IMITREX®

(sumatriptan succinate/sumatriptan)

50 and 100 mg Tablet
6 mg Subcutaneous Injection and Autoinjector
5 mg and 20 mg Nasal Spray

THERAPEUTIC CLASSIFICATION: Migraine Therapy

PHARMACOLOGIC CLASSIFICATION: 5-HT_1 Receptor Agonist

CLINICAL PHARMACOLOGY

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

Sumatriptan activates the 5-HT_{1D} receptor subtype which is present on cranial arteries, on the basilar artery and in the vasculature of dura mater. This action correlates with relief of headache. The antimigrainous effect of sumatriptan is believed to be due to vasoconstriction of cranial arteries, which are dilated and edematous during a migraine attack.

Experimental data from animal studies shows that sumatriptan also activates 5-HT_1 receptors on peripheral terminals of the trigeminal nerve which innervates cranial blood vessels. This causes the inhibition of neuropeptide release. It is thought that such an action may contribute to the anti-migraine action of sumatriptan in humans. Significant relief begins 10-15 minutes following subcutaneous injection, 15 minutes following intranasal administration and 30 minutes following oral administration.

Cardiovascular Effects: *In vitro* studies in human isolated epicardial coronary arteries suggest that the predominant contractile effect of 5-HT is mediated via 5-HT_2 receptors. However, 5-HT_1 receptors also contribute to some degree to the contractile effect seen. Transient increases in systolic and diastolic blood pressure (up to 20 mmHg) of rapid onset (within minutes), have occurred after intravenous administration of up to 64 µg/kg (3.2 mg for 50 kg subject) to healthy volunteers. These changes were not dose related and returned to normal within 10-15 minutes. Following oral administration of 200 mg or intranasal administration of 40 mg, however, mean peak increases in blood pressure were smaller and of slower onset than after intravenous or subcutaneous administration.

Pharmacokinetics: Sumatriptan is rapidly absorbed after oral, subcutaneous and intranasal administration with a mean bioavailability of 96% after subcutaneous dosing and 14% after oral dosing and 16% after intranasal administration. The low oral and intranasal bioavailability is primarily due to metabolism (hepatic and pre-systemic) and partly due to incomplete absorption. The oral absorption of sumatriptan is not significantly affected either during migraine attacks or by food.

Following an oral dose of 100 mg, a mean C_{max} of 54 ng/mL was attained, while the time to peak plasma level was variable (0.5-5 hours). However, 70% to 80% of C_{max} values were attained within 30-45 minutes of oral dosing. The mean plasma half-life was approximately 2 hours (range 1.9-2.2 hours). Following a 6 mg subcutaneous dose (standard injection) in the deltoid region of the arm or thigh or autoinjection into the thigh, a mean C_{max} value of 60 ng/mL was attained at approximately 15 minutes. Mean plasma half-life was approximately 2 hours (range 1.7-2.3 hours). Following a 5 mg, 10 mg and 20 mg intranasal dose, C_{max} values were 4.7 ng/mL, 8.5 ng/mL and 14.4 ng/mL, respectively. The time to peak plasma level was 1 to 1.5 hours. The elimination half life is approximately 2 hours (range 1.3-5.4 hours). Inter-patient and intra-patient variability was noted in most pharmacokinetic parameters assessed. Sumatriptan is extensively metabolised by the liver and cleared to a lesser extent by renal excretion. The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in the urine where it is present as a free acid (35%) and the glucuronide conjugate (11%). It has no known 5-HT_1 or 5-HT_2 activity. Minor metabolites have not been identified. Plasma protein binding of sumatriptan in humans is low (14%-21%). No differences have been observed between the pharmacokinetic parameters in healthy elderly volunteers compared with younger volunteers (less than 65 years old).

INDICATIONS AND CLINICAL USES IMITREX (sumatriptan succinate/sumatriptan) is indicated for the relief of migraine attacks with or without aura. Sumatriptan is not indicated for prophylactic therapy of migraine, or for the management of hemiplegic or basilar migraine.

