PRODUCT MONOGRAPH

Pr AVA-SUMATRIPTAN DF
(sumatriptan succinate tablets)

25 mg, 50 mg and 100 mg sumatriptan as sumatriptan succinate

5-HT_1 Receptor Agonist

Migraine Therapy

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	DF Tablets 25mg, 50 mg and 100 mg	Lactose Monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Adults
AVA-SUMATRIPTAN DF (sumatriptan succinate) are indicated for the acute treatment of migraine attacks with or without aura.

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

Pediatrics (<18 years of age):
The safety and efficacy of sumatriptan succinate in children has not been established and its use in this age group is not recommended. (See WARNINGS and PRECAUTIONS)

Geriatrics (>65 *x* years of age);
Experience of the use of sumatriptan succinate in patients aged over 65 years is limited. Therefore the use of AVA-SUMATRIPTAN DF in patients over 65 years is not recommended. (See WARNINGS and PRECAUTIONS)

CONTRAINDICATIONS

AVA-SUMATRIPTAN DF (sumatriptan succinate) are contraindicated in 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 AVA-SUMATRIPTAN DF. 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 WARNINGS AND PRECAUTIONS).

Because sumatriptan succinate may increase blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension.

Concurrent administration of MAO inhibitors or use within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see ACTION AND CLINICAL PHARMACOLOGY and DRUG INTERACTIONS).

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because sumatriptan succinate may also cause coronary vasospasm and these effects may be additive, the use of AVA-SUMATRIPTAN DF within 24 hours before or after treatment with other $5HT_1$ receptor agonists, or ergotamine-containing drugs or their derivatives (eg. dihydroergotamine, methysergide) is contraindicated.

AVA-SUMATRIPTAN DF should not be administered to patients with severe hepatic impairment.

AVA-SUMATRIPTAN DF are contraindicated in patients with hemiplegic, basilar, or ophthalmoplegic migraine.

AVA-SUMATRIPTAN DF are 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 the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

General

AVA-SUMATRIPTAN DF (sumatriptan succinate) 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 succinate 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.

Psychomotor Impairment: Patients should be cautioned that drowsiness may occur as a result of treatment with AVA-SUMATRIPTAN DF. They should be advised not to perform skilled tasks (e.g. driving or operating machinery) if drowsiness occurs.

Cardiovascular

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events*:*

Sumatriptan succinate 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 succinate. AVA-SUMATRIPTAN DF should not be given to patients who have documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that AVA-SUMATRIPTAN DF 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, AVA-SUMATRIPTAN DF should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are considered to have a satisfactory cardiovascular evaluation, the first dose of AVA-SUMATRIPTAN DF 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 AVA-SUMATRIPTAN DF 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 AVA-SUMATRIPTAN DF 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 AVA-SUMATRIPTAN DF, 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 AVA-SUMATRIPTAN DF.***

Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness, has been reported after administration of sumatriptan succinate. Because 5-HT_1 agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following AVA-SUMATRIPTAN DF 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 AVA-SUMATRIPTAN DF should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS and PRECAUTIONS and ADVERSE DRUG REACTIONS, Clinical Trial Adverse Reactions).

Cardiac Events and Fatalities Associated with 5-HT_1 Agonists:
Sumatriptan succinate 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 succinate 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 Succinate*:** Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan succinate, two experienced clinical adverse events shortly after receiving oral sumatriptan succinate that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Postmarketing Experience With Sumatriptan Succinate : Serious cardiovascular events, some resulting in death, have been reported in association with the use of sumatriptan succinate tablets. 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 succinate to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of sumatriptan succinate 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 succinate.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan succinate 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 succinate administration, almost all of the

patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see 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 sumatriptan succinate and some have resulted in fatalities. The relationship of sumatriptan succinate to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan succinate 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 AVA-SUMATRIPTAN DF 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=l0) with suspected coronary artery disease undergoing angiography, a 5-HT_1 agonist at a subcutaneous dose of 1.5mg 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 1.5mg 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 oral sumatriptan succinate. 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 succinate 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. AVA-SUMATRIPTAN DF are contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS). In patients with controlled hypertension, AVA-

SUMATRIPTAN DF should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

Hepatic

The effect of hepatic impairment on the efficacy and safety of AVA-SUMATRIPTAN DF has not been evaluated, however, the pharmacokinetic profile of sumatriptan in patients with moderate [1] hepatic impairment shows that these patients, following an oral dose of 50 mg, have much higher plasma sumatriptan concentrations than healthy subjects (Table 1). Therefore, an oral dose of 25 mg may be considered in patients with hepatic impairment.

