoplegic migraine.

Sumatriptan Injection, USP should not be given intravenously because of its potential to cause coronary vasospasm.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Adults

- Sumatriptan Injection, USP is indicated for the acute treatment of migraine headache with or without aura.
- Sumatriptan Injection, USP should not be used prophylactically.
- Sumatriptan is given subcutaneously.
- The safety of treating an average of more than four headaches in a 30-day period has not been established.
- The recommended dose of Sumatriptan Injection, USP should not be exceeded.
- In selecting the appropriate formulation for individual patients, consideration should be given to the patient's preference for formulation and the patient's requirement for rapid onset of relief. Significant relief begins about 10-15 minutes following subcutaneous injection.
- In addition to relieving the pain of migraine, sumatriptan (all formulations) has also been shown to be effective in relieving associated symptoms of migraine (nausea, vomiting, phonophobia, photophobia).
- Sumatriptan is equally effective when administered at any stage of a migraine attack.
- Long-term (12-24 months) clinical studies with maximum recommended doses of sumatriptan indicate that there is no evidence of the development of tachyphylaxis, or medication-induced (rebound) headache.

4.2 Recommended Dose and Dosage Adjustment

Sumatriptan injection, USP is available in 6 mg / 0.5 mL strength

Sumatriptan Injection, USP should be injected subcutaneously (on the outside of the thigh or in the upper arm) using an autoinjector.

The recommended adult dose of sumatriptan is a single 6 mg / 0.5 mL subcutaneous injection. The recommended dose should not be exceeded.

Clinical trials have shown that approximately 70-72% of patients have headache relief within one hour after a single subcutaneous injection. This number increases to 82% by 2 hours.

If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 1 hour. Not more than 12 mg (two 6 mg injections) should be taken in any 24-hour period.

If a patient does not respond to the first dose of Sumatriptan Injection, USP a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. Sumatriptan Injection, USP may be taken for subsequent attacks.

Administration during migraine aura prior to other symptoms occurring may not prevent the development of a headache.

Geriatrics (> 65 years of age)
No differences have been observed between the pharmacokinetic parameters in healthy elderly volunteers compared with younger volunteers (less than 65 years old).

Pediatrics (patients under 18 years of age)
The safety and efficacy of Sumatriptan Injection. USP in pediatrics has not been established and its use in this age group is not recommended (see 7.1.3 Pediatrics).

Hepatic Insufficiency

- **Adults with Mild to Moderate Hepatic Impairment: Injection**
  The pharmacokinetic parameters of 6 mg subcutaneous sumatriptan do not differ statistically between normal volunteers and moderately hepatically impaired subjects (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic). No dosage adjustment is necessary for patients with mild to moderate hepatic impairment.

- **Adults with Severe Hepatic Impairment: Injection**
  Sumatriptan is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS).

4.4 Administration
Patients should be advised to read the patient instruction leaflet regarding the safe disposal of syringes and needles.

5 OVERDOSAGE

There have been some reports of overdosage with sumatriptan. Patients have received single injections of up to 12 mg subcutaneously without significant adverse effects. Doses up to 16 mg subcutaneously were not associated with side effects other than those mentioned (see 8 ADVERSE REACTIONS).

If over dosage with sumatriptan occurs, the patient should be monitored and standard supportive treatment applied as required. Toxicokinetic data are not available.
The effect of hemodialysis or peritoneal dialysis on the serum concentration of sumatriptan is unknown.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Subcutaneous	0.5 mL of solution in a prefilled syringe 6 mg / 0.5 mL of sumatriptan (as sumatriptan succinate)	3.5 mg sodium chloride, water for injection.

Availability of Dosage Forms

Packaging:
Sumatriptan Injection, USP comes as a prefilled syringe within a disposable one-time use autoinjector device. Each prefilled syringe contains 0.5 mL of solution containing 6 mg of sumatriptan (as sumatriptan succinate). Each carton contains 2 autoinjectors, each with an associated single-dose prefilled syringe of 6 mg/0.5 mL.

The stopper and needle shield are not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

General
Sumatriptan Injection, USP should only be used where a clear diagnosis of migraine has been established.

Cluster Headache: There is insufficient information on the efficacy and safety of sumatriptan in the treatment of cluster headache, which is present in an older, predominantly male population. The need for prolonged use and the demand for repeated medication in this condition renders the dosing information inapplicable for cluster headache.

Medication Overuse Headache: Overuse of acute headache treatments has been associated with the exacerbation of headache (medication overuse headache, MOH) in susceptible patients. Withdrawal of the treatment may be necessary.

Cardiovascular
Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:
Sumatriptan has been associated with transient chest and/or neck pain, pressure, heaviness and tightness which may resemble angina pectoris. In rare cases, the symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of sumatriptan. Sumatriptan should not be given to patients who have documented ischemic or vasospastic coronary artery disease (CAD) (2 CONTRAINDICATIONS). It is strongly recommended that sumatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female who is surgically or physiologically postmenopausal, or male who is over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, Sumatriptan Injection, USP should not be administered (2 CONTRAINDICATIONS).

For patients with risk factors predictive of CAD who are considered to have a satisfactory cardiovascular evaluation, the first dose of sumatriptan should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining electrocardiograms in patients with risk factors during the interval immediately following Sumatriptan Injection, USP administration on the first occasion of use. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

Intermittent long term users of sumatriptan who have or acquire risk factors predictive of CAD as described above, should receive periodic interval cardiovascular evaluations over the course of treatment.

If symptoms consistent with angina occur after the use of sumatriptan, ECG evaluation should be carried out to look for ischemic changes.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to sumatriptan.

Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness, tightness, dyspnea) has been reported after administration of sumatriptan. Because 5-HT1 agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following sumatriptan should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome, following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm (2 CONTRAINDICATIONS and 8.2 Clinical Trial Adverse Reactions).

Cardiac Events and Fatalities Associated with 5-HT$_1$ Agonists: sumatriptan can cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life- threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT$_1$ agonists. Considering the extent of use of 5-HT$_1$ agonists in patients with migraine, the incidence of these events is extremely low. The fact that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.

Premarketing Experience With Sumatriptan: Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, two experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among the more than 1900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous sumatriptan, there were eight patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six of these eight patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these eight patients, four had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrolment. Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan Nasal Spray, one patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Post-marketing Experience With Sumatriptan: Serious cardiovascular events, some resulting in death, have been reported in association with the use of Sumatriptan Injection, USP The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency

between the administration of sumatriptan and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of sumatriptan.

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

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among reports from the USA of serious cardiac events occurring within 1 hour of sumatriptan administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (2 CONTRAINDICATIONS).

Cerebrovascular Events and Fatalities with 5-HT$_1$ Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous sumatriptan, and some have resulted in fatalities. The relationship of sumatriptan to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Before treating migraine headaches with sumatriptan in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. If a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA).

Special Cardiovascular Pharmacology Studies: In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT$_1$ agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.

In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increase in coronary resistance (~20%), and decrease in hyperemic myocardial blood flow (~10%) were noted. The relevance of these finding to the use of the recommended oral doses of this 5- HT$_1$ agonist is not known.

Similar studies have not been done with sumatriptan. However, owing to the common pharmacodynamic actions of 5-HT$_1$ agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.

Other Vasospasm-Related Events: 5-HT$_1$ agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of sumatriptan to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea, and in isolated cases there was no previous history or concomitant medications.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. sumatriptan are contraindicated in patients with uncontrolled or severe hypertension (2 CONTRAINDICATIONS). In patients with controlled hypertension, sumatriptan should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

Driving and Operating Machinery
Patients should be cautioned that drowsiness may occur as a result of treatment with sumatriptan. They should be advised not to perform skilled tasks (e.g. driving or operating machinery) if drowsiness occurs.

Hepatic/Biliary/Pancreatic

The pharmacokinetic parameters of 6 mg subcutaneous sumatriptan do not differ statistically between normal volunteers and moderately hepatically impaired subjects (Child Pugh B). All formulations of sumatriptan are contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS and 4.2 Recommended Dose and Dosage Adjustment, Hepatic Insufficiency).