CONTRAINDICATIONS IMITREX (sumatriptan succinate/sumatriptan) is contraindicated in patients with known hypersensitivity to any of the components of the formulation. Sumatriptan is contraindicated in patients with ischemic heart disease, angina pectoris including Prinzmetal angina (coronary vasospasm), previous myocardial infarction and uncontrolled hypertension. Sumatriptan is also contraindicated in patients taking ergotamine containing preparations or ergot derivatives (such as dihydroergotamine), and in patients receiving treatment with monoamine oxidase inhibitors or use within two weeks of discontinuation of MAOI therapy. Until further data are available the use of sumatriptan is contraindicated in patients with hemiplegic migraine, basilar migraine and in patients receiving treatment with selective 5-HT reuptake inhibitors and lithium.

WARNINGS

There is no experience in patients with recent cerebrovascular accidents or cardiac arrhythmias (especially tachycardias). Therefore the use of IMITREX (sumatriptan succinate) in these patients is not recommended.

Sumatriptan should only be used where there is a clear diagnosis of migraine headache. 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. There have been rare reports where patients received sumatriptan for severe headaches which subsequently were shown to have been secondary to an evolving neurological lesion (cerebrovascular accident, subarachnoid haemorrhage). In this regard, it should be noted that migraineurs may be at risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient ischemic attack). 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.

Sumatriptan has been associated with transient chest pain and tightness which may mimic angina pectoris and may be intense. Only in rare cases have the symptoms been identified as the result of coronary vasospasm. The vasospasm may result in arrhythmia, ischemia or myocardial infarction. Serious coronary events following sumatriptan have occurred but are extremely rare. Although it is not clear how many of these can be attributed to sumatriptan, because of its potential to cause coronary vasospasm, sumatriptan should not be given to patients in whom unrecognized coronary artery disease (CAD) is likely without a prior evaluation for underlying cardiovascular disease. Such patients include postmenopausal women, males over 40, patients with risk factors for CAD (hypertension, hypercholesterolaemia, obesity, diabetes, smoking, or strong family history of CAD). Consideration should be given to administering the first dose of IMITREX injection in the physician's office to patients in whom unrecognised coronary artery disease is comparatively likely. If the patient experiences symptoms which are severe or persistent and are consistent with angina, appropriate investigations should be carried out to check for the possibility of ischemic changes. A careful medical history should be taken before sumatriptan is prescribed to exclude pre-existing cardiovascular disease. Sumatriptan should be used with caution in patients in whom there is a concern of ischemic heart disease, as well as in patients with arteriosclerotic diseases such as peripheral and/or cerebral vascular disease. There have been rare reports of serious and/or life-threatening arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia and myocardial infarction, as well as transient ischemic ST wave elevations associated with IMITREX injection. Sumatriptan injection should never be given intravenously. The recommended dose of sumatriptan should not be exceeded.

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

General: Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 hours should elapse before sumatriptan can be taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations should not be taken until 6 hours have elapsed following sumatriptan administration. Sumatriptan should be used with caution in patients with a history of epilepsy or structural brain lesions which lower their convulsion threshold. Chest, jaw or neck tightness is relatively common (3-5% in controlled clinical trials) after IMITREX injection, but has only been rarely associated with ischemic ECG changes. Sumatriptan may cause a short-lived elevation of blood pressure (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS). Patients should be cautioned that drowsiness may occur as a result of treatment with sumatriptan. They should be advised not to perform skilled tasks e.g. driving or operating machinery if drowsiness occurs.

Concomitant Disease: Since there have been rare reports of seizures occurring, sumatriptan should be used with caution in patients with a history of epilepsy or structural brain lesions which lower their convulsive threshold.

Concomitant Medications: There have been reports of patients with known hypersensitivity to sulphonamides exhibiting an allergic reaction following administration of sumatriptan. Reactions ranged from cutaneous hypersensitivity to anaphylaxis.

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

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

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

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

*Statistically significant

The pharmacokinetic parameters of 6 mg subcutaneous sumatriptan do not differ statistically between normal volunteers and moderately hepatically impaired subjects.

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

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

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

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

Lactation: Sumatriptan is excreted in breast milk in animals. No data exists in humans, therefore, caution is advised when administering sumatriptan to nursing women.

Drug Interactions: Single dose pharmacokinetic drug interaction studies have not shown evidence of interactions with propranolol, flunarizine, pizotifen or alcohol. Multiple dose interaction studies have not been performed.