Table 1: Pharmacokinetic Parameters After Oral Administration of Sumatriptan succinate 50 mg to Healthy Volunteers and Moderately Hepatically Impaired Patients

Parameter	Mean Ratio (hepatic impaired/healthy) n=8	90% CI	p-value
AUC_∞	181%	130 to 252%	0.009*
C_{max}	176%	129 to 240%	0.007*
*Statistically significant			

[1] Assessed by aminopyrine breath test (>0.2-0.4 scaling units)

AVA-SUMATRIPTAN DF should not be administered to patients with severe hepatic impairment (see CONTRAINDICATIONS).

Immune

Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as AVA-SUMATRIPTAN DF. 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 CONTRAINDICATIONS). Owing to the possibility of cross-reactive hypersensitivity reactions, AVA-SUMATRIPTAN DF 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 succinate. Reactions ranged from cutaneous hypersensitivity to anaphylaxis.

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 AVA-SUMATRIPTAN DF.

Seizures: Caution should be observed if AVA-SUMATRIPTAN DF 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 succinate in patients without risk factors or previous history of seizures. (See ADVERSE REACTIONS, Post Market Adverse Drug Reactions, Nervous System Disorders.)

Opthalmologic

Binding to Melanin Containing Tissues: In rats treated with a single subcutaneous dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled 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 AVA-SUMATRIPTAN DF have not been evaluated. Therefore AVA-SUMATRIPTAN DF are not recommended in this patient population.

Special Populations

Pregnant Women: Reproduction studies, performed in rats, have not revealed any evidence of impaired fertility, teratogenicity, or post-natal development due to sumatriptan succinate. 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 succinate treatment is considered unlikely but cannot be excluded.

Post-marketing data from multiple prospective pregnancy registries have documented the pregnancy outcomes in approximately 1100 women exposed to sumatriptan. At this time, there is insufficient information to draw conclusions. Therefore, use of AVA-SUMATRIPTAN DF are 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 succinate 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.

Nursing Women:

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

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

Geriatrics (>65 *x* years of age):
Experience of the use of sumatriptan succinate in patients aged over 65 years is limited. Therefore the use of AVA-SUMATRIPTAN DF in patients over 65 years is not recommended.

Special Disease Conditions:
AVA-SUMATRIPTAN DF should be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function. (See WARNINGS and PRECAUTIONS, Hepatic; Renal).

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

ADVERSE REACTIONS

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 CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Experience in Controlled Clinical-Trials with Sumatriptan Succinate

Typical 5-HT_1 Agonist Adverse Reactions: As with other 5-HT_1 agonists, sumatriptan succinate 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, 3095 patients received at least one dose of sumatriptan succinate. The following table (Table 2) list adverse events occurring in these trials at an incidence of 1% or more in any of the sumatriptan succinate dose groups and that occurred at a higher incidence than in the placebo groups.