Immune
Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as sumatriptan. Such reactions can be life-threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see 2 CONTRAINDICATIONS). Owing to the possibility of cross-reactive hypersensitivity reactions, sumatriptan should not be used in patients having a history of hypersensitivity to chemically related 5-HT_1 receptor agonists. There have been reports of patients with known hypersensitivity to sulphonamides exhibiting an allergic reaction following administration of sumatriptan. Reactions ranged from cutaneous hypersensitivity to anaphylaxis.

Monitoring and Laboratory Tests
No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with sumatriptan.

Neurologic
Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of sumatriptan.

Seizures: Caution should be observed if sumatriptan is to be used in patients with a history of seizures or other risk factors, such as structural brain lesions, which lower the convulsion threshold. There have also been rare post-market reports of seizures following administration of sumatriptan in patients without risk factors or previous history of seizures. (See 8.5 Post-Market Adverse Reactions, Nervous System Disorders).

Serotonin toxicity / Serotonin Syndrome: Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported during use of triptans.

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus

If concomitant treatment with sumatriptan and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions, Selective Serotonin Reuptake Inhibitors (SSRIs)/Serotonin Norepinephrine Reuptake inhibitors (SNRIs). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Ophthalmologic
Binding to Melanin Containing Tissues: In rats treated with a single subcutaneous dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabelled sumatriptan, the elimination half-life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Because there could be an accumulation in melanin-rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in these tissues after extended use.
However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long term ophthalmologic effects.

Renal
The effects of renal impairment on the efficacy and safety of sumatriptan have not been evaluated. Therefore, sumatriptan is not recommended in this patient population.

7.1 Special Populations

7.1.1 Pregnant Women

Reproduction studies, performed in rats, have not revealed any evidence of impaired fertility, teratogenicity, or postnatal development due to sumatriptan. Reproduction studies, performed in rabbits by the oral route, have shown increased incidence of variations in cervico-thoracic blood vessel configuration in the fetuses. These effects were only seen at the highest dose tested, which affected weight gain in the dams, and at which blood levels were in excess of 50 times those seen in humans after therapeutic doses. A direct association with sumatriptan treatment is considered unlikely but cannot be excluded.

Post-marketing data from multiple prospective pregnancy registries have documented the pregnancy outcomes in approximately 1,100 women exposed to sumatriptan. At this time, there is insufficient information to draw conclusions. Therefore, use of sumatriptan is not recommended in pregnancy and it should be used only if the potential benefit to the mother justifies the potential risk to the fetus.

In a rat fertility study, oral doses of sumatriptan resulting in plasma levels approximately 150 times those seen in humans after a 6 mg subcutaneous dose and approximately 200 times those seen in humans after a 100 mg oral dose were associated with a reduction in the success of insemination. This effect did not occur during a subcutaneous study, where

maximum plasma levels achieved approximately 100 times those in humans by the subcutaneous route and approximately 150 times those in humans by the oral route.

7.1.2 Breast-feeding

Sumatriptan is excreted in human breast milk. Therefore, caution is advised when administering sumatriptan to nursing women. Infant exposure can be minimized by avoiding breast- feeding for 24 hours after treatment.

7.1.3 Pediatrics

Pediatrics (Patients under 18 years of age): The safety and efficacy of sumatriptan in children has not been established and its use in this age group is not recommended.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Experience of the use of sumatriptan in patients aged over 65 years is limited. Therefore, the use of sumatriptan in patients over 65 years is not recommended.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Serious cardiac events, including some that have been fatal, have occurred following the use of 5 -HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Experience in Controlled Clinical Trials with Sumatriptan

Typical 5-HT_1 Agonist Adverse Reactions: As with other 5-HT_1 agonists, sumatriptan has been associated with sensations of heaviness, pressure, tightness or pain, which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb.

Acute Safety: In placebo-controlled migraine trials, 1,432 patients received at least one dose of, 1432 subcutaneous, sumatriptan I). The following tables (2,) list adverse events occurring in these trials at an incidence of 1% or more in any of the sumatriptan dose groups and that occurred at a higher incidence than in the placebo groups.

Table 2 - Treatment-Emergent Adverse Events in Subcutaneous Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients with Migraine

	Placebo	Sumatriptan 6 mg
Number of Patients	615	1432

Number of Migraine Attacks Treated	742	2540
Symptoms of Potentially Cardiac Origin		
Chest Sensations*	1.6%	5.7%
Neck/Throat/Jaw Sensations*	1.3%	12.0%
Upper Limb Sensations*	2.0%	6.8%
Neurological		
Head/Face Sensations*	3.7%	16.6%
Dizziness	3.7%	7.9%
Headache	0.7%	3.4%
Drowsiness	1.8%	2.9%
Gastrointestinal		
Nausea	5.9%	9.4%
Hyposalivation	2.8%	3.3%
Musculoskeletal		
Muscle Atrophy Weakness & Tiredness	NR	1.7%
Ear / Nose and Throat		
Throat & Tonsil Symptoms	0.3%	1.0%
Respiratory		
Breathing Disorders	0.8%	1.3%
Non-Site Specific		
Sensations* (body region unspecified)	15.9%	39.0%
Injection Site Reactions**	10.4%	24.7%
Limb Sensations*	1.5%	6.0%
Malaise/Fatigue	2.3%	4.7%
Sweating	1.1%	1.7%
Trunk Symptoms*	0.5%	1.4%

* The term “sensations” encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning or cold sensation, paresthesia, hypoesthesia, numbness, flushing and strange sensations.
NR = Not Reported

** Includes transient injection site pain, stinging/burning, swelling, erythema, bruising and bleeding.

Sumatriptan is generally well tolerated. Most of the events were transient in nature and resolved within 45 minutes of subcutaneous administration

Dyspnea has commonly been observed following sumatriptan treatment.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Minor disturbances of liver function tests have occasionally been observed with sumatriptan treatment. There is no evidence that clinically significant abnormalities occurred more frequently with sumatriptan than with placebo.

8.5 Post-Market Adverse Reactions

The following section enumerates potentially important adverse events that have occurred in clinical practice and that have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and nondomestic use of sumatriptan. These events do not include those already listed in the previous subsections of the 8 ADVERSE REACTIONS section. Because the reports cite events reported spontaneously from worldwide post-marketing experience, the frequency of such events and the role of sumatriptan in their causation cannot be reliably determined.

Cardiac Disorders
Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, angina, myocardial infarction (see 2 CONTRAINDICATIONS, and 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Ophthalmologic Disorders
Patients treated with sumatriptan rarely exhibit visual disorders like flickering and diplopia. Additionally, cases of reduced vision have been observed. Very rarely, both transient and permanent loss of vision have occurred. These occurrences have included reports of retinal vascular occlusion, ocular venous thrombosis, vasospasm of the eye and ischemic optic neuropathy. Visual disorders may also occur during a migraine attack itself.

Gastrointestinal Disorders
Colonic ischemia (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Other Vasospasm-Related Events).

Immune System Disorders
Hypersensitivity reactions ranging from cutaneous hypersensitivity to anaphylaxis (see 7 WARNINGS AND PRECAUTIONS, Immune).

Nervous System Disorders
Seizures, although 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 (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

There have been very rare reports of dystonia and related extrapyramidal disorders, such as choreoathetoid movement, akathisia, parkinsonism and akinesia following subcutaneous treatment of sumatriptan. Patients with previous history of drug related dystonia and patients taking medications recognised to be associated with movement disorders such as SSRIs, may be at higher risk.

Nystagmus, scotoma.

Vascular Disorders
Hypotension, Raynaud's phenomenon, peripheral vascular ischemia (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular; Increase in Blood Pressure; and Other Vasospasm Related Events).

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions
Single-dose pharmacokinetic drug interaction studies have not shown evidence of interactions with propranolol, flunarizine, pizotifen or alcohol. Multiple-dose interaction studies have not been performed. The pharmacokinetics of sumatriptan nasal spray were unaltered when preceded by a single clinical dose of the nasal decongestant xylometazoline.