ADVERSE REACTIONS The most common adverse reaction associated with IMITREX (sumatriptan succinate/sumatriptan) administered subcutaneously is transient pain (local erythema and burning sensation) at the site of injection. Other side effects which have been reported for both the oral and subcutaneous routes, but were more common for the subcutaneous route, include sensations of tingling, heat, heaviness, pressure or tightness in any part of the body, chest symptoms, flushing, dizziness and feelings of weakness. Transient increases in blood pressure arising soon after treatment have been recorded. Hypotension, bradycardia, tachycardia and palpitations have been reported rarely. Sumatriptan may cause coronary vasospasm in patients with a history of coronary artery disease, known to be susceptible to coronary artery vasospasm, and, very rarely, without prior history suggestive of coronary artery disease. There have been rare reports of serious and/or life-threatening arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia, myocardial infarction, and transient ischemic ST elevation associated with IMITREX injection (see WARNINGS). Fatigue and drowsiness have been reported at slightly higher rates for the oral route, as were nausea and vomiting; the relationship of the latter adverse reactions to sumatriptan is not clear. Hypersensitivity reactions to sumatriptan have been reported including anaphylactic shock, anaphylactoid reactions, rash, urticaria, pruritis and erythema. There have been rare reports of seizures, the majority of these patients have a previous history of epilepsy or structural lesions predisposing to epilepsy (see PRECAUTIONS).

The following tables list the incidence of adverse reactions reported in clinical trials undertaken with the oral formulation and the subcutaneous injection (Table 1), and with the intranasal formulation (Table 2).

Most of the events were transient in nature and resolved within 45 minutes of subcutaneous administration and 2 hours of oral *or intranasal* administration.

Table 1: Incidence of Treatment-Emergent* Adverse Events in Controlled Clinical Trials

Event	Tablets n=1456	Placebo n=296	S.C. Injection n=2665	Placebo n=868
Gastrointestinal:				
nausea / vomiting	12%	4%	8%	4%
gastric symptoms, abdominal discomfort	1%	≤1%	1%	<1%
dysphagia	1%	0%	1%	0%
gastro-oesophageal reflux, diarrhea and abnormal stools	<1%	≤1%	<1%	0%
Neurological:				
tingling	1%	<1%	9%	2%
malaise/ fatigue	8%	2%	2%	<1%
dizziness/ vertigo	5%	2%	8%	3%
warm/ hot sensation	1%	<1%	8%	3%
burning sensation	<1%	0%	5%	<1%
numbness	1%	<1%	3%	1%
drowsiness/ sedation	3%	<1%	2%	<1%
paresthesia	1%	0%	1%	<1%
Cardiovascular:				
flushing	<1%	1%	5%	2%
hypertension, tachycardia	<1%	0%	<1%	<1%
bradycardia	<1%	0%	<1%	0%
palpitations	<1%	<1%	<1%	<1%
hypotension	<1%	0%	<1%	<1%
pallor	<1%	0%	<1%	0%
pulsating sensation	<1%	0%	<1%	<1%
Symptoms of Potentially Cardiac Origin:				
neck pain/ stiffness	2%	0%	3%	<1%
feeling of heaviness	3%	<1%	8%	1%
pressure sensation	1%	<1%	6%	1%
chest symptoms (including chest pain)	3%	<1%	4%	<1%
throat symptoms (including sore or swollen throat or throat spasms)	2%	0%	2%	<1%
Musculoskeletal:				
weakness	3%	<1%	3%	<1%
myalgia	2%	0%	1%	<1%
feeling of tightness	<1%	0%	3%	<1%
joint symptoms, backache, muscle stiffness or cramp	<1%	0%	0%	0%
Miscellaneous:				
sweating	2%	<1%	2%	<1%
disorder of mouth and tongue	2%	<1%	4%	2%
disturbance of hearing	<1%	0%	<1%	0%
visual disturbance	<1%	0%	<1%	<1%

Table 2: Incidence of Treatment-Emergent* Adverse Events Reported by at least 1% of patients in Controlled Clinical Trials with IMITREX Nasal Spray