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

	Placebo	Sumatriptan Succinate 25 mg	Sumatriptan Succinate 50 mg	Sumatriptan Succinate 100 mg **
Number of Patients	690	351	723	2021
Number of Migraine Attacks Treated	1187	945	1889	14750
Symptoms of Potentially Cardiac Origin				
•Chest Sensations*	0.6%	2.3%	2.6%	3.2%
•Neck/Throat/Jaw Sensations *	1.4%	2.3%	3.5%	5.2%
•Upper Limb Sensations*	1.2%	1.4%	2.5%	3.6%
•Palpitations	0.6%	0.3%	1.0%	1.1%
Neurological				
•Head/Face Sensations*	1.3%	2.3%	2.5%	4.7%
•Dizziness	2.5%	3.1%	3.3%	6.2%
•Headache	3.3%	4.0%	2.2%	3.3%
•Vertigo	0.6%	1.1%	1.1%	1.0%
•Drowsiness	1.6%	1.1%	1.2%	2.1%
•Tremor	0.4%	0.9%	0.4%	1.1%
Gastrointestinal				
•Nausea	5.8%	2.8%	4.4%	11.0%
•Hyposalivation	1.2%	1.4%	1.1%	1.2%
•Vomiting	2.9%	4.3%	1.1%	4.4%
•Gastrointestinal Discomfort and Pain	1.4%	1.1%	0.8%	2.0%
•Abdominal Discomfort and Pain	0.3%	NR	0.4%	1.2%
•Diarrhea	0.9%	0.3%	0.6%	1.1%
Musculoskeletal				
•Musculoskeletal Pain	0.7%	2.3%	0.4%	1.4%
•Muscle Pain	0.3%	0.9%	0.1%	1.0%
•Muscle Atrophy Weakness and Tiredness	NR	0.6%	0.4%	1.4%
Ear, Nose and Throat				
•Infections	0.6%	0.6%	1.1%	1.4%
•Nasal Signs and Symptoms	0.7%	1.4%	0.8%	1.0%
•Throat and Tonsil Symptoms	0.6%	NR	0.4%	2.3%
Respiratory				
•Viral Infection	0.3%	1.1%	0.1%	1.0%
Non-Site Specific				
•Limb Sensations*	0.4%	1.1%	0.4%	1.5%
•Sensations* (body region unspecified)	4.5%	5.7%	8.0%	9.0%
•Malaise/Fatigue	5.1%	3.7%	2.6%	9.5%
•Sweating	0.4%	0.6%	0.6%	1.6%

*The term "sensations" encompasses adverse events described as pain and discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling and strange sensations.
**Includes patients receiving upto 3 doses of 100 mg
NR = Not Reported

Sumatriptan succinate is generally well tolerated. Most of the events were transient in nature and

resolved within 2 hours of oral administration.

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.

Post-Market Adverse Drug 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 ADVERSE REACTIONS section above. Because the reports cite events reported spontaneously from worldwide postmarketing 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, myocardial infarction (see CONTRAINDICATIONS, and WARNINGS and PRECAUTIONS).

Ophthalmologic Disorders: Patients treated with sumatriptan succinate 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: Colonic ischemia (see WARNINGS and PRECAUTIONS, Cardiovascular, Other Vasospasm Related Events).

Immune System Disorders: Hypersensitivity reactions ranging from cutaneous hypersensitivity to rare cases of anaphylaxis (see 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 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 both subcutaneous and oral treatments of sumatriptan succinate. Patients with previous history of drug related dystonia and patients taking medications recognized 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 CONTRAINDICATIONS and WARNINGS and PRECAUTIONS, Increases in Blood Pressure;

Cardiovascular; and Other Vasospasm Related Events).

DRUG INTERACTIONS

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.

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 AVA-SUMATRIPTAN DF administration (see 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 AVA-SUMATRIPTAN DF in patients receiving MAO inhibitors is contraindicated (see CONTRAINDICATIONS, AND ACTION AND CLINICAL PHARMACOLOGY).

Other 5-HT$_1$, agonists: The administration of AVA-SUMATRIPTAN DF 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 co-administration of 5-HT$_1$ agonists, use of these drugs within 24 hours of each other is contraindicated.

Drug-Laboratory Interactions

Sumatriptan succinate is not known to interfere with commonly employed clinical laboratory tests.

DOSAGE AND ADMINISTRATION

Dosing Considerations

AVA-SUMATRIPTAN DF (sumatriptan succinate) are indicated for the acute treatment of migraine headache with or without aura. Sumatriptan should not be used prophylactically. The safety of treating an average of more than four headaches in a 30 day period has not been established.

In addition to relieving the pain of migraine, sumatriptan 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.

Recommended Dose and Dosage Adjustment

The minimal effective single adult dose of AVA-SUMATRIPTAN DF is 25mg. The maximum recommended single dose for AVA-SUMATRIPTAN DF is 100 mg.

The optimal dose is 50mg. However, depending on individual patient's needs and response to treatment, some patients may require 100mg.

AVA-SUMATRIPTAN DF is available in 25 mg, 50 mg and 100 mg tablets strengths.

Clinical trials have shown that approximately 50 - 75% of patients have headache relief within two hours after oral dosing with 100mg, and that a further 15 - 25% have headache relief by 4 hours. Comparator studies have shown similar efficacy rates with the 50mg and 100mg. There is evidence that doses of 50 and 100mg may provide greater effect than 25mg.