Ergot-Containing Drugs
Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis for these effects being additive, ergot-containing or ergot-type medications (like dihydroergotamine or methysergide) are contraindicated within 24 hours of sumatriptan administration (see 2 CONTRAINDICATIONS).

MAO Inhibitors
In studies conducted in a limited number of patients, MAO inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of sumatriptan in patients receiving MAO inhibitors is contraindicated (see 2 CONTRAINDICATIONS and 10.3 Pharmacokinetics).

Selective Serotonin Reuptake Inhibitors (SSRIs)/Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see 7 WARNINGS AND PRECAUTIONS, Serotonin Toxicity/Serotonin Syndrome).

Other 5-HT_1 agonists
The administration of sumatriptan with other 5-HT_1 agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with coadministration of 5-HT_1 agonists, use of these drugs within 24 hours of each other is contraindicated.

9.5 Drug-Food Interactions
Interactions with food have not been established.

9.6 Drug-Herb Interactions
Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions
Sumatriptan are not known to interfere with commonly employed clinical laboratory tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action
Sumatriptan have been shown to be effective in relieving migraine headache. Sumatriptan is an agonist for a vascular 5-hydroxytryptamine$_{1D}$ (5-HT_{1D}) receptor subtype (a member of the 5-HT_1 family), and has only weak affinity for 5-HT_{1A} receptors and no significant activity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_{5A}, or 5-HT_7 receptor subtypes, or at alpha$_1$-, alpha$_2$-, or beta-adrenergic; dopamine$_1$ or dopamine$_2$; muscarinic; or benzodiazepine receptors.

The therapeutic activity of sumatriptan in migraine is generally attributed to its agonist activity at 5-HT_{1B}/5-HT_{1D} receptors. Two current theories have been proposed to explain the efficacy of 5-HT_1 receptor agonists in migraine. One theory suggests that activation of 5-HT_1 receptors located on intracranial blood vessels, including those on the arteriovenous anastomoses, leads to vasoconstriction, which is believed to be correlated with the relief of migraine headache. The other hypothesis suggests that activation of 5-HT_1 receptors on perivascular fibres of the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release. These theories are not mutually exclusive.

Experimental data from animal studies show that sumatriptan also activates 5-HT_1 receptors on peripheral terminals of the trigeminal nerve, which innervates cranial blood vessels. This causes the inhibition of neuropeptide release. It is thought that such an action may contribute to the anti-migraine action of sumatriptan in humans.

Cardiovascular Effects
In vitro studies in human isolated epicardial coronary arteries suggest that the predominant

contractile effect of 5-HT is mediated via 5-HT_2 receptors. However, 5-HT_1 receptors also contribute to some degree to the contractile effect seen. Transient increases in systolic and diastolic blood pressure (up to 20 mmHg) of rapid onset (within minutes), have occurred after intravenous administration of up to 64 mcg/kg (3.2 mg for 50 kg subject) to healthy volunteers. These changes were not dose related and returned to normal within 10-15 minutes.

10.2 Pharmacodynamics
Significant relief begins about 10-15 minutes following subcutaneous injection.

Human Pharmacodynamics
Administration of subcutaneous sumatriptan 6 mg twice daily for 5 days to healthy subjects caused slight increases in mean systolic and diastolic blood pressures (6-8 mmHg) while heart rate decreased slightly (1-7 bpm).

Vasopressor effects were also evident following oral administration, with mean peak increases being somewhat smaller and of slower onset than after parenteral administration. A single oral dose of 200 mg sumatriptan caused significant increases in both systolic and diastolic blood pressures (16 mmHg and 5 mmHg, respectively); however, further dosing (200 mg three times daily for a further 7 days) did not cause any additional vasopressor effects.

In hypertensive patients with common or classical migraine, small, transient increases in both systolic and diastolic blood pressure (maximum mean increase: 6/6 mmHg) occurred shortly after subcutaneous doses of 6 mg, but resolved within 60 minutes. A dose-related increase of 14 mmHg in systolic blood pressure was found in elderly patients given 200 mg oral sumatriptan.

Sumatriptan had no effect on cardiac function in migraine patients when given as a 64 mcg/kg intravenous infusion. Exercise tests were performed after each infusion showing that sumatriptan had no effect on left ventricular ejection fraction either at rest or after exercise, and no differences were noted between placebo and sumatriptan.

Animal Pharmacodynamics
The action of sumatriptan has been studied in a range of isolated preparations *in vitro*, all known to contain different 5-HT receptor subtypes.

In Beagle dog isolated saphenous vein known to contain 5-HT_1 receptors, sumatriptan had a mean EC_{50} (molar concentration required to produce 50% of the maximum response) of 302 nM, while 5-HT had an EC_{50} of 44nM.

In cat isolated saphenous vein, sumatriptan (concentrations of up to 10 µM) had no activity on 5-HT_1 receptors, suggesting that sumatriptan is a highly selective agonist at some, but not all, 5-HT_1 receptors. The contrasting action of sumatriptan at these receptor sites in the Beagle dog and cat isolated saphenous veins provides evidence that 5-HT_1 receptors are heterogeneous.

Sumatriptan displayed virtually no activity at 5-HT_2 receptors mediating contraction of the rabbit isolated aorta (concentrations up to 50 µM) and at 5-HT_3 receptors mediating depolarization of the rat isolated vagus nerve (concentrations up to 100 µM).

The selectivity of sumatriptan was further confirmed by studies in dog isolated saphenous vein, and in dog and primate isolated basilar artery. In these assays sumatriptan was resistant to the selective 5-HT_2 and 5-HT_3 receptor antagonists, ketanserin and MDL72222, respectively. Radioligand binding studies provide yet additional support for the high degree of specificity of

sumatriptan. Sumatriptan was shown to have a high affinity for some 5-HT_1 binding sites, notably the 5-HT_{1D} subtype, and no significant affinity for other neurotransmitter binding sites such as, 5-HT_{1A}, 5-HT_{1C}, 5-HT_2, 5-HT_3, alpha$_1$, alpha$_2$, beta$_1$, dopamine D_1 and D_2, muscarinic and benzodiazepine receptors. In the human isolated basilar artery, methiothepin specifically and equally antagonised the contractile effects of both 5-HT and sumatriptan, suggesting that sumatriptan and 5-HT contract this artery by activating the same receptor type. This receptor appears to be identical to the 5-HT_1 receptor which mediates contraction of the dog isolated saphenous vein and cerebral blood vessels in both the dog and primate.

Sumatriptan selectively reduced the extravasation of plasma proteins in the duramater of rats and guinea pigs, in response to trigeminal nerve stimulation.

Although an inhibitory effect on neurotransmitter release from trigeminal nerve endings is implicated, the action of sumatriptan would still predominantly involve a direct vasoconstrictive action on dural blood vessels, which could be expected to inhibit extravasation. In fact, such a vasoconstrictive action during a migraine attack could also increase the threshold for activating perivascular nerve afferents by reducing pressure on edematous pain-sensitive vessels within the cranium.

The major metabolite of sumatriptan in humans and other animal species, GR49336, has no pharmacological activity at 5-HT_1 receptors or other vascular 5-HT receptor subtypes. Sumatriptan (1-1000 mcg/kg, iv) produced a selective long-lasting and dose-dependent decrease in carotid arterial blood flow, *in vivo* (anaesthetised Beagles), with little or no change in arterial blood pressure. The dose of sumatriptan producing 50% of its maximum vasoconstrictor action was 39 ± 8 mcg/kg, iv. Maximal vasoconstrictor responses were achieved with intravenous doses between 300-1000 mcg/kg.

The vasoconstrictor action of sumatriptan in the carotid arterial circulation of anaesthetised Beagles is mediated by the activation of 5-HT_1 receptors since it was antagonised by methiothepin, a selective 5- HT_1 receptor blocker.