Event	Placebo n=741	5 mg n=496	10 mg n=1007	20 mg n=1249
Atypical:				
warm / hot sensation	<1%	1%	<1%	<1%
burning sensation	<1%	<1%	<1%	1%
Gastrointestinal:				
nausea / vomiting	15%	17%	15%	16%
Neurological:				
dizziness/ vertigo	<1%	1%	2%	1%
malaise/ fatigue	<1%	2%	1%	<1%
headache	<1%	1%	<1%	<1%
Cardiovascular*:				
flushing	<1%	<1%	<1%	<1%
hypertension, tachycardia	<1%	<1%	<1%	<1%
palpitations	<1%	<1%	<1%	<1%
pulsating sensation	0%	0%	<1%	<0%
changes in ECG	<1%	<1%	<1%	<1%
Symptoms of Potentially Cardiac Origin*:				
neck pain / stiffness	<1%	0%	<1%	<1%
feeling of heaviness	<1%	<1%	<1%	<1%
feeling of tightness	<1%	0%	<1%	<1%
tight feeling in head	0%	0%	<1%	<1%
pressure sensation	<1%	<1%	<1%	<1%
chest symptoms (including chest pain)	<1%	<1%	<1%	<1%
throat symptoms (including sore or swollen throat or throat spasms)	1%	<1%	2%	3%
Ear, Nose and Throat:				
disturbance of nasal cavity / sinuses	3%	5%	3%	4%
throat symptoms	1%	<1%	2%	3%
Miscellaneous:				
disorder of mouth and tongue	0%	1%	<1%	<1%
disturbance of taste	2%	15%	20%	25%

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

Of the 3630 patients treated with IMITREX Nasal Spray in clinical trials, there was one report of a coronary vasospasm related to IMITREX administration.

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

SYMPTOMS AND TREATMENT OF OVERDOSE There have been no reports of overdosage with IMITREX (sumatriptan succinate/sumatriptan). Experience with doses outside of the recommended labelling are as follows: One patient received two 6 mg subcutaneous doses within 30 minutes and 1 patient received four 100 mg tablets within 24 hours, with no adverse events. The highest dose of IMITREX Nasal Spray administered without significant adverse effects was 20 mg given three times daily for 4 days. If overdosage with sumatriptan occurs, the patient should be monitored and standard supportive treatment applied as required. Toxicokinetics are not available. The effect of haemodialysis or peritoneal dialysis on the serum concentration of sumatriptan is unknown.

DOSAGE AND ADMINISTRATION **General:**

IMITREX (sumatriptan succinate/sumatriptan) is indicated only for the intermittent treatment of migraine headache with or without aura. Sumatriptan should not be used prophylactically. Sumatriptan may be given orally or subcutaneously or as a nasal spray. In selecting the appropriate formulation for individual patients, consideration should be given to the patient's preference for formulation and the patient's requirement for rapid onset of relief. Significant relief begins about 10-15 minutes following subcutaneous injection, 15 minutes following intranasal administration and 30 minutes following oral administration.

In addition to relieving the pain of migraine, sumatriptan (all formulations) has also been shown to be effective in relieving associated symptoms of migraine (nausea, vomiting, phonophobia, photophobia). Sumatriptan is equally effective when administered at any stage of a migraine attack. Long term (12-24 months) clinical studies with maximum recommended doses of sumatriptan indicate that there is no evidence of tachyphylaxis or medication-induced (rebound) headache.

Twenty-four hours should elapse before sumatriptan is taken following any ergotamine-containing preparation or ergot derivative (such as dihydroergotamine). Conversely, ergotamine-containing preparations or ergot derivatives should not be taken until 6 hours have elapsed following sumatriptan administration.

Tablets: The recommended adult dose of IMITREX Tablets is a single 100 mg tablet. Clinical trials have shown that approximately 50-75% of patients have headache relief within two hours after oral dosing, and that a further 15-25% have headache relief by 4 hours.

However, based on the physician's clinical judgement, a 50 mg dose may be considered adequate. The appropriateness should be based on the patient's needs and response to treatment.

If adequate relief has not been attained within 4 hours, additional doses should not be used as they are unlikely to be of clinical benefit. Sumatriptan may be taken to treat subsequent migraine attacks. Not more than 300 mg should be taken in any 24 hour period.

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

Hepatic Impairment: In patients with mild or moderate hepatic impairment, plasma sumatriptan concentrations up to two times those seen in healthy subjects have been observed. Therefore, a 50 mg dose (single tablet) may be considered in these patients (see Precautions).

