**IMIGRAN® Tablets GlaxoSmithKline**

**Sumatriptan**

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
Tablets containing 50 or 100 mg of sumatriptan base as the succinate salt.

**PHARMACEUTICAL FORM**
Sumatriptan tablets 50 mg are pink, film coated, with “Imigran” engraved on one face and “50” on the other face, or plain on one face and engraved “50” on the other.
Sumatriptan tablets 100 mg are white to off-white, film coated, with “Imigran” engraved on one face and “Glaxo” on the other face, or plain on one face and engraved “100” on the other.

**CLINICAL PARTICULARS**

**Indications**
Sumatriptan tablets are indicated for the acute relief of migraine attacks with or without aura, including the acute treatment of migraine attacks associated with the menstrual period in women.

**Dosage and Administration**
Sumatriptan should not be used prophylactically.
It is advisable that sumatriptan be given as early as possible after the onset of a migraine headache. It is equally effective at whatever stage of the attack it is administered.

- **Adults**
The recommended dose of oral sumatriptan is a single 50 mg tablet. Some patients may require 100 mg. If a patient does not respond to the first dose of sumatriptan, a second dose should not be taken for the same attack. Sumatriptan tablets may be taken for subsequent attacks. If the patient has responded to the first dose, but the symptoms recur a second dose may be given in the next 24 h, provided that not more than 300 mg is taken in any 24-h period. The tablets should be swallowed whole with water.

- **Children (under 12 years of age)**
Sumatriptan tablets have not been studied in children.

- **Adolescents (12 to 17 years of age)**
The efficacy of sumatriptan tablets in this population has not been demonstrated (see Clinical Studies).

- **Elderly (over 65 years of age)**
Experience of the use of sumatriptan tablets in patients aged over 65 years is limited. The pharmacokinetics do not differ significantly from a younger population, but until further clinical data are available, the use of sumatriptan in patients aged over 65 years is not recommended.

**Contraindications**
- Hypersensitivity to any component of the preparation.
- Sumatriptan should not be given to patients who have had myocardial infarction or have ischaemic heart disease (IHD), Prinzmetal’s angina/coronary vasospasm, peripheral vascular disease or patients who have symptoms or signs consistent with IHD.
- Sumatriptan should not be administered to patients with a history of previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- The use of sumatriptan in patients with uncontrolled hypertension is contraindicated.
- Sumatriptan should not be administered to patients with severe hepatic impairment.
- The concomitant use of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (see Interactions).
- Concurrent administration of monoamine oxidase inhibitors (MAOIs) and sumatriptan is contraindicated. Sumatriptan must not be used within 2 weeks of discontinuation of therapy with MAOIs.

Warnings and Precautions
Sumatriptan should only be used where there is a clear diagnosis of migraine.
Sumatriptan is not indicated for use in the management of hemiplegic, basilar or ophthalmoplegic migraine.
As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g. CVA, TIA).
Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat (see Adverse Reactions). Where such symptoms are thought to indicate Ischaemic Heart Disease appropriate evaluation should be carried out.
Sumatriptan 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. However, these evaluations may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.
Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.
There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan.
Serotonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline reuptake inhibitors (SNRIs). If concomitant treatment with sumatriptan and an SSRI/SNRI is clinically warranted, appropriate observation of the patient is advised (see Interactions).
The concomitant administration of any triptan/5-HT1 agonist with sumatriptan is not recommended.
Sumatriptan should be administered with caution to patients with conditions that may affect significantly the absorption, metabolism or excretion of the drug, e.g. impaired hepatic or renal function.
Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold.
Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. 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.
The recommended dose of sumatriptan should not be exceeded.
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.

Interactions
There is no evidence of interactions with propanolol, flunarizine, pizotifen or alcohol.
Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 h should elapse before sumatriptan can be taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations should not be taken until 6 h have elapsed following sumatriptan administration.
An interaction may occur between sumatriptan and MAOIs and concomitant administration is contraindicated (see Contraindications).
There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of SSRIs and sumatriptan. Serotonin syndrome has also been reported following concomitant treatment with triptans and SNRIs (see Warnings and Precautions).

Pregnancy and Lactation
Pregnancy
Caution should be exercised by considering the expected benefit to the mother against possible risk to the foetus.
Post-marketing data from multiple prospective pregnancy registries have documented the pregnancy outcomes in over 1,000 women exposed to sumatriptan. Although there is insufficient information to draw definitive conclusions, the findings have not detected an increase in the frequency of birth defects nor a consistent pattern of birth defects, amongst women exposed to sumatriptan compared with the general population.