Sumatriptan (30-1000 mcg/kg, iv) produced a dose-dependent reduction in the proportion of cardiac output passing through arteriovenous anastomoses (AVAs) in anaesthetised cats.

At doses up to 1000 mcg/kg iv, sumatriptan had little effect upon vascular resistance in a variety of other vascular beds. In contrast, the administration of ergotamine (30 mcg/kg) caused marked increases in vasoconstriction in most vascular beds examined.

Sumatriptan did not modify efferent vagal activity by either a central action or by interference with cholinergic neurotransmission from vagal nerve endings in the myocardium of anaesthetised cats.

It had no antinociceptive effects in rodents, and is, therefore, unlikely that its effectiveness in alleviating migraine headache is due to a generalized analgesic action.

In conscious monkeys, at cumulative doses of up to 1000 mcg/kg, there were no significant effects on arterial blood pressure, heart rate, ECG or respiratory rate that could be attributed to the intravenous administration of sumatriptan.

Sumatriptan up to 1 mg/kg had little or no effect upon either pulmonary artery or esophageal pressure in Beagle dogs. There was also little or no effect upon total peripheral resistance, and only a slight increase in cardiac output and stroke volume.

In the rat, sumatriptan (1 and 10 mg/kg, ip) caused a dose-related increase in the rate of gastric emptying, the magnitude of this effect being comparable with that obtained with metoclopramide at doses of 5-20 mg/kg, ip.

10.3Pharmacokinetics
Pharmacokinetic parameters following subcutaneous administration is shown in Table 3.

Inter-patient and intra-patient variability was noted in most pharmacokinetic parameters assessed.

Table 3 - Summary of Pharmacokinetic Parameters

Parameter	Subcutaneous
Bioavailability	96%
C_{max} (ng/mL)	6 mg: 72 ng/mL
Tmax	6 mg: 15min
$T_{½}$	2 hr (1.7-2.3 hr)
Protein Binding	14-21%
Volume of Distribution	170 L
Total Plasma Clearance	1160 mL/min
Renal Plasma Clearance	260 mL/min

* 70% to 80% of C_{max} values were attained within 30-45 minutes of dosing.

Absorption/Metabolism
Sumatriptan is rapidly absorbed after subcutaneous administration..

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme. In studies conducted in a limited number of patients, MAO inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure.

Excretion
Non-renal clearance of sumatriptan accounts for about 80% of the total clearance. The major metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine where it is present as a free acid (35%) and the glucuronide conjugate (11%). It has no known 5-HT_1 or 5-HT_2 activity. Minor metabolites have not been identified.

Special Populations and Conditions

Geriatrics*:* No differences have been observed between the pharmacokinetic parameters in healthy elderly volunteers and those in younger volunteers (less than 65 years old).

Animal Pharmacokinetics
Absorption of radiolabelled drug-related material following single-dose oral administration of sumatriptan was both rapid and extensive in mice, rats, rabbits and dogs. Oral bioavailabilities of 37% in rat (5 mg/kg), 23% in rabbit (5 mg/kg) and 58% in dog (1 mg/kg) indicate that first-pass metabolism is moderate to high in these species. In dogs, this was supported by low metabolic clearance relative to hepatic blood flow. Following intravenous administration, the parent compound was rapidly eliminated from the plasma of mice, rats and rabbits ($t_{½} \leq 1.2$ h) and less rapidly in dogs ($t_{½} = 2.1$ h). Active tubular secretion of sumatriptan occurred in the kidneys of rats and rabbits but not in the dog, where clearance was primarily metabolic.

The repeat-dose pharmacokinetics of sumatriptan in the mouse, rat, rabbit and dog were

generally consistent with the single-dose data. Plasma levels attained in these species showed that sumatriptan concentrations were linearly-related to oral doses up to 160 mg/kg in mice, 200 mg/kg in rats (subcutaneous doses up to 25 mg/kg), 400 mg/kg in rabbits and 100 mg/kg in dogs (subcutaneous doses up to 24 mg/kg).

Following intranasal administration to the rat or dog, plasma concentrations of sumatriptan peaked at approximately 30 minutes; in the monkey it peaked at 15 minutes. A second peak was observed in some animals at 90-120 minutes, suggesting absorption of a swallowed portion of the dose.

The maximum concentrations of sumatriptan detected in plasma following oral or subcutaneous administration to dogs were 35- and 75-fold higher, respectively, than were measured in human plasma following standard therapeutic doses.

There was no evidence of accumulation or enzyme inhibition/induction in any of the species studied.

Radioactive drug-related material was widely distributed throughout the body following both oral and intravenous administration of radiolabelled sumatriptan. Transfer into the central nervous system was limited.

Drug-related material was cleared rapidly from all tissues with the exception of the eye in which it appeared to be bound to the melanin in the uveal tract.

The binding of sumatriptan to plasma proteins over the concentration range 10 to 1000 ng/mL was low, 21% or less, in all species studied. Erythrocyte-associated ^{14}C-GR43175 was reversibly bound.

Placental transfer studies in rat and rabbit showed that in both species the fetuses were exposed to low levels of drug-related material. Sumatriptan and drug-related material were secreted into the milk of lactating rats and were present at higher concentrations than those seen in maternal plasma.

Following oral administration to the rabbit and dog, and intravenous administration to the dog, and intranasal administration to the rat and dog, the indole acetic acid derivative GR49336 was the major metabolite formed.

This metabolite was also a major component in the urine of rats after both oral and intravenous and intranasal administration and in rabbits after intravenous administration, indicating that oxidative deamination is the major metabolic pathway in all animal species studied.

Metabolism of the methylaminosulphonylmethyl side chain resulting in the formation of an N-demethylated derivative of sumatriptan was apparent in the urine of the mouse, rat, and rabbit but not in the dog.

The major route of excretion was via the urine in the mouse, rabbit and dog following oral and intravenous administration and in the rat following intravenous dosing only.

Following oral administration to rats, the major route of excretion of drug-related material was via the feces.

11 STORAGE, STABILITY AND DISPOSAL

Sumatriptan Injection, USP should be stored between 15°C and 30°C and protected from light.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

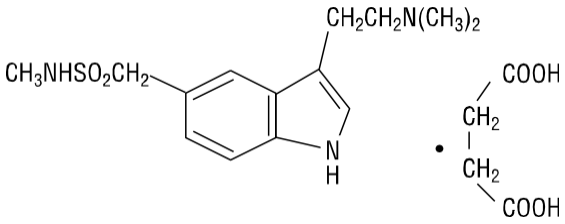
Injection:

Proper name: Sumatriptan succinate (USAN, BAN and INN)

Chemical name: 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulphonamide succinate (1:1)

Molecular formula and molecular mass: $C_{18}H_{27}N_3O_6S$,413.49 g / mol

Structural formula:



Physicochemical properties:

Physical Characteristics: White or almost white powder

Solubility: Sumatriptan succinate is freely soluble in water, sparingly soluble in methanol and practically insoluble in methylene chloride

pH: Between 4.5 to 5.3

pKa: 9.34 at 30°C in water medium.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Migraine

Injection: The efficacy of sumatriptan was established in three controlled clinical trials for the treatment of migraine. Patients enrolled and treated in these studies were predominantly female (88%), Caucasian (93%) and with a mean age of 39 years (range of 18 to 75 years). Patients with headache severity of at least grade 2 that was not improving were selected as subjects. The response of one headache attack was studied over a period of at least 2 hours. Studies 2 and 3 allowed for an optimal second dose after one hour.

Headache relief at one and two hours was statistically significantly greater for sumatriptan when compared to placebo (see Table 4).