If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 2 hours. Not more than 200mg should be taken in any 24 hour period.

If a patient does not respond to the first dose of AVA-SUMATRIPTAN DF Tablets, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. AVA-SUMATRIPTAN DF may be taken to treat subsequent migraine attacks.

The tablet should be swallowed whole with water, not crushed, chewed or split.

Hepatic Impairment

In patients with mild or moderate hepatic impairment, plasma sumatriptan concentrations up to two times those seen in healthy subjects have been observed. Therefore, a 25 mg dose may be considered in these patients (see WARNINGS AND PRECAUTIONS). Sumatriptan should not be administered to patients with severe hepatic impairment (see CONTRAINDICATIONS).

OVERDOSAGE

There have been some reports of overdosage with sumatripan succinate. Doses up to 400 mg orally were not associated with side effects other than those mentioned.

If overdosage with sumatriptan occurs, the patient should be monitored and standard supportive treatment applied as required. Toxicokinetic data are not available.

The effect of haemodialysis or peritoneal dialysis on the serum concentration of sumatriptan is unknown.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Sumatriptan succinate has 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 succinate 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_1receptor 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 shows 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 μg/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. Following oral administration of 200 mg or intranasal administration of 40 mg, however, mean peak increases in blood pressure were smaller and of slower onset than after intravenous or subcutaneous administration.

Pharmacodynamics
Significant relief begins about 30 minutes following oral administration.

Pharmacokinetics
Pharmacokinetic parameters following oral administration are shown in Table 3.
Inter-patient and intra-patient variability was noted in most pharmacokinetic parameters assessed.

Table 4: Summary of Pharmacokinetic Parameters

Parameter	Oral
Bioavailability	14%
Cmax (ng/mL)	100 mg: 50-60 ng/mL 25 mg : 18 ng/mL
Tmax	100 mg: 0.5-5hr*
$T_{½}$	2 hr (1.9-2.2 hr)
Protein Binding	14 – 21 %
Volume of Distribution	170 L
Total Plasma Clearance	1160 mL/min

Parameter	Oral
Renal Plasma Clearance	260 mL/min

* 70% to 80% of Cmax values were attained within 30-45 minutes of dosing

Absorption/ Metabolism
Sumatriptan is rapidly absorbed after oral administration. The low oral bioavailability is primarily due to metabolism (hepatic and presystemic) and partly due to incomplete absorption. The oral absorption of sumatriptan is not significantly affected either during migraine attacks or by food.

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 compared with younger volunteers (less than 65 years old).

STORAGE AND STABILITY

AVA-SUMATRIPTAN DF Tablets should be stored between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AVA-Sumatriptan DF Tablets
AVA-SUMATRIPTAN DF Tablets contain sumatriptan (base) as the succinate salt.
AVA-SUMATRIPTAN DF Tablets also contain colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose and crospovidone.
The film-coating for the 25 mg and 50 mg tablets consists of titanium dioxide, polydextrose, hydroxypropyl methylcellulose, triacetin, polyethylene glycol.
The film-coating for the 100 mg tablet consists of Titanium dioxide, polydextrose, hydroxypropyl methylcellulose, triacetin, polyethylene glycol, synthetic red iron oxide.

AVA-SUMATRIPTAN DF is available as:
25 mg - White, triangular, film-coated tablet, engraved with "N" on one side and "25" on the other side, supplied in bottles of 50 and blister packs of 6 (1 sheet of 6 unit dose tablets), 24 (4 sheets of 6 unit dose tablets) & 100 (10 sheets of 10 unit dose tablets).

50 mg - White, triangular, film-coated tablet, engraved with "N" on one side and "50" on the other side, supplied in bottles of 50 and blister packs of 6 (1 sheet of 6 unit dose tablets), 24 (4 sheets of 6 unit dose tablets) & 100 (10 sheets of 10 unit dose tablets).