Lactation
It has been demonstrated that following subcutaneous administration sumatriptan is excreted into breast milk. Infant exposure can be minimised by avoiding breast feeding for 12 h after treatment.

Effects on Ability to Drive and Use Machines
Drowsiness may occur as a result of migraine or its treatment with sumatriptan.
Caution is recommended in patients performing skilled tasks, e.g. driving or operating machinery.

Adverse Reactions
Adverse events are listed below by system organ class and frequency. Frequencies are defined as:
very common: ≥1 in 10
common: ≥1 in 100 and <1 in 10
uncommon: ≥1 in 1,000 and <1 in 100
rare: ≥1 in 10,000 and <1 in 1,000
very rare: <1/10,000 including isolated reports.
The data from clinical trials are estimates. It should be noted that the background rate in comparator groups was not taken into account. Post-marketing data refer to reporting rate rather than true frequency.

Clinical Trial Data
Nervous System Disorders
Common: Dizziness, drowsiness, sensory disturbance including paraesthesia and hypoaesthesia.

Vascular disorders
Common: Transient increases in blood pressure arising soon after treatment. Flushing.

Respiratory, Thoracic and Mediastinal Disorders
Common: Dyspnoea.

Gastrointestinal Disorders
Common: Nausea and vomiting occurred in some patients but the relationship to sumatriptan is not clear.

Musculoskeletal and Connective Tissue Disorders
The following symptom is usually transient and may be intense and can affect any part of the body including the chest and throat:
Common: Sensations of heaviness.
General Disorders and Administration Site Conditions
The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat:
Common: Pain, sensations of heat or cold, pressure or tightness.
The following symptoms are mostly mild to moderate in intensity and transient:
Common: Feelings of weakness, fatigue.

Investigations
Very rare: Minor disturbances in liver function tests have occasionally been observed.

Post-Marketing Data
Immune System Disorders
Very rare: Hypersensitivity reactions ranging from cutaneous hypersensitivity to anaphylaxis.

Nervous System Disorders
Very rare: 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. Tremor, dystonia, nystagmus, scotoma.

Eye disorders
Very rare: Flickering, diplopia, reduced vision. Loss of vision (usually transient). However, visual disorders may also occur during a migraine attack itself.

Cardiac disorders
Very rare: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, angina, myocardial infarction (see Contraindications, Warnings and Precautions).

Vascular disorders
Very rare: Hypotension, Raynaud's phenomenon.

Gastrointestinal Disorders
Very rare: Ischaemic colitis.

Overdose
Symptoms and Signs
Doses in excess of 400 mg orally and 16 mg subcutaneously were not associated with side effects other than those mentioned. Patients have received single injections of up to 12 mg subcutaneously without significant adverse effects.

Treatment
If overdosage occurs, the patient should be monitored for at least 10 h and standard supportive treatment applied as required.
It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of sumatriptan.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
ATC Code
N02CC01.
**Mechanism of Action**
Pharmacotherapeutic group: Selective 5-HT1 receptor agonists.
Sumatriptan has been demonstrated to be a selective vascular 5-hydroxytryptamine-1-(5-HT1D) receptor agonist with no effect at other 5-HT receptor (5-HT2-7) subtypes. The vascular 5-HT1D 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.

**Pharmacodynamic Effects**
Clinical response begins 10 to 15 min following a 6 mg subcutaneous injection, 15 min following a 20 mg dose given by intra-nasal administration and around 30 min following a 100 mg oral dose or 25 mg rectal dose.
Although the recommended dose of oral sumatriptan is 50 mg, migraine attacks vary in severity both within and between patients. Doses of 25 to 100 mg have shown greater efficacy than placebo in clinical trials, but 25 mg is statistically significantly less effective than 50 and 100 mg. Sumatriptan is effective in the acute treatment of migraine including menstrually-associated migraine.

**Pharmacokinetics**
The pharmacokinetics of sumatriptan do not appear to be significantly affected by migraine attacks.

**Absorption**
After oral administration, sumatriptan is rapidly absorbed, 70% of maximum concentration occurring at 45 min. After a 100 mg dose the mean maximum plasma concentration is 54 nanograms/ml.
Mean absolute oral bioavailability is 14% partly due to pre-systemic metabolism and partly due to incomplete absorption.

**Distribution**
Plasma protein binding is low (14 to 21%); the mean total volume of distribution is 170 litres.

**Metabolism**
The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in urine, where it is present as a free acid and the glucuronide conjugate. It has no known 5-HT1 or 5-HT2 activity. Minor metabolites have not been identified.