Table 4 - Percentage of Patients with Headache Relief (grade 0/1)[1] at 1 and 2 Hours Post Subcutaneous Injection for the Treatment of Migraine

Study	Placebo† (%)	6 mg‡ (%)
Study 1		
1 hour	24	73*
2 hour	21 (n = 62)	70* (n=30)
Study 2		
1 hour	18	70*
2 hour	31 (n=190)	81* (n=384)
Study 3	26	70*
1 hour	39	82*
2 hour	(n=180)	(n=350)

1 Headache relief is defined as a reduction in headache severity from grade 3 or 2 (severe or moderate) to grade 1 or 0 (mild or no pain).
* $p < 0.05$ versus placebo.
† Includes patients that may have received an additional placebo injection 1 hour after the initial injection.
‡ Includes patients that may have received an additional 6 mg of sumatriptan injection 1 hour after the initial injection.

For patients with migraine-associated nausea, photophobia and/or phonophobia at baseline, there was a decreased incidence of these symptoms following administration of sumatriptan compared to placebo.

Menstrually-Associated Migraine

Injection: A double-blind, placebo-controlled parallel group study evaluated the efficacy of the 6 mg sumatriptan in the acute treatment of menstrual migraine with optional open follow-up treatment. A total of 226 patients, aged 18 to 50 years, experiencing menstrual migraine (defined as migraine without aura occurring -3 to 5 days relative to the first day of menstruation), for at least 6 months prior to the study, were enrolled and treated. Up to two moderate to severe attacks could be treated.

Headache relief at 2 hours post first dose was achieved for a significantly greater proportion of patients treated with sumatriptan 6 mg subcutaneous injection than with placebo (see Table 5).

Table 5 - Percentage of Patients with Complete Headache Pain Relief[1] at 1 and 2 Hours Post Subcutaneous Injection for the Treatment of Menstrually-Associated Migraine

Time	Placebo (%)	6 mg (%)
1 hour	22	71*
2 hour	31 (n=88)	73* (n=73)

1Complete Headache Pain Relief is defined as grade 1 (mild pain) reduced to grade 0 (no pain).
*$p<0.001$ vs. placebo

For migraine-associated symptoms, the results showed that there were significantly fewer patients experiencing nausea and photophobia and /or phonophobia in the sumatriptan group compared to placebo.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology
Acute studies: Administration of single oral doses of sumatriptan up to 2000 mg/kg in rats and 1200 mg/kg in mice was well tolerated.

Dogs also survived high oral doses of sumatriptan (500 mg/kg).

In subcutaneous studies, a dose of 2 mg/kg to rats was lethal. Dogs received subcutaneous doses of 20 and 100 mg/kg which were non-lethal. The reactions to treatment were similar irrespective of species or route of administration. Apart from local damage at the injection sites, there were no macroscopic or microscopic changes noted in any tissue (Table 6).

Table 6 - Results from Acute Toxicity (LD50) Studies in Mice, Rats and Dogs

SPECIES/STRAIN	ROUTE	APPROX. LD_{50} (mg/kg)	MNLD (mg/kg)	MLD (mg/kg)
Mouse: CRH	Oral	1500	≥ 1200	> 1200
Mouse: CRH	Intravenous	>15, <20	≥ 15	≤ 20
Rat: RH	Oral Oral	> 2000	≥ 2000	> 2000
Rat: SD		> 2000	≥ 2000	> 2000
Rat: RH	Intravenous	> 40	> 20	≤ 32
Rat: SD	Subcutaneous	1200 (M) 1400 (F)	≥ 500	≤ 1000
Dog: Beagle	Oral	> 500	> 500	> 500
Dog: Beagle	Subcutaneous	> 100	≥ 100	> 100

MNLD - Maximum non-lethal dose MLD - Minimum lethal dose
(M) - Male
(F) - Female

Long Term Studies: Subacute toxicity studies were conducted for periods up to 6 weeks in RH rats. Sumatriptan was given orally (by gavage) at doses up to 500 mg/kg/day and given subcutaneously at doses up to 81 mg/kg/day.

Clinical signs observed following oral administration were generally minor and transient in nature and occurred predominantly at 500 mg/kg/day. These signs included post-dosing erythema, mydriasis, ataxia, salivation, subdued temperament, postural changes and moist eyes.

Reactions were similar in subcutaneous studies in rats receiving doses of sumatriptan up to 81 mg/kg/day. Local irritation at the injection site was accompanied by a marked inflammatory response, local necrosis, hemorrhage, infiltration, granulation tissue formation and local muscle degeneration and repair. These reactions were dose-dependent.

In dogs administered oral sumatriptan (1-100 mg/kg/day) in studies up to 6 weeks, clinical signs observed included head shaking, scratching, salivation, trembling, agitated behaviour,

vocalization, mydriasis and vasodilation. These effects were dose-related. The dogs also developed tachycardia lasting for several hours, often followed by bradycardia. No changes in ECG were detected.

Subcutaneous administration of sumatriptan (1-16 mg/kg/day) up to 6 weeks in dogs caused injection site reactions similar to the reactions described in rats.

Chronic toxicity studies were carried out for 24 weeks and 72 weeks in rats and 26 and 60 weeks in dogs.

In both the 24-week and 72-week studies in rats receiving sumatriptan doses of 5, 50 and 500 mg/kg/day orally, clinical signs were similar to those seen in previous oral toxicity studies in rats and were mild and transient in nature.

Animals of each sex receiving 50 and 500 mg/kg/day gained weight more rapidly than controls. This was considered to be related to increased food consumption.

Small reductions in cholesterol levels were frequently noted at 500 mg/kg/day. As well, dose-related increases in urine-specific gravity were seen throughout the 72-week study at 500 mg/kg/day. These increases were of no toxicological significance. Cessation of treatment showed good evidence of recovery.

There were no macroscopic or histological treatment-related findings in any of the organs in either study.

A long term repeat-dose subcutaneous toxicity study of 24 weeks' duration was performed in RH rats receiving sumatriptan at doses of 1, 8 and 64 mg/kg/day.

There was occasional temporary appearance of masses at the injection sites in the animals receiving the highest dose of sumatriptan. Evidence of injection site injury was also apparent in the recovery animals. Rats in this group showed signs of neutrophilia and lymphocytosis.

Injection site reactions in animals in the high-dose group were similar to those reported during previous toxicity studies.

Studies of 26 and 60 weeks at oral doses of 2, 10 and 50 mg/kg/day were performed in Beagle dogs.

A moderate increase in heart rate was observed in the intermediate (10 mg/kg/day) -dose group (60 week study) and in the high (50 mg/kg/day) -dose group (26 and 60 week studies). The increase lasted for up to 7 hours after dosing and a dose-related decrease in heart rate was evident 24 hours after dosing, at 10 and 50 mg/kg/day. There were no changes in rhythm. Animals of either sex receiving 50 mg/kg/day showed slight reductions in body weight gain in both studies.

In the 60-week study, a dose-related incidence of transient changes was noted on the surface of the cornea. However, these changes were not considered to be treatment-related as evidenced by microscopic examination.

Organ weight analyses revealed significantly increased heart weights in all groups of treated females in the 26-week study. There were no treatment-related effects on organ weights in the 60-week study.

A long term repeat-dose subcutaneous study of 24 weeks' duration was performed in the Beagle dog at doses of 1, 3.5 and 12 mg/kg/day. Injection site reactions included edema, marked hemorrhage, moderate/chronic inflammation and minimal arteritis. Some minimal injection site changes were also seen in treated animals after a 5-week recovery period.

Transient dose-related changes in the precorneal tear film of treated dogs were observed. There was, however, no histological evidence of damage to the cornea or surrounding tissues.

Analysis of hematological parameters revealed a slight lowering of some red cell parameters in the high-dose (12 mg/kg/day) group. No reticulocyte response was evident. Although no effect on total leucocyte count was observed, lymphocyte numbers were generally lower and neutrophils were generally slightly higher at this dose level. The only change observed during the recovery period was a statistically significantly reduced hemoglobin level in the males.

Carcinogenicity
The carcinogenic potential of sumatriptan was evaluated in a 78-week oncogenicity study conducted in mice given oral doses of 10, 60 and 160 mg (base)/kg/day. There were two groups (102 mice each) given the vehicle only.

Tumours were found in more than half of the male mice and in less than half of the females across all groups. There was a statistically significant increase in the incidence of non-fatal hemolymphoreticular tumours observed in males at the dose of 60 mg/kg/day group only when compared with controls.