100 mg - Pink, triangular, film-coated tablet, engraved with "N N" on one side and "100" on the other side, supplied in bottles of 50 and blister packs of 6 (1 sheet of 6 unit dose tablets), 24 (4 sheets of 6 unit dose tablets) & 100 (10 sheets of 10 unit dose tablets).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

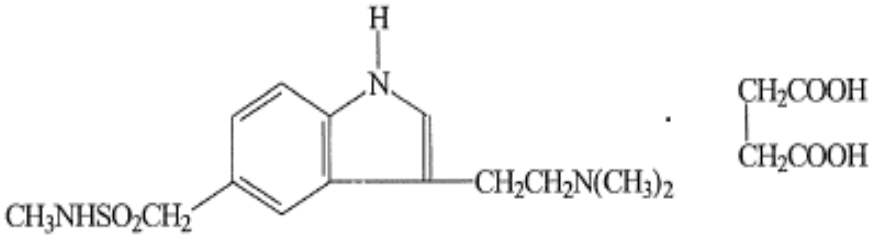
Proper name: sumatriptan succinate (USAN, BAN and INN)

Chemical name: 3-[2-(Dimethyl amino)ethyl]-N-methyl-1H-indole-5-methane sulfonamide, butane-1,4-dioate (1:1)

Molecular formula: $C_{14}H_{21}N_3O_2S.\ C_4H_6O_4$

Molecular mass: 413.5

Structural formula:



Physicochemical properties: White to off-white powder with a melting point between 164.6°C-165.5°C. The solubility in water at 4°C and 20°C are 54 mg/mL and 101 mg/mL respectively. In saline, the solubility for 0.9% w/v at 4°C and for 0.9% w/v at 20°C are 62 mg/mL and 109 mg/mL respectively. The pH of a 1% w/v solution of sumatriptan succinate in water is approximately 4.9.

pka_1 (succinic acid) = 4.21, 5.67
pka_2 (3° amine group) = 9.63
pka_3 (sulphonamide) = >12

The partition coefficient between n-octanol and water is as follows:
log P= 1.07 at a pH of 10.7

CLINICAL TRIALS

Comparative Bioavailability Studies

AVA-Sumatriptan DF Tablets

A randomized, two-way crossover, single-dose bioavailability study was performed on AVA-SUMATRIPTAN DF 100 mg tablets and Imitrex™ DF 100 mg tablets in (32) healthy male and female subjects, aged 18 to 40 years of age, under fasting conditions.

Sumatriptan (1 x 100 mg sumatriptan tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	AVA-Sumatriptan DF * (1 X 100 mg)	Imitrex™ DF † (1 X 100 mg)	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng*h/mL)	237.27 250.67 (38)	244.10 261.79 (41)	97.21	92.98 - 101.63
AUC_I (ng*h/mL)	247.55 261.23 (38)	254.67 272.58 (41)	97.20	93.15 - 101.43
C_{max} (ng/mL)	50.09 53.70 (41)	54.66 59.70 (43)	91.63	83.57 - 100.46
$AUC_{RefTmax}$ (ng*h/mL)	37.36 52.97 (75)	44.75 56.82 (63)	83.48	75.64-92.13
T_{max} § (h)	2.05 (62)	1.76 (61)		
$T_{½}$ § (h)	2.36 (21)	2.37 (25)		

* AVA-Sumatriptan DF 100 mg Tablets (Avanstra Inc., Canada)
† Imitrex™ DF 100 mg Tablets (GlaxoSmithKline Inc., Canada) Purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only

Clinical Studies:

Migraine:

The efficacy of sumatriptan succinate tablets for the treatment of migraine was established in four multicentre, randomized, placebo-controlled studies. Patients enrolled and treated in these studies were primarily female (84%), Caucasian (98%) and with a mean age of 40 years (range of 18 to 65 years). Patients were instructed to treat a moderate to severe headache. In Study 2, up to three doses were permitted to treat a single attack within a 24 hour period, non-responders could take a second dose at two hours, while any recurrence of migraine could be treated with a third dose. Study 1, 3 and 4 were designed to allow for the treatment of up to three attacks.

Headache relief at two hours was statistically significantly greater for all sumatriptan groups when compared to placebo (see Table 5).

Table 5: Percentage of Patients with Headache Relief (0/1)[1] at 2 hours Post Oral Dose for the Treatment of Migraine

Study	Placebo (%)	25 mg (%)	50 mg (%)	100 mg (%)
Study 1	27 (n=212)	-	-	67 * (n=313)
Study 2	19 (n=84)	-	-	50%* (n=149)
Study 3	23 (n=154)	-	49 (n=331)	-
Study 4	28 (n=98)	47** (n=303)	61* (n=302)	61* (n=298)

[1] Headache relief is defined as a reduction in headache severity from grade 3 or 2 (severe or moderate) to grade 1 to 0 (mild or no pain)

- \- = not evaluated
- * p<0.001 vs placebo
- ** p = 0.001 vs placebo

In Study 4, the 50mg (p=0.002) and 100mg (p=0.003) groups had significantly more patients experience headache relief compared to the 25mg group at 2 hours.

