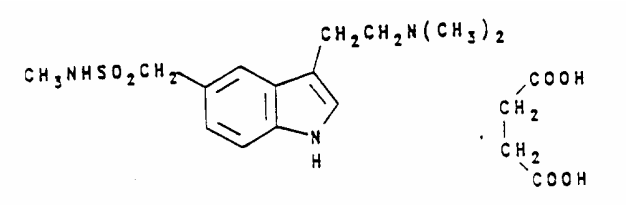
IMIGRAN® TABLETS, INJECTION AND NASAL SPRAY

NAME OF THE MEDICINE:

Sumatriptan is the therapeutically active ingredient in Imigran nasal spray and sumatriptan succinate is the therapeutically active ingredient in Imigran tablets and injection.



sumatriptan succinate

DESCRIPTION:

The chemical name of sumatriptan is 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulphonamide. The molecular formula of sumatriptan is $C_{14}H_{21}N_3O_2S$, the relative molecular mass is 295.4. It takes the form of a white to pale yellow powder. Chemically, sumatriptan succinate is: 3-[2-(dimethylamino) ethyl]-N-methyl-1H-indole-5-methane sulphonamide, butane-1,4-dioate (1:1). The molecular formula of sumatriptan succinate is $C_{14}H_{21}N_3O_2SC_4H_6O_4$, the relative molecular mass is 413.5. It takes the form of a white to off-white powder. CAS Registry number is 103628-48-4.

PHARMACOLOGY:

Pharmacology:
Sumatriptan has been demonstrated to be a specific vascular 5-hydroxytryptamine-1 ($5HT_1$) receptor agonist with no effect at other 5HT receptor ($5HT_2$-$5HT_7$) subtypes. The vascular $5HT_1$ receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals, sumatriptan selectively constricts the carotid arterial circulation, but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges, and dilatation and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man. In addition, experimental evidence suggests that sumatriptan inhibits trigeminal nerve activity. Both these actions may contribute to the anti-migraine action of sumatriptan in humans.

Pharmacokinetics:
Following subcutaneous injection, sumatriptan has a high mean bioavailability (96%) with peak serum concentrations occurring in 25 minutes. Average peak serum concentration after a 6 mg subcutaneous dose is 72 ng/mL. The elimination phase half-life is approximately 2 hours. After oral administration, sumatriptan is rapidly absorbed, 70% of maximum concentration occurring at 45 minutes. After a 100 mg dose the mean

maximum plasma concentration is 54 ng/mL. Mean absolute oral bioavailability is 14% partly due to pre-systemic metabolism and partly due to incomplete absorption. Oral absorption of sumatriptan is not significantly affected by food.

Imigran FDT tablets and Imigran tablets have been established to be bioequivalent in the fasted state. In the fasted state, sumatriptan t_{max} was, on average, 10-15 minutes earlier for Imigran FDT relative to Imigran tablets. Imigran FDT after a high fat meal resulted in an average 12% increase in $AUC_{(0-\infty)}$ and 15% increase in C_{max} relative to Imigran FDT in the fasted state. $AUC_{(0-2)}$ was estimated to be an average of only 5% lower and t_{max} delayed by only 6.5 minutes for Imigran FDT in the fed, relative to the fasted state. These variations are not considered to be of clinical significance.

After intranasal administration, sumatriptan is rapidly absorbed, maximum plasma concentration occurring in 1-1.5 hours. After a 20 mg dose, the mean maximum concentration is 12.9 ng/mL. Mean intranasal bioavailability, relative to subcutaneous administration is 15.8%, partly due to pre-systemic metabolism. Plasma protein binding is low (14-21%), mean volume of distribution is 170 litres. Mean total plasma clearance is approximately 1160 mL/min and the mean renal plasma clearance is approximately 260 mL/min.

A pharmacokinetic study in adolescent subjects (12-17 years) indicated that the mean maximum plasma concentration was 13.9 ng/ml and mean elimination half-life was approximately 2 hours following a 20 mg intranasal dose. Population pharmacokinetic modelling indicated that clearance and volume of distribution both increase with body size in the adolescent population resulting in higher exposure in lower bodyweight adolescents. The model predicted that a subject with a body weight of 40 kg would have an apparent clearance of 222 L/h and a volume of distribution of 850 L whilst the corresponding figures for a body weight of 66 kg would be 366 L/h and 1204 L. The predicted dependence of these parameters on body size should not pose any significant safety concern as the recommended initial dose range is 10-20 mg.

Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A. The major metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in the urine, where it is present as a free acid and the glucuronide conjugate. It has no known $5HT_1$ or $5HT_2$ activity. Minor metabolites have not been identified. The pharmacokinetics of oral or intranasal sumatriptan do not appear to be significantly affected by migraine attacks.

In a pilot study no significant differences were found in the pharmacokinetic parameters between elderly and young healthy volunteers.

CLINICAL TRIALS:

Clinical Studies Conducted In The Adult Population

Table 1 shows 1 and 2 hour efficacy results for two placebo-controlled trials of sumatriptan injection in 1,104 adult migraineurs with moderate or severe migraine pain.

Table 1: Efficacy Data for Phase III Placebo-controlled Trials of Sumatriptan Injection‡

Results at 1 hour	Study 1		Study 2	
	Placebo (n=190)	Sumatriptan 6 mg (n=384)	Placebo (n=180)	Sumatriptan 6 mg (n=350)
Patients with pain relief^	18%	70%*	26%	70%*
Patients with no pain	5%	48%*	13%	49%*
Patients without nausea	48%	73%*	50%	73%*
Patients without photophobia	23%	56%*	25%	58%*
Patients with little or no clinical disability	34%	76%*	34%	76%*
Results at 2 hours	Study 1		Study 2	
	Placebo+	Imigran 6 mg++	Placebo+	Imigran 6 mg++
Patients with pain relief^	31%	81%*	39%	82%*
Patients with no pain	11%	63%*	19%	65%*
Patients without nausea	56%	82%*	63%	81%*
Patients without photophobia	31%	72%*	35%	71%*
Patients with little or no clinical disability	42%	85%*	49%	84%*

^ Pain relief defined as a reduction in headache severity from moderate or severe pain to mild or no pain.

\+ Includes patients that may have received 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.

* P<0.05 versus placebo.

‡ Patients were administered the study drug according to the recommended dosing regimen (see **DOSAGE AND ADMINISTRATION**).

The following table demonstrates 2 and 4 hour efficacy results in two placebo-controlled studies of sumatriptan tablets in 332 adult migraineurs experiencing moderate or severe pain.

Table 2: Efficacy Data for Placebo-controlled Studies of Sumatriptan tablets‡

	Study 1			Study 2		
	Placebo (n=65)	Sumatriptan 50 mg (n=62)	Sumatriptan 100 mg (n=68)	Placebo (n=47)	Sumatriptan 50 mg (n=46)	Sumatriptan 100 mg (n=46)
Results at 2 hours						
Patients with pain relief^	26%	50%*	56%*	17%	54%*	57%*
Patients with no pain	8%	16%	23%*	6%	17%	24%*
Patients with meaningful relief#	34%	55%*	56%*	21%	54%*	57%*
Patients without nausea	57%	68%	65%	40%	61%	72%*
Patients without photophobia	22%	37%*	44%*	13%	26%	39%*
Patients with little or no clinical disability##	35%	60%*	59%*	28%	52%*	67%*
Results at 4 hours						
Patients with pain relief^	38%	68%*	71%*	19%	72%*	78%*
Patients with no pain	15%	32%*	52%*	11%	41%*	41%*
Patients with meaningful relief#	45%	71%*	79%*	26%	72%*	83%*
Patients without nausea	60%	79%*	83%*	45%	70%*	91%*
Patients without photophobia	40%	66%*	71%*	28%	65%*	65%*
Patients with little or no clinical disability##	40%	71%*	71%*	23%	70%*	83%*

^ Pain relief defined as a reduction in headache severity from moderate or severe pain to mild or no pain.

Meaningful relief is a patient assessment of when he/she felt onset of relief of headache pain.

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

* P<0.05 versus placebo.

‡ Patients were administered either the 50 mg or 100 mg tablet according to the recommended dosing regimen (see **DOSAGE AND ADMINISTRATION**). The dose of the tablet was not titrated.

Table 3 shows primary efficacy results at 2 hours for 5 placebo-controlled trials of sumatriptan nasal spray in 2547 adult migraineurs experiencing moderate or severe pain.

Table 3: Efficacy Data (Pain Relief^) at 2 Hours for Placebo-controlled studies of Sumatriptan Nasal Spray‡

	Placebo	Sumatriptan Nasal Spray 10 mg	Sumatriptan Nasal Spray 20 mg
Study 1	25% (n=63)	46%* (n=112)	64%*+ (n=118)
Study 2	25% (n=138)	44%* (n=273)	55%*+ (n=227)
Study 3	35% (n=100)	54%* (n=106)	63%* (n=202)
Study 4	29% (n=112)	43% (n=106)	62%*+ (n=215)
Study 5#	36% (n=198)	53%* (n=291)	60%* (n=286)

^ Pain relief defined as a reduction in headache severity from moderate or severe pain to mild or no pain.