**Elimination**
The elimination half-life is approximately 2 h. The mean total plasma clearance is approximately 1,160 ml/min and the mean renal plasma clearance is approximately 260 ml/min.
Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A.

**Special Patient Populations**
- **Hepatic impairment**
Following oral administration, pre-systemic clearance is reduced in patients with hepatic impairment resulting in increased plasma levels of sumatriptan.
Clinical Studies
A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan standard tablets in 600 adolescent migraineurs aged 12 to 17 years. These studies failed to demonstrate a statistically significant difference in headache relief at 2 hours between placebo and any sumatriptan dose. The undesirable effects profile of oral sumatriptan in adolescents aged 12 to 17 years was similar to that reported from studies in the adult population.

Pre-clinical Safety Data
Carcinogenesis, mutagenesis
Sumatriptan was devoid of genotoxic and carcinogenic activity in in-vitro systems and animal studies.

Reproductive toxicology
In a rat fertility study, oral doses of sumatriptan resulting in plasma levels approximately 200 times those seen in man 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 150 times those in man by the oral route.

Pregnancy and lactation
No teratogenic effects have been seen in rats or rabbits, and sumatriptan had no effect on the post-natal development of rats. When administered to pregnant rabbits throughout the period of organogenesis sumatriptan has occasionally caused embryolethality at doses that were sufficiently high to produce maternal toxicity.

PHARMACEUTICAL PARTICULARS
List of Excipients
50 mg
Lactose (monohydrate)
Lactose (anhydrous)
Microcrystalline cellulose
Crocarmellose sodium
Magnesium stearate
Purified water

100 mg
Lactose (monohydrate)
Microcrystalline cellulose
Crocarmellose sodium
Magnesium stearate
Purified water

Incompatibilities
None reported.

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
Sumatriptan tablets should be stored below 30°C.
Nature and Contents of Container
Sumatriptan tablets 50 mg are packed in individual pockets in double foil blister packs and placed in a cardboard carton.
Sumatriptan tablets 100 mg are packed in individual pockets in double foil blister packs and placed in a cardboard carton.

Instructions for Use/Handling
None.
Not all presentations are available in every country.

Version number: GDS 21 / IPI 05

Date of issue: 02 April 2007

Imigran is a trademark of the GlaxoSmithKline group of companies
QUALITATIVE AND QUANTITATIVE COMPOSITION
Pre-filled syringes containing 6 mg of sumatriptan base as the succinate salt in an isotonic solution (total volume: 0.5 ml). An autoinjector is available.

PHARMACEUTICAL FORM
Sumatriptan injection is a clear, colourless to pale yellow liquid, practically free from particles.

CLINICAL PARTICULARS
Indications
Sumatriptan injection is indicated for the acute relief of migraine attacks with or without aura, including the acute treatment of migraine attacks associated with the menstrual period in women. Sumatriptan injection is also indicated for the acute treatment of cluster headache.

Dosage and Administration
Sumatriptan should not be used prophylactically.
It is advisable that sumatriptan be given as early as possible after the onset of a migraine headache or associated symptoms such as nausea, vomiting or photophobia. It is equally effective at whatever stage of the attack it is administered.
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.
Sumatriptan injection should be injected subcutaneously using an autoinjector.
Patients should be advised to observe strictly the instruction leaflet for the sumatriptan autoinjector, especially regarding the safe disposal of syringes and needles.

• Adults
Migraine
The recommended dose of sumatriptan injection is a single 6 mg subcutaneous injection.
If a patient does not respond to the first dose of sumatriptan, a second dose should not be taken for the same attack. Sumatriptan injection may be taken for subsequent attacks.
If the patient has responded to the first dose, but the symptoms recur a second dose may be given in the next 24 h, provided that there is a minimum interval of 1 h between the two doses.
The maximum dose in 24 h is two 6 mg injections (12 mg).

Cluster headache
The recommended dose of sumatriptan injection is a single 6 mg subcutaneous injection for each cluster attack. The maximum dose in 24 h is two 6 mg injections (12 mg) with a minimum interval of 1 h between the two doses.

• Children and Adolescents (under 18 years of age)
Sumatriptan injection has not been studied in adolescents or children.
• Elderly (over 65 years of age)
Experience of the use of sumatriptan in patients aged over 65 years is limited. The pharmacokinetics do not differ significantly from a younger population, but until further clinical data are available, the use of sumatriptan in patients aged over 65 years is not recommended.