For patients with migraine-associated nausea, photophobia, phonophobia at baseline, there was a decrease incidence of these symptoms following administration of sumatriptan succinate tablets compared to placebo.

Menstrually-Associated Migraine*:*

Two multicentre, randomized, placebo-controlled studies evaluated sumatriptan succinate 50mg and 100 mg tablets administered during the mild phase of a menstrually-associated migraine attack. A total of 816 subjects with a mean age of 37 (18-65 years of age), with at least a 1-year history of migraine, and a 6-month history of regularly occurring MAM, were enrolled and treated. MAM was defined as any migraine beginning on Day -2, to + 4 with day 1 = the first day of flow. Patients were instructed to treat a single, mild, moderate or severe headache within one hour of mild pain onset.

A statistically significantly higher proportion of patients following sumatriptan succinate 50 mg and 100 mg achieved pain-free status at 2 hours post-dose compared with placebo in the treatment of menstrually-associated migraine (see Table 6).

Table 6: Percentage of Patients with Complete Headache Pain Relief [1] at 2 hours Post Oral Dose for the treatment of Menstrually-associated Migraine

Study	Placebo (%)	50 mg (%)	100 mg (%)
Study 1	22 (n=132)	51* (n=138)	58* (n=133)
Study 2	29 (n=118)	51* (n=116)	61* (n=115)
[1] Complete Headache Pain Relief is defined as grade 1 (mild pain) reduced to grade 0 (no pain) *p<0.001 vs placebo			

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

DETAILED PHARMACOLOGY

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}[3] 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_{lC}, 5-HT_2, 5-HT_3, $alpha_1$, $alpha_2$, $beta_1$,dopamine D_1 and D_2, muscarinic

3 molar concentrations required to product 50% of the maximum response.

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 oedematous 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 μg/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 μg/kg, iv. Maximal vasoconstrictor responses were achieved with intravenous doses between 300-1000 μg/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 μg/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 μg/kg iv, sumatriptan had little effect upon vascular resistance in a variety of other vascular beds. In contrast, the administration of ergotamine (30 μg/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 μg/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 oesophageal 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.

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 (1mg/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 foetuses 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 faeces.

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 μg/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.

TOXICOLOGY

Acute Toxicity

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 7).

Table 7: Results from acute toxicity (LD_{50}) 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	>2000	≥2000	>2000
Rat: SD	Oral	>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

Key: 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, vocalisation, 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 study 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 oedema, marked haemorrhage, 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 haematalogical 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 haemoglobin 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 haemolymphoreticular 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 phaeochromocytomas) 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.

Mutagenicity

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 metabolising enzyme system. In addition, no statistically significant clastogenic effects were seen *in vitro* using cultured human peripheral lymphocytes at a maximum dose of 1000 μg/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 μg/mL tested *in vitro* with V-79 mammalian cells.

Reproduction and Teratology

In organogenesis studies, oral doses of up to 500 mg/kg/day in the rat were without adverse effects upon foetal 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 foetuses (3 out of 10 litters affected). At the maternally toxic dose of 100 mg/kg, 23.1% of foetuses 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 bodyweight gain. There were also various foetal effects ascribed to maternal toxicity. There was a slight reduction in mean foetal 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 l2.8%, 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 foetus 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 foetuses 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 post-natal 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 post-natal development of their offspring was seen. However, oral administration of 1000 mg/kg/day during periods of pregnancy and lactation resulted in a decrease in maternal and foetal bodyweight.

A comprehensive evaluation of the effects of sumatriptan on reproduction indicate 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 foetuses, 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.

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 was 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 behavioral changes observed upon withdrawal of sumatriptan were limited in their number, sporadic, unsustained and were 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.

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PART III: CONSUMER INFORMATION

Pr AVA-SUMATRIPTAN DF
(sumatriptan succinate tablets)

This leaflet is part III of a three-part "Product Monograph" published when AVA-SUMATRIPTAN DF were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AVA-SUMATRIPTAN DF. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this leaflet carefully before you take AVA-SUMATRIPTAN DF Tablets. This provides a summary of the information available on your medicine. Please do not throw away this leaflet until you have finished your medicine. You may need to read it again.