Since there was no dose relationship, this increase was considered to be of no toxicological significance. There was no evidence that administration of sumatriptan at any of the dose levels caused any alteration in the incidence of any specific tumours or non-neoplastic lesions.

A 104-week study was conducted in the Sprague-Dawley rat given oral doses of 10, 60 and 360 mg (base)/kg/day. Two control groups of 100 animals each were given vehicle control only.

There was a significant increase in the incidence of non-fatal adrenal medullary tumours (benign and malignant pheochromocytomas) in males given doses of 10 and 60 mg/kg/day and in males dosed at 360 mg/kg/day. A significant increase in the incidence of benign testicular interstitial (Leydig) cell tumours occurred when compared with controls. Adrenal medullary tumours also increased significantly in females dosed at 60 and 360 mg/kg/day. Comparison of both types of tumours with historical control data indicated that the observations were within the expected background range for the species and that long-term exposure to sumatriptan does not induce any treatment-related increases in the incidences of any tumours for the species tested.

Genotoxicity
Sumatriptan produced no detectable or reproducible mutagenic potential above that seen in controls, in studies conducted *in vitro* with mutant strains of Salmonella typhimurium, Escherichia coli, or Saccharomyces cerevisiae with or without a rat hepatic drug metabolizing enzyme system. In addition, no statistically significant clastogenic effects were seen in vitro using cultured human peripheral lymphocytes at a maximum dose of 1000 mcg/mL in the presence of the rat hepatic drug metabolism enzyme system or *in vivo* in a rat micronucleus test, at a maximum dosage of 1000 mg/kg.

Sumatriptan showed only weak cytotoxic activity at the highest concentration of 5000 mcg/mL tested *in vitro* with V-79 mammalian cells.

Reproduction and Developmental Toxicology
In organogenesis studies, oral doses of up to 500 mg/kg/day in the rat were without adverse effects upon fetal parameters measured, but an oral dose of 1000 mg/kg/day in the rat proved toxic to both dams and embryos.

Two oral organogenesis studies were conducted in rabbits, one using daily oral doses of 5, 25 or 100 mg/kg/day and the other using 5, 15 or 50 mg/kg/day. Sumatriptan was administered from days 8- 20 of pregnancy.

In the first study, there were no adverse effects at the two lower doses. At the highest dose (100 mg/kg), there was a severe decrease in maternal body weight gain indicating that this dose is maternally toxic. A non-significant increase in post-implantation intra-uterine death from 8.3% in the untreated control group to 21.2% in the high-dose (background range in untreated control animals 1.7% - 15.2%) was observed. In addition there was an increased incidence of subtle variations in the position of certain blood vessels emanating from the aortic arch. In the untreated control these were present at 5.5% of fetuses (3 out of 10 litters affected). At the maternally toxic dose of 100 mg/kg, 23.1% of fetuses had these variations (4 out of 5 litters affected). This type of change is commonly found in untreated control animals (historical control incidence 17.5%; proportion of litters affected 44 out of 91), and does not compromise either health or survival.

In the second oral study, the findings were similar to those seen in the first study. There were no adverse effects at the two lower doses. At the highest dose (50 mg/kg), there was a severe decrease in maternal body weight gain. There were also various fetal effects ascribed to maternal toxicity. There was a slight reduction in mean fetal weight (37.7 g in control, 35.3 g at 50 mg/kg); small increases in the incidence of common skeletal variants (control incidence 8.8%; at 50 mg/kg 20.8%; background mean 6.2%; background range 1.3% - 13.3%) and again an increased incidence of positional changes of certain aortic arch blood vessels; (control incidence 12.8%, 3 out of 20 litters affected; at 50 mg/kg 25%, 10 out of 14 litters affected).

Placental transfer studies in pregnant rabbits have shown that sumatriptan can cross the placental barrier in small amounts. After a 5 mg/kg oral dose, 71.2 ng sumatriptan per gram of fetus was detected. The blood levels at this dose were 172 - 269 ng/mL. At the maternally toxic dose of 50 mg/kg in rabbits, blood levels reached 3180-6750 ng/mL.

Organogenesis studies conducted using intravenous doses of up to 12.5 mg/kg/day in rats revealed fused ribs at a dose of 2.5 mg/kg/day and rudimentary tail and dilatation of the renal pelvis at a dose of 12.5 mg/kg/day. The treatment had no adverse effects on either the dams or the fetuses and the malformations were considered unrelated to treatment since they are known to occur spontaneously in the control groups of the rat strain employed.

Rabbits were also studied using intravenous doses of up to 8.0 mg/kg/day which revealed no teratological response. However, in the first study a statistically significant dose-related increasing trend in prenatal mortality was seen due to apparent maternal toxicity. In the second study, using intravenous doses up to 2.0 mg/kg/day, no maternal toxicity or increased prenatal mortality were observed.

Fertility studies conducted in rats with oral doses of up to 500 mg/kg/day and subcutaneous doses of up to 60 mg/kg/day indicated that there were no adverse effects upon the

reproductive performance of the treated, parental generation, or upon the growth and development of two successive untreated generations.

In peri- and postnatal studies conducted in rats given oral doses of up to 1000 mg/kg/day and subcutaneous doses of up to 81 mg/kg/day, no toxicological adverse effects that may have been relevant to the peri- and postnatal development of their offspring were seen. However, oral administration of 1000 mg/kg/day during periods of pregnancy and lactation resulted in a decrease in maternal and fetal body weight.

A comprehensive evaluation of the effects of sumatriptan on reproduction indicates that the compound is devoid of teratogenic potential in the rat. In addition, there were no adverse effects on fertility or postnatal development. In rabbit oral reproduction studies, there were increased incidences of variations in cervico-thoracic blood vessel configuration in the fetuses, but these were only seen at maternally toxic doses in which blood levels were in excess of 50 times those seen after therapeutic doses in humans. A direct association with sumatriptan treatment is considered unlikely but cannot be excluded. The relevance to humans is unknown.

Special Toxicology
Local Tolerance: The subcutaneous and intramuscular administration of 1 mL of a solution of sumatriptan (50 mg/mL) to rabbits produced no overt signs of irritancy and caused only slight necrotic changes in the deepest layers of the subcuticular muscle. While the subcutaneous lesions healed in a rapid and uncomplicated manner, the intramuscular lesions were moderately slow to heal.

At a lower concentration (2.5 mg/mL) no signs of subcutaneous or intramuscular irritancy were apparent.

In inhalation toxicity studies (dog, monkey), no irritants of the nasal passages or respiratory tract tissues were identified after intranasal administration of sumatriptan.

Skin and Eye Irritancy: Sumatriptan produced little or no irritant reaction when applied topically to the skin of guinea pigs and was a non-irritant in the rabbit eye.

Sumatriptan was shown to be devoid of detectable skin sensitizing potential in guinea pigs subjected to a 12-day induction period (0.05 mL of a 10% solution, applied epicutaneously) prior to challenge with sumatriptan.

Dependence Liability: The physical dependence liability of sumatriptan was assessed in Cynomolgus monkeys at an oral dose of 5 mg/kg, the lowest tolerable dose causing mild to moderate CNS effects.

The behavioural changes observed upon withdrawal of sumatriptan were limited in number, sporadic, unsustained and not observed in all animals. It would appear that sumatriptan does not share with compounds such as opiates and benzodiazepines the ability to cause physical dependence.

17 SUPPORTING PRODUCT MONOGRAPHS

IMITREX® Subcutaneous Injection and Autoinjector, submission control 248682, Product Monograph, GlaxoSmithKline Inc. September 25, 2021.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PrSumatriptan Injection. USP
6 mg / 0.5 mL
Sumatriptan (as sumatriptan succinate)

Read this carefully before you start taking **Sumatriptan Injection, USP.** This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Sumatriptan Injection, USP**.