Data is for attack 1 only of multiattack study.

* $P<0.05$ versus placebo; + $P<0.05$ versus 10 mg nasal spray.

‡ Patients were administered either the 10 mg or 20 mg nasal spray according to the recommended dosing regimen (see **DOSAGE AND ADMINISTRATION**). The dose of the nasal spray was not titrated.

Patients who had a history of migraine, with or without aura, and experienced between one and six attacks per month of severe/moderately severe migraine during the previous 12 months were entered in the nasal spray studies. The following categories were not selected for the clinical studies: age <18 years or >65 years, history of non-migraine headaches (ie. tension type headache), cardiovascular disease (ie. ischaemic heart disease, coronary vasospasm, atherosclerotic disease, diastolic blood pressure >95mmHg and systolic blood pressure >160 mmHg), pregnancy and breast feeding, females unless adequate contraception was employed, concurrent medication (ergotamine or dihydroergotamine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, or lithium), history of substance abuse (alcohol, opiates or ergotamine), hypersensitivity or prior exposure to sumatriptan nasal spray or intranasal dihydroergotamine.

Specific studies involving asthmatic patients have not been conducted, however a few asthmatic patients were included in the clinical trials.

Clinical Studies Conducted In The Adolescent Population

Table 4 shows 60 and 120 minute efficacy results for sumatriptan nasal spray 10 mg and 20 mg in a placebo-controlled study in adolescent migraineurs experiencing moderate or severe migraine pain.

Table 4: Efficacy Data for Placebo-controlled Studies of Sumatriptan nasal spray‡

(Intent-to-Treat Population)

	Placebo (n=130)	Sumatriptan 10 mg (n=133)	Sumatriptan 20 mg (n=117)
Results at 60 minutes			
Patients with headache relief ^	41%	56%*	56%*
Patients headache-free	9%	13%	14%
Results at 120 minutes			
Patients with headache relief ^	53%	64%	63%**
Patients headache-free	25%	33%	36%***

^ Headache relief defined as a reduction in headache severity from severe or moderate pain to mild or no pain.
* P<0.05 versus placebo.
** P = 0.059 versus placebo.
*** P = 0.037 versus placebo.
‡ Patients were administered either the 10 mg or 20 mg nasal spray according to the recommended dosing regimen (see DOSAGE AND ADMINISTRATION).

Both Sumatriptan nasal spray 10 mg and 20 mg were statistically superior to placebo at 60 minutes for headache relief, but 20 mg has the best overall efficacy profile for the acute treatment of migraine in adolescents compared with placebo.

Sumatriptan nasal spray 20 mg was shown to be associated with a number of secondary benefits, including headache free rates; and relieving migraine associated symptoms of photophobia at 120 minutes (p=0.025) and phonophobia at 30, 60 and 120 minutes (p=0.032, 0.023 and 0.001 respectively). No statistically significant differences were found with nausea or vomiting.

INDICATIONS:

Imigran tablets, injection and nasal spray are indicated for the acute relief of migraine attacks with or without aura.

Imigran injection is also indicated for the acute treatment of cluster headaches.

There is no information available on the use of Imigran in the treatment of basilar or hemiplegic migraine.

CONTRAINDICATIONS:

Imigran should not be used in patients who have:

- Hypersensitivity to any component of the preparation (see **PRESENTATIONS**).
- A history of myocardial infarction

- Peripheral vascular disease or symptoms or signs consistent with ischaemic heart disease.
- Prinzmetal's angina/coronary vasospasm.
- Uncontrolled hypertension.
- Cerebrovascular accident or transient ischaemic attack.
- Severe hepatic impairment.

Imigran should not be used within 24 hours of treatment with an ergotamine-containing or ergot-type medication such as dihydroergotamine or methysergide.

Imigran should not be given to patients receiving monoamine oxidase inhibitors (MAOIs) or within two weeks of discontinuation of MAOI therapy.

Imigran should not be administered to patients with hemiplegic, basilar or ophthalmoplegic migraine.

PRECAUTIONS:

General:

Imigran should only be used where there is a clear diagnosis of migraine. However, 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. The recommended doses of Imigran should not be exceeded.

Drowsiness may occur as a result of migraine or its treatment with Imigran. Caution is recommended in patients performing skilled tasks, eg. driving or operating machinery.