Contraindications
- Hypersensitivity to any component of the preparation.
- Sumatriptan should not be given to patients who have had myocardial infarction or have ischaemic heart disease (IHD), Prinzmetal's angina/coronary vasospasm, peripheral vascular disease or patients who have symptoms or signs consistent with IHD.
- Sumatriptan should not be administered to patients with a history of previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- The use of sumatriptan in patients with uncontrolled hypertension is contraindicated.
- Sumatriptan should not be administered to patients with severe hepatic impairment.
- The concomitant use of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (see Interactions).
- Concurrent administration of monoamine oxidase inhibitors (MAOIs) and sumatriptan is contraindicated. Sumatriptan must not be used within 2 weeks of discontinuation of therapy with MAOIs.

Warnings and Precautions
Sumatriptan should only be used where there is a clear diagnosis of migraine or cluster headache. Sumatriptan injection should not be given intravenously.
Sumatriptan is not indicated for use in the management of hemiplegic, basilar or ophthalmoplegic migraine.
As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g. CVA, TIA).
Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat (see Adverse Reactions). Where such symptoms are thought to indicate Ischaemic Heart Disease appropriate evaluation should be carried out.
Sumatriptan 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. However, these evaluations may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.
Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.
There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan.
Serotonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline reuptake inhibitors (SNRIs).
If concomitant treatment with sumatriptan and an SSRI/SNRI is clinically warranted, appropriate observation of the patient is advised (see Interactions).
The concomitant administration of any triptan/5-HT1 agonist with sumatriptan is not recommended.
Sumatriptan should be administered with caution to patients with conditions that may affect significantly the absorption, metabolism or excretion of the drug, e.g. impaired hepatic or renal function.
Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold.
Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. 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. The recommended dose of sumatriptan should not be exceeded. 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.

**Interactions**
There is no evidence of interactions with propanolol, flunarizine, pizotifen or alcohol. Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 h should elapse before sumatriptan can be taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations should not be taken until 6 h have elapsed following sumatriptan administration.
An interaction may occur between sumatriptan and MAOIs and concomitant administration is contraindicated (see Contraindications). There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of SSRIs and sumatriptan. Serotonin syndrome has also been reported following concomitant treatment with triptans and SNRIs (see Warnings and Precautions).

**Pregnancy and Lactation**
**Pregnancy**
Caution should be exercised by considering the expected benefit to the mother against possible risk to the foetus. Post-marketing data from multiple prospective pregnancy registries have documented the pregnancy outcomes in over 1,000 women exposed to sumatriptan. Although there is insufficient information to draw definitive conclusions, the findings have not detected an increase in the frequency of birth defects nor a consistent pattern of birth defects, amongst women exposed to sumatriptan compared with the general population.

**Lactation**
It has been demonstrated that following subcutaneous administration sumatriptan is excreted into breast milk. Infant exposure can be minimised by avoiding breast feeding for 12 h after treatment.

**Effects on Ability to Drive and Use Machines**
Drowsiness may occur as a result of migraine or its treatment with sumatriptan. Caution is recommended in patients performing skilled tasks, e.g. driving or operating machinery.

**Adverse Reactions**
Adverse events are listed below by system organ class and frequency. Frequencies are defined as:
- very common: ≥1 in 10
- common: ≥1 in 100 and <1 in 10
- uncommon: ≥1 in 1,000 and <1 in 100
- rare: ≥1 in 10,000 and <1 in 1,000
- very rare: <1/10,000 including isolated reports.
The data from clinical trials are estimates. It should be noted that the background rate in comparator groups was not taken into account. Post-marketing data refer to reporting rate rather than true frequency.

**Clinical Trial Data**
**Nervous System Disorders**
Common: Dizziness, drowsiness, sensory disturbance including paraesthesia and hypoaesthesia.
**Vascular disorders**
Common: Transient increases in blood pressure arising soon after treatment. Flushing.

**Respiratory, Thoracic and Mediastinal Disorders**
Common: Dyspnoea.

**Gastrointestinal Disorders**
Common: Nausea and vomiting occurred in some patients but the relationship to sumatriptan is not clear.

**Musculoskeletal and Connective Tissue Disorders**
The following symptom is usually transient and may be intense and can affect any part of the body including the chest and throat:
Common: Sensations of heaviness.