What is Sumatriptan Injection, USP used for?
Sumatriptan Injection, USP is used in adults to relieve migraine headaches. These migraine headaches may or may not be accompanied by an aura. This is when you may see black spots, flashes of light or shimmering spots or stars. **Sumatriptan Injection, USP** should not be used to prevent or reduce the number of headaches you experience. Use **Sumatriptan Injection, USP** only to treat an actual migraine headache attack.

How does Sumatriptan Injection, USP work?
Migraine headache is believed to be caused by a widening of the blood vessels in the head. **Sumatriptan Injection, USP** narrows these vessels and relieves the symptoms of migraine headache.

What are the ingredients in Sumatriptan Injection, USP?
Medicinal ingredients: sumatriptan succinate

Non-medicinal ingredients: sodium chloride and water for injection.

Sumatriptan Injection, USP comes in the following dosage forms:

Sumatriptan Injection, USP comes as a prefilled syringe within a disposable one-time use autoinjector device.

Each prefilled syringe contains 0.5 mL of solution containing 6 mg of Sumatriptan (as succinate).

Each carton contains 2 autoinjectors, each with an associated single-dose prefilled syringe.

The stopper and needle shield are not made with natural rubber latex.

Do not use Sumatriptan Injection, USP if:
- you are allergic to sumatriptan or to any of the ingredients in Sumatriptan Injection, USP. (See “What are the ingredients in Sumatriptan Injection, USP?”).
- if you have a heart problem such as heart failure or chest pains (angina), or have already had a heart attack.
- you have had a stroke or a mini-stroke (also called a transient ischaemic attack or TIA).
- you have a history, symptoms or signs of peripheral vascular disease. This is a reduced blood flow to the limbs and organs other than the heart and brain, such as ischemic bowel disease and Raynaud’s syndrome.
- you have uncontrolled or severe high blood pressure.
- you are taking or have taken within the past 2 weeks, a monoamine oxidase inhibitor (MAO) inhibitor, medication (such as phenelzine sulfate, tranylcypromine sulfate,

moclobemide or selegiline).
- You are taking or have taken within the past 24 hours, medication containing ergotamine, dihydroergotamine, methysergide, or another triptan used to treat migraine headaches. If you are not sure if you have been prescribed these types of medications, ask your healthcare professional.
- you have severe liver problems.
- you have certain other types of migraine headaches including:
    - hemiplegic migraines. These are migraine headaches where you have weakness on one side of your body, or
    - basilar migraines. These are migraine headaches that start in the lower part of the brain, or
    - ophthalmoplegic migraines. These are migraine headaches where you have pain around the eyes.

If you are not sure if you have these types of migraines, ask your healthcare professional.

Sumatriptan Injection, USP should not be used for the treatment of other types of headaches that are different from migraine attacks.

Sumatriptan Injection, USP should not be given intravenously, but only into the tissues just below the skin (on the outside of the thigh or in the upper arm).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sumatriptan Injection, USP. Talk about any health conditions or problems you may have, including if you:

- are pregnant, think you might be pregnant, or are trying to become pregnant.
- are breastfeeding. The active ingredient in Sumatriptan Injection, USP, sumatriptan, will pass into your breast milk. Avoid breastfeeding for 24 hours after taking Sumatriptan Injection, USP.
- have risk factors for heart disease. This includes high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40.
- have ever had to stop taking this or any other medication because of an allergy or other problems, or you are allergic to drugs containing sulphonamides.
- are under 18 years of age
- are over 65 years of age.
- had or have any liver or kidney problems.
- had or have epilepsy or seizures.
- experience a headache that is different from your usual migraine attacks

Other warnings you should know about:
Taking Sumatriptan Injection, USP can cause serious side effects, including:
- Serious heart problems
- Long term eye problems
- Raynaud's Syndrome

See the **Serious side effects and what to do about them** table, below for more information on these and other serious side effects.

Serotonin toxicity (also know as Serotonin syndrome): Sumatriptan Injection, USP can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take

Sumatriptan Injection, USP with certain medication to treat depression.

Serotonin toxicity symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Continuous use of Sumatriptan Injection, USP: Sumatriptan Injection, USP should not be used continuously to prevent or reduce the number of attacks you experience. Use Sumatriptan Injection, USP only to treat an actual migraine headache attack. If you use Sumatriptan Injection, USP too often, it may make your migraine headaches worse. If this happens, your healthcare professional may tell you to stop taking Sumatriptan Injection, USP.

Driving and Operating Machines: Sumatriptan Injection, USP can cause dizziness which may affect your ability to drive or use machines. Wait to see how you respond to Sumatriptan Injection, USP before you drive or use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Sumatriptan Injection, USP:

- Medicines used to treat depression such as MAO Inhibitors, selective serotonin reuptake inhibitors (SSRIs), and serotonin noradrenaline reuptake inhibitors (SNRIs).

- Other medicines used to treat migraine headaches such as triptans, 5-HT_1 agonists, ergotamine, dihydroergotamine, and methysergide.

How to use Sumatriptan Injection, USP:

- Sumatriptan Injection, USP is available as a prefilled syringe within a disposable one-time use Autoinjector device.
- Before using the Sumatriptan Injection, USP Autoinjector System, see the instructions below
- Sumatriptan Injection, USP Autoinjector System is given as a single injection into the tissues just below the skin on the outside of the thigh or the upper arm.
- Sumatriptan Injection, USP can be taken at any time during your migraine headache.
- It may take up to 15 minutes for Sumatriptan Injection, USP to start working.
- If after taking Sumatriptan Injection, USP you need more pain relief, you can take another pain medication. This medication should not contain ergotamine. If you are not sure which medications you can use talk to your healthcare professional.

Remember, this medicine has been prescribed only for you. Do not give it to anybody else, as they may experience undesirable effects, which may be serious.

Instructions For Use of your Sumatriptan Disposable Autoinjector

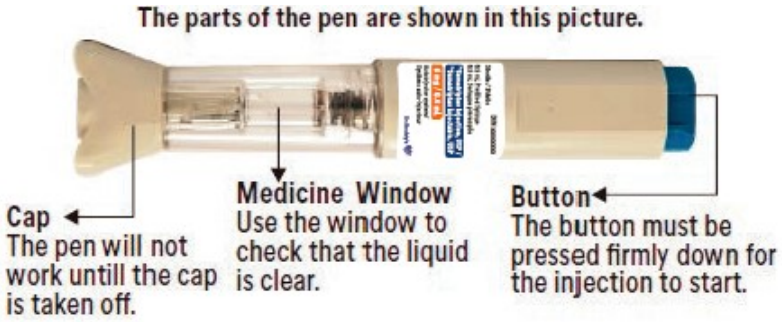
The Instructions for use explains how to use the Sumatriptan Autoinjector System. Read them several times to make sure you understand them, before you begin the first step. If you have any questions, ask your healthcare professional.

- **Use the device immediately once the cap has been removed; do NOT postpone the injection.**
- **Keep the Sumatriptan Autoinjector System out of the reach of children**

Important things that you need to know
This device is called an Autoinjector pen. Here we use the shorter name 'pen'.

1. Follow these step-by-step instructions every time you use the pen.
2. Only use each pen once - do not try to use more than once.

A. ABOUT THE AUTOINJECTOR PEN



B. GETTING READY

Getting ready for the injection.

1. Wash your hands.
2. Choose an area with an adequate fatty tissue layer such as upper arm or thigh (see below).
3. Clean the skin area to be injected with alcohol or a new sterile swab (see Figure A).

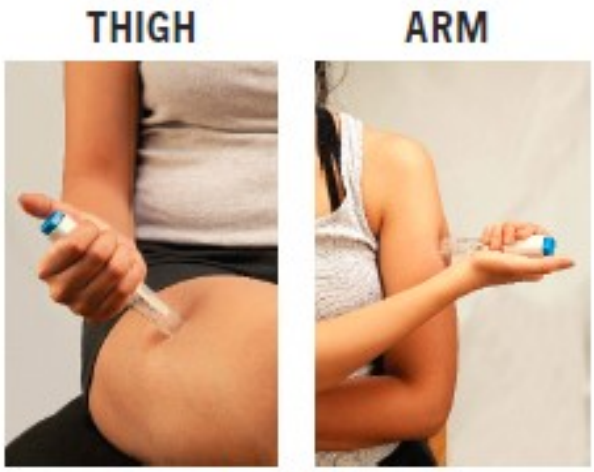


Figure A

Getting the pen ready.