ABOUT THIS MEDICATION

The name of your medicine is AVA-SUMATRIPTAN DF (sumatriptan succinate) Tablets. They can be obtained only by prescription from your doctor, The decision to use AVA-SUMATRIPTAN DF Tablets is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances. If you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40), you should tell your doctor, who should evaluate you for heart disease in order to determine if AVA-SUMATRIPTAN DF Tablets are appropriate for you.

What the medication is used for:
AVA-SUMATRIPTAN DF Tablets are intended to relieve your migraine headache and other associated symptoms of a migraine attack. **AVA-SUMATRIPTAN DF Tablets should not be used continuously to prevent or reduce the number of attacks you experience. Use AVA-SUMATRIPTAN DF Tablets only to treat an actual migraine headache attack.**

What it does:
Migraine headache is believed to be caused by a widening of the blood vessels in the head. AVA-SUMATRIPTAN DF narrows these vessels and relieves the symptoms of migraine headache.

When it should not be used:
Do not use AVA-SUMATRIPTAN DF if:

- **you are allergic to sumatriptan succinate or any of the non-medicinal ingredients in the product (See What the nonmedicinal ingredients are, below).**
- **you have a history, or any symptoms or signs of a heart condition**
- **you have high blood pressure**
- **you are taking or have recently taken (within 2 weeks) a monoamine oxidase inhibitor (MAOI)**
- **you are taking or have recently taken (within 24 hours) an ergotamine-containing medication or its derivatives, or another triptan used to treat migraine**
- **you have severe liver disease**

AVA-SUMATRIPTAN DF Tablets should not be used for the treatment of other types of headaches that are different from migraine attacks.

What the medicinal ingredient is:
Sumatriptan succinate

What the nonmedicinal ingredients are:
AVA-Sumatriptan DF: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose and crospovidone
The film-coating for the 25 mg and 50 mg tablets consists of titanium dioxide, polydextrose, hydroxypropyl methylcellulose, triacetin, polyethylene glycol.
The film-coating for the 100 mg tablet consists of titanium dioxide, polydextrose, hydroxypropyl methylcellulose, triacetin, polyethylene glycol, synthetic red iron oxide.

What dosage forms it comes in:
AVA-SUMATRIPTAN DF is available as pink 100 mg, white 50 mg, or white 25 mg film-coated tablets in bottles of 50 and blister packs of 6, 24 & 100 Tablets.

WARNINGS AND PRECAUTIONS

BEFORE you use AVA-SUMATRIPTAN DF talk to your doctor or pharmacist if :

- you are pregnant, think you might be pregnant, are trying to become pregnant, are using inadequate contraception or are breast-feeding.
- **you have any chest pain, heart disease, shortness of breath, or irregular heartbeats, you have had a heart attack, or you have angina.**
- **you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or are postmenopausal or a male over 40).**
- you have ever had to stop taking this or any other medication because of an allergy or other problems or you are allergic to sulpha-containing drugs.
- you are taking any medications, including migraine medications such as other 5-HT[1] agonists or those containing ergotamine, dihydroergotamine, or methysergide.
- you have ever experienced difficulty moving one side of your body when you have a headache.
- you have ever had a stroke, transient ischemic attacks (TIAs), or Raynaud Syndrome.
- you are under 18 years of age
- you are over 65 years of age.
- you are taking any medication for depression (lithium, monoamine oxidase inhibitors or selective serotonin reuptake inhibitors (SSRIs)
- you had, or you have any disease of the liver or kidney.

- you had, or have epilepsy or seizures.
- this headache is different from your usual migraine attacks.

AVA-SUMATRIPTAN DF Tablets should not be used continuously to prevent or reduce the number of attacks you experience. Use AVA-SUMATRIPTAN DF Tablets only to treat an actual migraine headache attack.

The Use of AVA-SUMATRIPTAN DF During Pregnancy
Do not use AVA-SUMATRIPTAN DF Tablets if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.