**General Disorders and Administration Site Conditions**
The most common side effects associated with treatment with sumatriptan administered subcutaneously are:
Very common: Transient injection site pain. Injection site stinging/burning, swelling, erythema, bruising and bleeding have also been reported.
The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat:
Common: Pain, sensations of heat or cold, pressure or tightness.
The following symptoms are mostly mild to moderate in intensity and transient:
Common: Feelings of weakness, fatigue.

**Investigations**
Very rare: Minor disturbances in liver function tests have occasionally been observed. Although direct comparisons are not available, flushing, paraesthesia and sensations of heat, pressure, and heaviness may be more common after sumatriptan injection. Conversely, nausea, vomiting and fatigue appear to be less frequent with subcutaneous administration of sumatriptan injection than with tablets.

**Post-Marketing Data**

**Immune System Disorders**
Very rare: Hypersensitivity reactions ranging from cutaneous hypersensitivity to anaphylaxis.

**Nervous System Disorders**
Very rare: 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. Tremor, dystonia, nystagmus, scotoma.

**Eye disorders**
Very rare: Flickering, diplopia, reduced vision. Loss of vision (usually transient). However, visual disorders may also occur during a migraine attack itself.

**Cardiac disorders**
Very rare: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, angina, myocardial infarction (see Contraindications, Warnings and Precautions).

**Vascular disorders**
Very rare: Hypotension, Raynaud's phenomenon.

Always refer to the Manufacturer's Prescribing Information before you prescribe
Gastrointestinal Disorders

Very rare: Ischaemic colitis.

Overdose

Symptoms and Signs

There have been some reports of overdosage with sumatriptan injection.

Patients have received single injections of up to 12 mg subcutaneously without significant adverse effects. Doses up to 16 mg subcutaneously were not associated with side effects other than those mentioned.

Treatment

If overdosage occurs, the patient should be monitored for at least 10 h and standard supportive treatment applied as required.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

N02CC01.

Mechanism of Action

Pharmacotherapeutic group: Selective 5-HT₁ receptor agonists.

Sumatriptan has been demonstrated to be a selective vascular 5-hydroxytryptamine-1-(5-HT₁D) receptor agonist with no effect at other 5-HT receptor (5-HT₂–7) subtypes. The vascular 5-HT₁D 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.

Pharmacodynamic Effects

Clinical response begins 10 to 15 min following a 6 mg subcutaneous injection, 15 min following a 20 mg dose given by intra-nasal administration and around 30 min following a 100 mg oral dose or 25 mg rectal dose.

Sumatriptan is effective in the acute treatment of migraine including menstrually-associated migraine.

Pharmacokinetics

The pharmacokinetics of sumatriptan do not appear to be significantly affected by migraine attacks.

Absorption

Following subcutaneous injection sumatriptan has a high mean bioavailability (96%) with peak serum concentrations occurring in 25 min. Average peak serum concentration after a 6 mg subcutaneous dose is 72 nanograms/ml.

Distribution

Plasma protein binding is low (14 to 21%); the mean total volume of distribution is 170 litres.

Metabolism
The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in urine, where it is present as a free acid and the glucuronide conjugate. It has no known 5-HT₁ or 5-HT₂ activity. Minor metabolites have not been identified.

**Elimination**
The elimination half-life is approximately 2 h. The mean total plasma clearance is approximately 1,160 ml/min and the mean renal plasma clearance is approximately 260 ml/min. Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A.

**Pre-clinical Safety Data**
**Carcinogenesis, mutagenesis**
Sumatriptan was devoid of genotoxic and carcinogenic activity in in-vitro systems and animal studies.

**Reproductive toxicology**
In a rat fertility study, oral doses of sumatriptan resulting in plasma levels approximately 150 times those seen in man after a 6 mg subcutaneous 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 man by the subcutaneous route.

**Pregnancy and lactation**
No teratogenic effects have been seen in rats or rabbits, and sumatriptan had no effect on the post-natal development of rats.
When administered to pregnant rabbits throughout the period of organogenesis sumatriptan has occasionally caused embryolethality at doses that were sufficiently high to produce maternal toxicity.

**PHARMACEUTICAL PARTICULARS**
**List of Excipients**
- Sodium chloride
- Water for injection
- Nitrogen

**Incompatibilities**
None reported.

**Shelf Life**
The expiry date is indicated on the packaging.

**Special Precautions for Storage**
Sumatriptan injection should be stored below 30°C, protected from light.

**Nature and Contents of Container**
A syringe, with an integrated needle, which is designed to be disposable, and consists of the following components:
- Glass syringe barrel, Type I glass
- Stainless steel needle cannula
- Natural rubber needle shield
- Chlorobutyl rubber plunger stopper
All the above components are received pre-sterilised from the suppliers. The pre-filled syringes should be used in conjunction with an autoinjector.