Imigran should also be administered with caution to patients with diseases which may affect significantly the metabolism, absorption and excretion of the drug, such as impaired hepatic or renal function. Studies have shown reduced sumatriptan clearance in patients with hepatic impairment. Lower doses should be considered in these patients. If appropriate, the first dose should be given under supervision to these patients.

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of Imigran. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Evidence of cross sensitivity is limited, however, caution should be exercised before using sumatriptan in these patients.

It is theoretically possible that asthmatic patients may react to nasal spray formulations; It is recommended that the physicians consider the benefit/risk ratio of using this formulation in this group of patients.

Physicians should alert patients with a history of latex or rubber allergy that the unit dose vial within the nasal spray device is sealed with a rubber stopper.

Patients should be advised to pay strict attention to the instruction leaflet for sumatriptan injection, especially regarding the safe disposal of needles and syringes. Needles and syringes may be hazardous and should be disposed of safely and hygienically.

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

Co-administration of Sumatriptan within 24 hours of other 5-HT1 agonists is not recommended due to the potential for vasocontrictive effects.

Cardiovascular:

It is strongly recommended that sumatriptan not be given to patients in whom risk factors indicate a possibility of unrecognised coronary artery disease (CAD) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischaemic myocardial disease or other significant underlying cardiovascular disease. The risk factors include hypertension, hypercholesterolaemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best and, in extremely rare cases (less than 1 in 10,000), serious cardiac events have occurred in patients without underlying cardiovascular disease. If during the cardiovascular evaluation, the patient's medical history of electrocardiographic investigations reveal findings indicative of, or consistent with coronary artery vasospasm or myocardial ischaemia, sumatriptan should not be administered (see **CONTRAINDICATIONS**).

Imigran may cause short lived elevation of blood pressure and peripheral vascular resistance. Sumatriptan should therefore be administered with caution to patients with controlled hypertension. Transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

Serious cardiac events, including some that have been fatal, have occurred within a few hours following the use of Imigran Injection or Tablets. These events are extremely rare (less than 1 in 10,000) and the majority of these case reports were confounded by patients having pre-existing heart disease or risk factors for ischaemic heart disease and may reflect underlying disease and spontaneous events. Under these circumstances the specific contribution of Imigran cannot be determined. Events reported have included coronary artery vasospasm, transient myocardial ischaemia, myocardial infarction, and cardiac arrhythmias including ventricular tachycardia and ventricular fibrillation. Therefore Imigran should not be given to patients in whom unrecognised cardiac disease is likely without a prior evaluation for underlying cardiovascular disease. Such patients include postmenopausal women, males over 40 and patients with risk factors for coronary artery disease. Significant cardiovascular sequelae have been reported in patients in whom risk factors were not readily identifiable. There is no experience in patients with recent cardiac arrhythmias (especially tachycardias). Until further information is available, the use of Imigran is not recommended in these patients.

A myocardial infarct has been reported in a 14 year old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration.

When given intravenously Imigran can cause angina in susceptible patients. Imigran injection should therefore not be given intravenously.

Following administration, Imigran can be associated with transient symptoms, including chest pain and tightness, which may be intense and involve the throat. If symptoms consistent with ischaemic heart disease occur, appropriate investigations should be carried out and further doses should not be given until the results of these investigations are known. Patients should be advised to contact their doctor immediately if they experience symptoms consistent with ischaemic heart disease (see **CONTRAINDICATIONS**).

Cerebrovascular:

Cerebral haemorrhage, subarachnoid haemorrhage, 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. Sumatriptan should not be administered if the headache being experienced is atypical of the patient. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (eg. cerebrovascular accident, transient ischaemia attack).

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

Imigran should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold.

There is no experience in patients with recent cerebrovascular accidents. Until further information is available, the use of Imigran is not recommended in these patients (see **CONTRAINDICATIONS**).

There is no information available on the use of Imigran in the treatment of ophthalmoplegic migraine.

Other Vasospastic Events:

Sumatriptan may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischaemia and colonic ischaemia with abdominal pain and bloody diarrhoea have been reported.

Interactions With Other Medicines:

Pharmacodynamic
Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, concomitant use of ergotamine or ergotamine derivatives and Imigran should be avoided. Twenty-four hours should elapse before Imigran is taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations should not be taken until 6 hours have elapsed following Imigran administration (see **CONTRAINDICATIONS**).

Pharmacokinetic
An interaction may occur between sumatriptan and MAOIs and concomitant administration is contraindicated (see **CONTRAINDICATIONS**). Rarely an interaction may occur between sumatriptan and selective serotonin reuptake inhibitors. There have been rare postmarketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability, neuromuscular abnormalities, weakness, hyper-reflexia and incoordination) following the use of a SSRI. Seretonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline reuptake inhibitors (SNRIs).