INTERACTIONS WITH THIS MEDICATION

Do not use AVA-SUMATRIPTAN DF Tablets if you are taking or have recently taken a monoamine oxidase inhibitors (MAOI) in the last 2 weeks, or any migraine medications containing ergotamine, ergot derivatives (such as dihydroergotamine, or methysergide), or other triptans used to treat migraine within 24 hours.

You should tell your doctor if you are taking or have recently taken any other medications (prescription, non prescription or natural/herbal), before you start taking AVA-SUMATRIPTAN DF Tablets, especially any anti depressants such as selective serotonin reuptake inhibitors (SSRIs) and certain tricyclics.

PROPER USE OF THIS MEDICATION

The label on the container of your medicine or the leaflet inside should tell you how often to take a dose and the amount you should take in each dose. If it does not or you are not sure, ask your doctor or pharmacist. DO NOT take more medicine or take your medicine more often than you are told.

Usual dose:

Adults: Take as directed by your doctor. If the first tablet does not relieve your headache, do not take further doses of sumatriptan for the same attack. Another tablet should not be taken for two hours after the first dose. You may take pain medication other than ergotamine-containing preparations for further pain relief. AVA-SUMATRIPTAN DF Tablets may be taken for subsequent attacks.

AVA-SUMATRIPTAN DF Tablets can be taken at any time during your migraine headache.

If your symptoms come back, and it has been two hours since your first tablet, you may take a second tablet.

Do not take more than 200 mg in any 24 hour period.

AVA-SUMATRIPTAN DF Tablets may be taken with or without food. The tablet should be swallowed whole with water. It should not be crushed, chewed or split.

Overdose:
If you have taken more medication than you have been told, contact either your doctor, hospital emergency department, or nearest poison control center immediately .

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, AVA-SUMATRIPTAN DF Tablets can cause some side effects. You may not experience any of them. For most patients these side effects are likely to be minor and temporary. However, some may be serious. Consult your doctor if you experience these or other side effects.

The most commonly reported side effects of AVA-SUMATRIPTAN DF Tablets are:

- pain, pressure tightness in any part of the body, including chest and throat
- sensations of heaviness
- sensations of heat/burning
- flushing (redness of the face lasting for a short time)
- feeling sick or vomiting
- dizziness
- drowsiness
- tiredness
- weakness

As drowsiness may occur as a result of using AVA-SUMATRIPTAN DF Tablets, do not drive or operate machinery until you are sure that you are not drowsy.

Other side effects include:
• unusually slow or fast heartbeats, a feeling of irregular and/or forceful heartbeats
• visual disturbances, usually temporary (scotoma, nystagmus, flickering, diplopia).
• dystonia, (shaking, tremors or uncontrolled movements)
• loss of normal colouration in the fingers and toes.

Tell your doctor of these symptoms at your next visit. Very rarely, some people have reported the following more serious side effects, For information on what to do if you experience these side effects, see the table at the end of this section.

• pain or tightness in the chest or throat
• loss of vision
• shortness of breath; wheeziness; chest tightening; swelling of eyelids, face, or lips; or a skin rash, skin lumps
• a seizure or fit
• sudden and/or severe abdominal pain
• persistent purple discolouration of hands or feet

If you feel unwell in any other way or have any symptoms that you do not understand or find distressing, you should contact your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptoms/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Pain or sensation of tingling, heat, or pressure in any part of the body	√		
Very rare	Symptoms of a heart attack [chest pain, sweating, shortness of breath]			√
Very rare	Unusually slow or fast heartbeats, or a feeling of irregular and/or forceful heartbeats	√		
Very rare	Seizures [loss of consciousness with uncontrollable shaking("fit")]			√
Very rare	Lower abdominal pain and/or severe rectal bleeding.			√
Very rare	Raynaud's phenomenon [persistent purple discolouration of hands or feet]			√
Very rare	Loss of vision		√	√
Very rare	Allergic reactions [shortness of breath, sudden wheeziness, chest tightness, swelling of the eyelids, face or lips, lumpy skin rash or hives]			√

This is not a complete list of side effects. For any unexpected effects while taking AVA-SUMATRIPTAN DF, contact your doctor or pharmacist.

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. It may be harmful to children.

Keep your tablets in a cool, dry place (15°C to 30°C).

If your medication has expired (the expiration date is printed on the treatment pack), throw it away as instructed.

If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

Reminder:
REMEMBER: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms appear to be similar to yours.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Avanstra Inc. at:
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