**Instructions for Use/Handling**
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.

**Version number:** GDS 21 / IPI 05

**Date of issue:** 02 April 2007

Imigran is a trademark of the GlaxoSmithKline group of companies.
IMIGRAN® Nasal Spray GlaxoSmithKline
Sumatriptan

QUALITATIVE AND QUANTITATIVE COMPOSITION
Unit dose spray device for intranasal administration. The device delivers either 10 or 20 mg of sumatriptan in 0.1 ml of an aqueous buffered solution. The solution has a characteristic taste.

PHARMACEUTICAL FORM
Imigran nasal spray is a clear, pale to yellow to dark yellow liquid.

CLINICAL PARTICULARS
Indications
Sumatriptan nasal spray is indicated for the acute relief of migraine attacks with or without aura. It is particularly suitable for patients who suffer with nausea and vomiting or who require a rapid onset of effect during an attack.

Dosage and Administration
Sumatriptan should not be used prophylactically. It is advisable that sumatriptan be given as early as possible after the onset of a migraine headache. It is equally effective at whatever stage of the attack it is administered.

- **Adults (18 years of age and over)**
The optimal dose of sumatriptan nasal spray is 20 mg for administration into one nostril. Due to inter/intra patient variability of both the migraine attacks and the absorption of sumatriptan, 10 mg may be effective in some patients and attacks. If the patient does not respond to the first dose of sumatriptan, a second dose should not be taken for the same attack. Sumatriptan nasal spray may be taken for subsequent attacks. If the patient has responded to the first dose, but the symptoms recur a second dose may be given in the next 24 h, provided that there is a minimum interval of 2 h between the doses. No more than two sumatriptan 20 mg nasal sprays should be used in any 24-h period.

- **Adolescents (12 to 17 years of age)**
The recommended dose of sumatriptan nasal spray is 10 mg for administration into one nostril. Due to inter/intra patient variability of migraine attacks and the exposure to sumatriptan, a dose of 20 mg may be required in some patients. If a patient does not respond to the first dose of sumatriptan, a second dose should not be taken for the same attack. Sumatriptan nasal spray may be taken for subsequent attacks. If the patient has responded to the first dose of sumatriptan nasal spray, but the symptoms recur a second dose may be given in the next 24 h, provided that there is a minimum interval of 2 h between the doses. No more than two sumatriptan 20 mg nasal sprays to be used in any 24-h period.

- **Children (under 12 years of age)**
The safety and effectiveness of sumatriptan nasal spray in children has not yet been established.

- **Elderly (over 65 years of age)**
There is no clinical experience of the use of sumatriptan nasal spray in patients over 65 years of age.
Contraindications
- Hypersensitivity to any component of the preparation.
- Sumatriptan should not be given to patients who have had myocardial infarction or have ischaemic heart disease (IHD), Prinzmetal's angina/coronary vasospasm, peripheral vascular disease or patients who have symptoms or signs consistent with IHD.
- Sumatriptan should not be administered to patients with a history of previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- The use of sumatriptan in patients with uncontrolled hypertension is contraindicated.
- Sumatriptan should not be administered to patients with severe hepatic impairment.
- The concomitant use of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated (see Interactions).
- Concurrent administration of monoamine oxidase inhibitors (MAOIs) and sumatriptan is contraindicated. Sumatriptan must not be used within 2 weeks of discontinuation of therapy with MAOIs.

Warnings and Precautions
Sumatriptan should only be used where there is a clear diagnosis of migraine.
Sumatriptan is not indicated for use in the management of hemiplegic, basilar or ophthalmoplegic migraine.
As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g. CVA, TIA).
Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat (see Adverse Reactions). Where such symptoms are thought to indicate Ischaemic Heart Disease appropriate evaluation should be carried out.
Sumatriptan 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. However, these evaluations may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.
Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.
There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan.
Serotonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline reuptake inhibitors (SNRIs).
If concomitant treatment with sumatriptan and an SSRI/SNRI is clinically warranted, appropriate observation of the patient is advised (see Interactions).
The concomitant administration of any triptan/5-HT1 agonist with sumatriptan is not recommended.
Sumatriptan should be administered with caution to patients with conditions that may affect significantly the absorption, metabolism or excretion of the drug, e.g. impaired hepatic or renal function.
Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold.
Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. 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.
The recommended dose of sumatriptan should not be exceeded.
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.
Interactions
There is no evidence of interactions with propanolol, flunarizine, pizotifen or alcohol. Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 h should elapse before sumatriptan can be taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations should not be taken until 6 h have elapsed following sumatriptan administration. An interaction may occur between sumatriptan and MAOIs and concomitant administration is contraindicated (see Contraindications).