If concomitant treatment with sumatriptan and an SSRI/SRNI is clinically warranted, appropriate observation of the patient is advised.

The concomitant administration of any triptan/5-HT_1 agonist with sumatriptan is not recommended.

There is no evidence of interactions with propranolol, flunarizine, pizotifen or alcohol.

Although there is no clear evidence, it is possible that an interaction may occur between serotonin 5-HT_1 agonists and the herbal remedy St John's Wort (hypericum perforatum), which may result in an increase in side effects.

Ophthalmic:

Intermittent transient changes on the surface of the cornea have been observed in toxicology studies in dogs. No causative mechanism has been established for these changes but there is no evidence to suggest that this is relevant to clinical exposure.

In studies carried out to test for local and ocular irritancy, following administration of sumatriptan nasal spray, there was no irritancy seen in laboratory animals and no ocular irritancy observed when the spray was applied directly to the eyes of rabbits.

Use in Pregnancy: Pregnancy Category B3.

No obvious teratogenic effects have been seen in rats given oral doses of 500 mg/kg and intravenous doses up to 12.5 mg/kg or in rabbits given oral doses up to 100 mg/kg and intravenous doses up to 8 mg/kg during organogenesis (although it is noted that the number of pregnant rabbits investigated was limited).

Reproduction studies in rats have not revealed any clear evidence of impaired fertility (oral doses up to 500 mg/kg, subcutaneous doses up to 60 mg/kg, given before and during mating) or of impaired post-natal pup development (oral doses up to 1000 mg/kg, subcutaneous doses up to 81 mg/kg, given during the peri and post-natal period). In the rabbit embryotoxicity cannot be ruled out. After oral administration, at doses of 5, 25 and 100 mg/kg on days 8-20 of gestation (severe maternal toxicity at 100 mg/kg) there was evidence of a small, increasing dose-related trend in post-implantation intrauterine death with a similar, and significant trend being recorded after intravenous treatment (0.5 to 8 mg/kg, days 8-20 of gestation).

Term foetuses from Dutch Stride rabbits treated during the period of organogenesis with oral sumatriptan exhibited an increased incidence of cervicothoracic vascular defects and skeletal abnormalities.

Administration of this drug should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Use in Lactation:

Sumatriptan is excreted in breast milk in animals. In rats given oral sumatriptan at 1000 mg/kg during the lactation period, 3 dams out of 20 showed total litter loss whilst in another litter, only 9/15 survived to the end of nursing. It has been demonstrated that following subcutaneous administration sumatriptan is excreted into breast milk. Infant exposure can be minimised by avoiding breastfeeding for 24 hours after treatment. Caution should be exercised when considering the administration of sumatriptan to a breast feeding woman.

Special populations:

Adolescents (12-17 years) and Children (under 12 years)
The efficacy of oral sumatriptan has not been established in placebo-controlled trials carried out in 794 adolescent migraineurs. High placebo responses were found in these studies and there was a lack of statistically significant difference between placebo and oral doses ranging from 25 to 100 mg. The safety profile of oral and intranasal sumatriptan is similar to that of adults. The safety and effectiveness of sumatriptan in children under the age of 12 years has not been established.

Patients Over 65 Years
Experience of the use of Imigran in patients aged over 65 is limited. However the pharmacokinetics do not differ significantly from a younger population. Until further clinical data are available, the use of Imigran in patients aged over 65 is not recommended.

ADVERSE EFFECTS:

The most common side effect associated with treatment with Imigran administered subcutaneously is:

- transient pain at the site of injection.
- stinging/burning, swelling, erythema, bruising and bleeding at the injection site have also been reported.

The most common side effects associated with treatment with Imigran are:-

- Pain, sensations of tingling, heat or cold, heaviness, pressure or tightness. These are usually transient and may be intense and can affect any part of the body including the chest and throat.
- Flushing, dizziness and feelings of weakness. These are mostly mild to moderate in intensity and transient.
- Fatigue, drowsiness, sensory disturbance including paraesthesia and hypoaesthesia have been reported.

- Nausea and vomiting occurred in some patients but the relationship to Imigran is not clear.
- Transient increases in blood pressure arising soon after treatment have been recorded.
- Dyspnoea.

Following administration of Imigran nasal spray, mild transient irritation or burning sensation in the nose or throat, or epistaxis, have been reported.