4. Take the pen out of the package.
5. Check the expiration date on the pen. Do not use if the expiration date has passed.
6. Look in the transparent medicine window on the pen.

- Before injection, to check that the liquid is clear (see Figure B).
- If it is difficult to see what is in the window, hold the pen up.to the light and check.
- Do not inject the medicine if the liquid inside the pen looks discolored, cloudy, contains particles, or if there are any signs of leakage.
- After injection, the blue plunger rod completely fills the medicine window (see Figure C).
- If the blue plunger rod can be seen through the medicine window, the device is spent and cannot be used again.

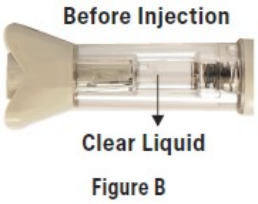


Figure B

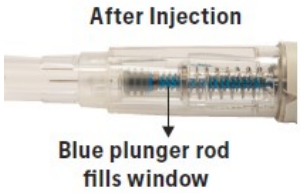


Figure C

7. **Pull the grey cap off the pen.**
   - Do not twist the cap.
   - Pull it straight off (see Figure D).

Figure D

8. **Look inside the cap, check that the grey needle cover is inside** (see Figure E).
   - Do **NOT** use the pen if the grey needle cover is not inside the cap

Figure E

9. **Do not try to put the cap back**

- If you try to put it back, this will damage the needle.

You are now ready to inject the medicine, go to step 10

C. INJECTING THE MEDICINE

10. Without pressing the blue button, push the pen firmly against your skin until you feel the stop point (see Figure F).

- Pushing to the stop point unlocks the blue button. **Do NOT push the blue button until you are ready to inject.**
- **When the pen is firmly pressed against the skin, the safety lock is deactivated. So, if the button is pressed by accident, the pen could fire unintentionally.**
- **Do not attempt to reengage the safety lock at any time.**
- **Keep the pen pressed against your skin for the next steps.**

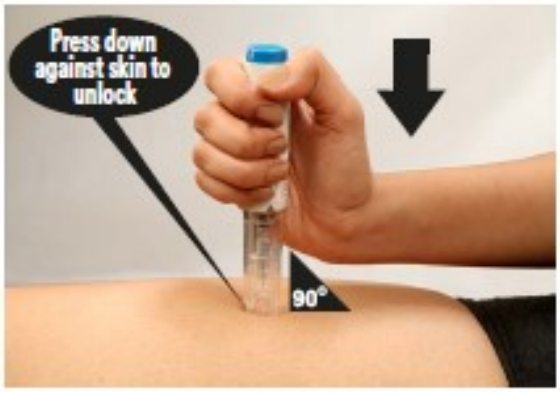


Figure F

11. Keep pushing the pen against your skin then firmly press down the blue button on the top of the pen until it will not go further (see Figure G).

- You will hear a click, this indicates that the injection has started (see Figure G).
- If the injection did not start, release the blue button, make sure the pen is pushed down against the skin and push down harder on the blue button.

Figure G

12. Do not take the pen off your skin.

- Monitor the injection through the medicine window to make sure that the entire dose is injected. The blue plunger will move down the window, completely fill it, and stop moving when the injection is done (see Figure H).
- When the injection is done, keep holding the pen against the skin for 5 more seconds (see Figure I). If you take the pen off before, not all of the medicine will be injected.

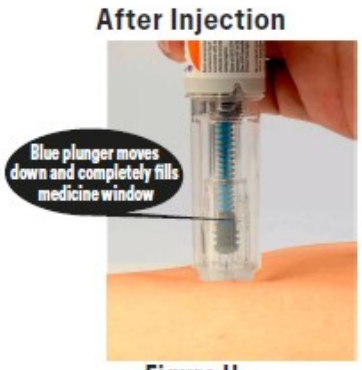


Figure H

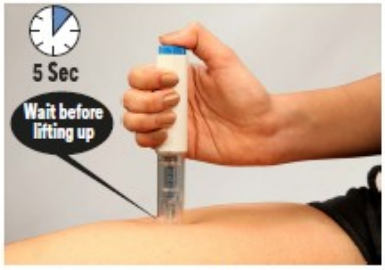


Figure I

13. Carefully take the pen off your skin (see Figure J).

- The protective sleeve automatically covers the needle. It is then locked and the needle is protected.

Figure J

D. WHAT TO DO AFTER THE INJECTION

14. If you notice a spot of blood at the injection site, dab away with a cotton ball or tissue paper. Do not rub the injection site. If needed, you may cover the injection site with an adhesive bandage.

15. Visually check that there is no liquid left at the bottom of the medicine window. If there is liquid, consult your healthcare professional.

E. DISPOSE THE AUTOINJECTOR PEN

16. Discard the whole Sumatriptan Injection, USP pen after use and discard the cap.

• Discard the whole Sumatriptan Injection, USP pen and cap as instructed by your pharmacist. Do not discard in regular home waste.

Do not try to reuse the autoinjector pen. To avoid any injury, never try to touch the needle.

Usual dose:

- The usual adult dose is 6 mg / 0.5 mL. Do not exceed the usual adult dose.
- If you do not respond to the first dose of Sumatriptan Injection, USP, do not take a second dose for the same attack.
- If your symptoms come back, and it has been 1 or more hour since your first injection, you may take a second injection.
- DO NOT take more than 12 mg (two 6 mg injections) in any 24-hour period.

Overdose:

If you think you, or a person you are caring for, have taken too much Sumatriptan Injection, USP contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Sumatriptan Injection, USP?
These are not all the possible side effects you may feel when taking **Sumatriptan Injection, USP**. If you experience any side effects not listed here, contact your healthcare professional.

The most commonly reported side effects of **Sumatriptan Injection, USP** are:

- flushing (redness of the face lasting for a short time)
- feeling sick or vomiting
- dizziness
- drowsiness
- tiredness
- weakness
- temporary increase in blood pressure
- temporary pain at the site of injection
- stinging or burning, redness, swelling, bruising and bleeding at the site of injection

Other side effects include:

- trouble with eyesight, such as blind spots, flashes of light, and seeing two images of a single object.
- shaking, tremors or uncontrolled movements.
- loss of normal colour in the fingers and toes.
- Sweating.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Unusual sensations or discomfort including numbness, tingling, feeling hot or cold; pain, heaviness or pressure in any part of the body including chest, throat, neck, jaw and upper limbs.	√		
VERY RARE			
Symptoms of a heart attack: chest pain, sweating, shortness of breath.			√
Heart rhythm problems:			

unusually slow or fast heartbeats, or a feeling of irregular and/or forceful heartbeats.	√		
Allergic reactions: shortness of breath, sudden wheeziness, chest tightness, swelling of the eyelids, face or lips, lumpy skin rash or hives.			√
Seizures: loss of consciousness with uncontrollable shaking ("fit").			√
Lower abdominal pain and/or severe rectal bleeding.			√
Raynaud's syndrome: persistent purple discolouration of hands or feet.			√
Loss of vision.			√
UNKNOWN			
Serotonin toxicity: a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38 °C), or rigid muscles.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep Sumatriptan Injection, USP away from heat and light. Always keep Sumatriptan Injection, USP in the carton provided and store between 15°C and 30°C.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

Needles and syringes may be hazardous and should be disposed of safely and hygienically.

Keep out of reach and sight of children.

If you want more information about Sumatriptan Injection, USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this

  Patient Medication Information by visiting the Health Canada website:(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.drreddys.com or by calling 1-855-845-1739

This leaflet was prepared by Dr. Reddy's Laboratories Ltd.

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