Pregnancy and Lactation
Pregnancy
Caution should be exercised by considering the expected benefit to the mother against possible risk to the foetus. Post-marketing data from multiple prospective pregnancy registries have documented the pregnancy outcomes in over 1,000 women exposed to sumatriptan. Although there is insufficient information to draw definitive conclusions, the findings have not detected an increase in the frequency of birth defects nor a consistent pattern of birth defects, amongst women exposed to sumatriptan compared with the general population.

Lactation
It has been demonstrated that following subcutaneous administration sumatriptan is excreted into breast milk. Infant exposure can be minimised by avoiding breast feeding for 12 h after treatment.

Effects on Ability to Drive and Use Machines
Drowsiness may occur as a result of migraine or its treatment with sumatriptan. Caution is recommended in patients performing skilled tasks, e.g. driving or operating machinery.

Adverse Reactions
Adverse events are listed below by system organ class and frequency. Frequencies are defined as:
very common: ≥1 in 10
common: ≥1 in 100 and <1 in 10
uncommon: ≥1 in 1,000 and <1 in 100
rare: ≥1 in 10,000 and <1 in 1,000
very rare: <1/10,000 including isolated reports.
The data from clinical trials are estimates. It should be noted that the background rate in comparator groups was not taken into account. Post-marketing data refer to reporting rate rather than true frequency.

Clinical Trial Data
Nervous System Disorders
Common: Dizziness, drowsiness, sensory disturbance including paraesthesia and hypoesthesia.

Vascular disorders
Common: Transient increases in blood pressure arising soon after treatment. Flushing.

Respiratory, Thoracic and Mediastinal Disorders
Common: Dyspnoea; following administration of sumatriptan nasal spray mild, transient irritation or burning sensation in the nose or throat or epistaxis have been reported.

Gastrointestinal Disorders
Common: Nausea and vomiting occurred in some patients but the relationship to sumatriptan is not clear.
Musculoskeletal and Connective Tissue Disorders
The following symptom is usually transient and may be intense and can affect any part of the body including the chest and throat:
Common: Sensations of heaviness.

General Disorders and Administration Site Conditions
The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat:
Common: Pain, sensations of heat or cold, pressure or tightness.
The following symptoms are mostly mild to moderate in intensity and transient:
Common: Feelings of weakness, fatigue.

Investigations
Very rare: Minor disturbances in liver function tests have occasionally been observed.

Post-Marketing Data
Immune System Disorders
Very rare: Hypersensitivity reactions ranging from cutaneous hypersensitivity to anaphylaxis.

Nervous System Disorders
Very rare: 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. Tremor, dystonia, nystagmus, scotoma.

Eye disorders
Very rare: Flickering, diplopia, reduced vision. Loss of vision (usually transient). However, visual disorders may also occur during a migraine attack itself.

Cardiac disorders
Very rare: Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, angina, myocardial infarction (see Contraindications, Warnings and Precautions).

Vascular disorders
Very rare: Hypotension, Raynaud’s phenomenon.

Gastrointestinal Disorders
Very rare: Ischaemic colitis.

Overdose
Symptoms and Signs
Single doses of sumatriptan, up to 40 mg intranasally have not been associated with side effects other than those mentioned.
In clinical studies volunteers have received 20 mg of sumatriptan by the intranasal route three times a day for a period of 4 days without significant adverse effects.
Treatment
If overdosage occurs, the patient should be monitored for at least 10 h and standard supportive treatment applied as required.
It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of sumatriptan.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics

ATC Code
N02CC01.

Mechanism of Action
Pharmacotherapeutic group: Selective 5-HT1 receptor agonists.
Sumatriptan has been demonstrated to be a selective vascular 5-hydroxytryptamine-1-(5-HT1D) receptor agonist with no effect at other 5-HT receptor (5-HT2–7) subtypes. The vascular 5-HT1D 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.

Pharmacodynamic Effects
Clinical response begins 10 to 15 min following a 6 mg subcutaneous injection, 15 min following a 20 mg dose given by intra-nasal administration and around 30 min following a 100 mg oral dose or 25 mg rectal dose.