Although direct comparisons are not available, nausea, vomiting and fatigue appear to be less frequent with subcutaneous administration of Imigran than with tablets. Conversely, flushing, paraesthesia and sensations of tingling, heat or cold, pressure and heaviness may be more common after the injection.

Serious coronary events have been reported (see **PRECAUTIONS**). Other cardiovascular adverse reactions include hypotension, bradycardia, tachycardia and palpitations. Very rarely (less than 1 in 10,000) Raynaud's phenomenon, angina and ischaemic colitis have been reported.

There have been rare (less than 1 in 1,000) reports of seizures following migraine attacks treated with sumatriptan. 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.

Patients treated with Imigran very rarely (less than 1 in 10,000) exhibit visual disorders like flickering and diplopia. Additionally cases of nystagmus, scotoma and reduced vision have been observed. Very rarely loss of vision has occurred, which is usually transient. However, visual disorders may also occur during a migraine attack itself.

Hypersensitivity reactions ranging from cutaneous hypersensitivity (eg. rash, urticaria, pruritus or erythema) to, in rare (less than 1 in 10,000) cases, anaphylaxis have been recorded (see **PRECAUTIONS**).

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

In the clinical trial programme, decreased lymphocyte count post treatment was observed in a number of patients receiving either oral or subcutaneous Imigran. This effect was not dose-related and was also observed in patients receiving placebo. The significance of these findings is uncertain.

In the clinical trial programme, a similar profile of clinical adverse events was reported in the adolescent and adult populations taking Imigran tablets or nasal spray.

In four bioequivalence studies, the safety profile for Imigran FDT was similar to that observed for Imigran tablets.

Post-Marketing Data: In addition to the drug-related adverse reactions reported from clinical trials, the following serious spontaneous events, reported to be possibly,

probably or almost certainly caused following use of either subcutaneous, oral or intranasal sumatriptan in patients less than 18 years of age have been identified.

Cardiovascular: myocardial infarction.
Cerebrovascular: cerebellar infarction.
Neurology: seizures, tremor & dystonia.
Non-site specific: anaphylaxis.
Skin: urticaria, rash.

Table 5: Incidence of Treatment-Emergent* Adverse Events (%) Reported by at least 1% of Patients and all Cardiovascular Events Irrespective of Frequency in Controlled Clinical Trials with Sumatriptan Tablets and Injection.

Event	Tablets (n=1456)	Placebo (n=296)	Subcutaneous Injection (n=2665)	Placebo (n=868)
Atypical:				
tingling	1	<1	9	3
warm/hot sensation	1	<1	9	3
burning sensation	<1	0	5	<1
numbness	2	1	3	2
feeling strange	0	0	1	<1
cold sensation	1	<1	1	<1
Gastrointestinal:				
nausea/vomiting	14	7	10	10
gastric symptoms, abdominal discomfort	3	3	1	<1
dysphagia	1	0	<1	<1
Neurological:				
dizziness/vertigo	6	2	8	4
malaise/fatigue	9	3	3	1
drowsiness/sedation	3	1	3	1
paraesthesia	1	0	1	<1
headache	1	1	2	<1
syncope	1	0	<1	<1
Cardiovascular:				
flushing	<1	1	6	2
hypertension, tachycardia	<1	0	2	<1
bradycardia	<1	0	<1	0
palpitations	1	<1	<1	<1
hypotension	<1	0	<1	<1
pallor	<1	0	<1	<1
pulsating sensation	<1	0	<1	<1
changes in ECG	0	0	<1	0
Symptoms Potentially of Cardiac Origin:				
neck pain/stiffness	3	0	3	<1
feeling of heaviness	3	1	8	1
feeling of tightness	1	0	3	<1
tight feeling in head	<1	0	1	<1
pressure sensation	1	<1	6	1
chest symptoms (including chest pain)	3	<1	5	1
throat symptoms (including sore or swolllen throat or throat spasms)	3	0	2	<1
Musculoskeletal:				

Weakness	3	<1	3	<1
Myalgia	2	<1	1	<1
Ear, Nose and Throat:				
disturbance of nasal cavity/sinuses	<1	1	1	<1
Miscellaneous:				
injection site reactions	NA	NA	40	17
Sweating	2	<1	2	1
disorder of mouth and tongue	2	<1	4	2
disturbance of taste	11	3	1	2
dyspnoea	1	0	<1	<1

* Includes all events regardless of causality that occurred at a frequency of ≥ 1% in any sumatriptan treatment group and were more frequent in this group than in the placebo group.

NA Not Applicable.