Pharmacokinetics
The pharmacokinetics of sumatriptan do not appear to be significantly affected by migraine attacks.

Absorption
After intranasal administration, sumatriptan is rapidly absorbed, with maximum plasma concentration occurring in 1 to 1.5 h. After a 20 mg dose, the mean maximum concentration is 12.9 nanograms/ml. Mean intranasal bioavailability, relative to subcutaneous administration is 15.8%, partly due to pre-systemic metabolism.

Distribution
Plasma protein binding is low (14 to 21%); the mean total volume of distribution is 170 litres.

Metabolism
The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in urine, where it is present as a free acid and the glucuronide conjugate. It has no known 5-HT1 or 5-HT2 activity. Minor metabolites have not been identified.

Elimination
The elimination half-life is approximately 2 h. The mean total plasma clearance is approximately 1,160 ml/min and the mean renal plasma clearance is approximately 260 ml/min.
Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A.
Special Patient Populations

• Hepatic impairment
Following oral administration, pre-systemic clearance is reduced in patients with hepatic impairment resulting in increased plasma levels of sumatriptan. A similar increase would be expected following intranasal administration.

• Adolescents (12 to 17 years of age)
A pharmacokinetic study in adolescent subjects (12 to 17 years) indicated that the mean maximum plasma concentration was 13.9 nanograms/ml and mean elimination half-life was approximately 2 h 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.

Pre-clinical Safety Data
Carcinogenesis, mutagenesis
Sumatriptan was devoid of genotoxic and carcinogenic activity in in-vitro systems and animal studies.

Reproductive toxicology
In a rat fertility study oral doses of sumatriptan resulting in plasma levels approximately 750 times those seen in man after a 20 mg intranasal dose were associated with a reduction in the success of insemination. This effect did not occur during a subcutaneous study where maximum plasma levels in rats achieved approximately 500 times those seen in man by the intranasal route.

Pregnancy and lactation
No teratogenic effects have been seen in rats or rabbits, and sumatriptan had no effect on the post-natal development of rats.
When administered to pregnant rabbits throughout the period of organogenesis sumatriptan has occasionally caused embryolethality at doses that were sufficiently high to produce maternal toxicity.

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

PHARMACEUTICAL PARTICULARS
List of Excipients
Potassium dihydrogen phosphate.
Dibasic sodium phosphate anhydrous.
Sulphuric acid.
Sodium hydroxide.
Purified water.

Incompatibilities
None reported.

Shelf Life
The expiry date is indicated on the packaging.
**Special Precautions for Storage**
Sumatriptan nasal spray should be stored between 2 to 30°C. It should be kept in the sealed blister, preferably in the box, to protect from light.

**Nature and Contents of Container**
Unit dose disposable nasal spray device.

**Instructions for Use/Handling**
The nasal spray must only be removed from the blister packaging immediately before use.

The nasal spray consists of the following parts:
The Nozzle: This is the part that you put into your nostril. The spray comes out of a tiny hole in the top.
The Finger Grip: This is the part that you hold when you use the Spray.
The Blue Plunger: When you press the Plunger the whole dose sprays into your nostril in one go.
The Plunger only works once, so do not press it until you have put the Nozzle into your nostril or you will waste the dose.

First, get into a comfortable position.
You may like to sit down if there is a seat close-by.
Blow your nose if it feels blocked, or if you have a cold.
Peel open a blister pack and take out a nasal spray.
Hold the nasal spray gently with your fingers and thumb as shown in the picture.
Do not press the blue plunger yet.
Block one nostril by pressing a finger firmly on the side of your nose.
Breathe out gently through your mouth.
Put the nozzle of the nasal spray into the other nostril, as far as feels comfortable (about 1cm or ½ inch).
Hold your head in an upright position and close your mouth.
Start to breathe in gently through your nose and at the same time press the blue plunger firmly with your thumb.
The plunger may feel a bit stiff and you may hear it click.
Keep your head upright and breathe gently in through your nose and out through your mouth for 10 to 20 seconds. DO NOT BREATHE DEEPLY.
You can remove the spray and your finger from the other side of your nose while you do this.
Your nose may feel wet inside and you may notice a slight taste after using the spray – this is normal and will soon pass.
After being used once, your nasal spray is empty. It should be disposed of safely and hygienically.

**Version number:** GDS 21 / IPI 05

**Date of issue:** 02 April 2007

Imigran is a trademark of the GlaxoSmithKline group of companies.

---

Always refer to the Manufacturer's Prescribing Information before you prescribe.