Table 6: Incidence of Treatment-Emergent* Adverse Events (%) Reported by at least 1% of Patients and all Cardiovascular Events Irrespective of Frequency in Controlled Clinical Trials with Sumatriptan Nasal Spray

Event	Placebo (n=741)	10 mg NS (n=1007)	20 mg NS (n=1249)
Atypical:			
burning sensation	<1	<1	1
Gastrointestinal:			
nausea/vomiting	15	15	16
Neurological:			
dizziness/vertigo	<1	2	1
malaise/fatigue	<1	1	<1
Cardiovascular:			
flushing	<1	<1	<1
hypertension, tachycardia	<1	<1	<1
palpitations	<1	<1	<1
pulsating sensation	0	<1	<1
changes in ECG	<1	<1	<1
Symptoms Potentially of Cardiac Origin:			
neck pain/stiffness	<1	<1	<1
feeling of heaviness	<1	<1	<1
feeling of tightness	<1	<1	<1
tight feeling in head	0	<1	<1
pressure sensation	<1	<1	<1
chest symptoms (including chest pain)	<1	<1	<1
throat symptoms (including sore or swollen throat or throat spasms)	1	2	3
Ear, Nose and Throat:			
disturbance of nasal cavity/sinuses	3	3	4
throat symptoms	1	2	3
Miscellaneous:			
disorder of mouth and tongue	0	<1	<1
disturbance of taste	2	20	25

* Includes all events regardless of causality that occurred at a frequency of ≥1% in any sumatriptan treatment group and were more frequent in this group than in the placebo group.

Table 7: Incidence of Drug-Related Adverse Events (%) Reported by at least 1% of Adolescent Patients and all Cardiovascular Events Irrespective of Frequency in the Adolescent Controlled Clinical Trial with Sumatriptan Nasal Spray.

Event	Placebo (n=130)	Sumatriptan 10 mg (n=133)	Sumatriptan 20 mg (n=117)
Cardiovascular:			
palpitations	0	0	<1
Ear, Nose and Throat:			
throat and tonsil signs and symptoms	<1	0	4
Gastrointestinal:			
nausea	8	5	11
vomiting	2	3	5
Characteristic sensations:			
burning/stinging sensation	0	0	2
paraesthesia	2	2	3
Neurological:			
migraines	4	0	0
dizziness	<1	2	<1
somnolence	0	0	2
disturbances of sense of taste	2	30	26
Pain/pressure sensations:			
chest symptoms	0	0	0
other pressure/tightness	2	<1	0

DOSAGE AND ADMINISTRATION:

Imigran is indicated for the acute intermittent relief of both migraine and cluster headache. It should not be used prophylactically.

Ergotamine or ergotamine derivatives and Imigran should not be administered concurrently (see **CONTRAINDICATIONS**).

Injection: Imigran injection should be injected subcutaneously using an autoinjector. Patients should be advised to observe strictly the instruction leaflet for the Imigran autoinjector, especially regarding the safe disposal of syringes and needles.

The first dose of Imigran injection should be given by, or under the direct supervision of, a physician. As with the administration of the first dose of any injectable therapeutic product, appropriate resuscitative equipment should be available. Appropriate advice on the future use of the autoinjector by the patient should also be given at this time. The physician should ensure that the patient is familiar with and understands the Consumer Medicine Information.

Migraine
It is recommended to start the treatment at the first sign of a migraine headache or associated symptoms such as nausea, vomiting or photophobia. The efficacy of sumatriptan is independent of the duration of the attack when starting treatment. Administration during a migraine aura prior to other symptoms occurring may not prevent the development of a headache.

If a patient does not respond to the first dose of Imigran, a second dose should not be taken for the same attack. Imigran may be used for subsequent attacks.

Injection: The recommended adult dose of Imigran is a single 6 mg, subcutaneous injection. If symptoms recur a further subcutaneous dose of 6 mg may be given at any time in the next 24 hours provided that one hour has elapsed since the first dose. The maximum dose in 24 hours is 2 x 6 mg injections (12 mg).

Tablets: The initial recommended adult dose of oral Imigran is 50 mg. Some patients may require 100 mg. The dose should be adjusted according to the individual's response. If symptoms recur further doses may be given in the next 24 hours provided not more than 300 mg are taken in any 24 hour period. The tablet should be swallowed whole with water.

Nasal Spray:

Imigran nasal spray is particularly suitable for patients who suffer with nausea and vomiting or who require a rapid onset of effect during an attack.

Adults: The optimal dose of Imigran nasal spray is 20 mg, administered into one nostril. For some patients 10 mg may be effective.

Adolescents (12-17 years): The recommended dose of Imigran nasal spray is 10 mg – 20 mg (see Clinical Trials section), with consideration given to the patient's body weight and patient variability of migraine attacks. The dose of Imigran nasal spray should be administered into one nostril.

If symptoms recur a second dose may be given in the next 24 hours, provided that there is a minimum interval of two hours between the two doses. Not more than 40 mg of nasal spray should be used in any 24 hour period.

Cluster Headache
The recommended adult dose is a single 6 mg subcutaneous injection for each cluster attack. The maximum dose in 24 hours is two 6 mg injections (12 mg) providing at least one hour has elapsed between injections.

OVERDOSAGE:

There have been some reports of overdosage with Imigran injection. Patients have received single injections of up to 12 mg subcutaneously without significant adverse effects. Single doses up to 40 mg intranasally, up to 16 mg subcutaneously and up to

400 mg with Imigran tablets orally were not associated with side effects other than those mentioned. There is no experience of doses greater than these.

If overdosage with Imigran occurs, the patient should be monitored for at least ten hours and standard supportive treatment applied as required.

It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of sumatriptan.

Contact the Poisons Information Centre (telephone 131126) for advice on overdose management.

PRESENTATIONS AND STORAGE CONDITIONS:

Tablets

Sumatriptan tablets are presented in two formulations: Imigran tablets and Imigran FDT tablets.

Imigran tablets are available in two strengths, 100 mg and 50 mg.

Imigran brand tablets 100 mg are white to off white capsule shaped, film coated, tablets with "GX ET2" on one face and blank on the other. Each tablet contains 100 mg sumatriptan base as the succinate salt.

The tablets also contain: lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hypromellose, Opaspray white M-1-7120.

Imigran tablets 100 mg are available in packs containing 2 tablets in foil blisters.

Imigran brand tablets 50 mg are pink, capsule-shaped film-coated tablets with “GX ES3” on one face and blank on the other. Each tablet contains 50 mg sumatriptan base as the succinate salt.

The tablets also contain: lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, Opadry YS-1-1441-G.

Imigran tablets 50 mg are available in packs containing 2 and 4 tablets in foil blisters.

Store below 30°C.

Imigran FDT tablets are available in two strengths, 100 mg and 50 mg.

Imigran FDT 100 mg are white film coated, triangular shaped, biconvex tablets debossed with ‘GS YE7’ on one face and ‘100’ on the other. Each tablet contains 100 mg sumatriptan base as the succinate salt.

Imigran FDT also contains: calcium hydrogen phosphate anhydrous, cellulose – microcrystalline, sodium bicarbonate, croscarmellose sodium, magnesium stearate and Opadry white OY-S-7322.

Imigran FDT 100 mg are available in packs containing 2 tablets in foil blisters.

Imigran FDT 50 mg are pink film coated, triangular shaped, biconvex tablets debossed with 'GS 1YM' on one face and '50' on the other. Each tablet contains 50 mg sumatriptan base as the succinate salt.

Imigran FDT also contains: calcium hydrogen phosphate anhydrous, cellulose – microcrystalline, sodium bicarbonate, croscarmellose sodium, magnesium stearate and Opadry YS-1-1441-G.

Imigran FDT 50 mg are available in packs containing 2 and 4 tablets in foil blisters.

Store below 30°C.

Injection
Imigran MK II injection is available in pre-filled syringes containing 6 mg of sumatriptan base as the succinate salt, in an isotonic solution containing sodium chloride and water for injections (total volume 0.5 mL). Imigran Mk II injection is available in an autoinjector kit containing two pre-filled syringes and one autoinjector; and in refill packs of two pre-filled syringes.

Store below 30°C. Protect from light.

Nasal Spray
Two strengths of nasal spray are available: Imigran S nasal spray 10 mg and Imigran nasal spray 20 mg. Each nasal spray is a single dose unit of sumatriptan base in 0.1 mL aqueous solution containing sulfuric acid, monobasic potassium phosphate, dibasic anhydrous sodium phosphate, sodium hydroxide and purified water. The pH of the nasal spray solution is 5.5.

The nasal spray solution is supplied in Type I glass vials sealed with chlorobutyl rubber stoppers. The stoppered vial is assembled into a unit dose nasal spray device.

Packs contain 2 individual nasal sprays each in a blister pack with an integral actuator .

Store below 30°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR:

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155

Approved by the Therapeutic Goods Administration on: 30 July 2004
Date of last amendment: 21 June 2007
Date of Safety Related Notification: 13 July 2007

® Imigran is a registered trade mark of the GlaxoSmithKline group of companies.

Issue No. 24 (M)