Injection: IMITREX Injection should be injected subcutaneously (on the outside of the thigh) using an autoinjector. The recommended adult dose of sumatriptan is a single 6 mg subcutaneous injection.

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

If adequate relief has not been attained within 2 hours, additional doses should not be used as they are unlikely to be of clinical benefit. Sumatriptan may be taken for subsequent attacks provided a minimum of 1 hour has elapsed since the last dose. Not more than 12 mg (two 6 mg injections) should be taken in any 24 hour period.

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

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

Nasal Spray: The minimal effective single adult dose of sumatriptan nasal spray is 5 mg, the maximum recommended single dose is 20 mg.

If adequate relief has not been attained within 2 hours of initial treatment, additional doses should not be administered for the same attack as they are unlikely to be of clinical benefit. Sumatriptan may be taken for subsequent attacks provided a minimum of 2 hours has elapsed since the last dose. Not more than a total of 40 mg should be taken in any 24 hour period.

Placebo-controlled clinical trials revealed the following incidence of headache relief, defined as a decrease in migraine severity from severe or moderate to mild or no pain, within 2 hours after treatment with intranasal sumatriptan at doses of 5, 10 or 20 mg. (see Table 3 below).

Table 3: Percentage of patients with headache relief at 2 hours

Study	Placebo (n)	5 mg (n)	10 mg (n)	20 mg (n)
Study 1*	35% (40)	67%$^{\sqrt}$ (42)	67%$^{\sqrt}$ (39)	78%$^{\sqrt}$ (40)
Study 2*	42% (31)	45% (33)	66%$^{\sqrt}$ (35)	74%$^{\sqrt}$ (39)
Study 3	25% (63)	49%$^{\sqrt}$ (122)	46%$^{\sqrt}$ (115)	64%$^{\sqrt{\dagger}}$ (119)
Study 4	25% (151)	–	44%$^{\sqrt}$ (288)	55%$^{\sqrt{\dagger}}$ (292)
Study 5	32% (198)	44%$^{\sqrt}$ (297)	54%$^{*\sqrt}$ (293)	60%$^{*\sqrt{\dagger}}$ (288)

https://doi.org/10.1017/S0317167100021727 Published online by Cambridge University Press

Continued on page xxxix.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In acute **TOPAMAX** (topiramate) overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*.

Therefore, its use in overdosage is not recommended. Treatment should be appropriately supportive.

Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, including doses of over 20 g in one individual, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

Adults

The recommended total daily dose of **TOPAMAX** (topiramate) as adjunctive therapy is 200-400 mg/day in two divided doses. It is recommended that therapy be initiated at 50 mg/day, followed by titration to an effective dose. Doses above 400 mg/day have not been shown to improve responses and have been associated with a greater incidence of adverse events. The maximum recommended dose is 800 mg/day. Daily doses above 1,600 mg have not been studied.

Titration should begin at 50 mg/day. At weekly intervals, the dose should be increased by 50 mg/day and taken in two divided doses. Dose titration should be guided by clinical outcome. Some patients may achieve efficacy with once-a-day dosing.

THE RECOMMENDED TITRATION RATE IS:

	AM Dose	PM Dose
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

TOPAMAX Tablets can be taken without regard to meals. Tablets should not be broken.

Geriatrics

See PRECAUTIONS section.

Pediatrics

As yet there is limited experience on the use of **TOPAMAX** (topiramate) in children aged 18 years and under and dosing recommendations cannot be made for this patient population.

Patients with Renal Impairment

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m^2), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease

In hepatically impaired patients topiramate plasma concentrations are increased approximately 30%. This moderate increase is not considered to warrant adjustment of the topiramate dosing regimen. Initiate topiramate therapy with the same dose and regimen as for patients with normal hepatic function. The dose titration in these patients should be guided by clinical outcome, i.e., seizure control and avoidance of adverse effects. Such patients will require a longer time to reach steady-state at each dose.

PHARMACEUTICAL INFORMATION

i) Drug Substance

Proper Name: topiramate

Chemical Name: 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate

Molecular Formula: $C_{12}H_{21}NO_8S$

Molecular Weight: 339.36

Description: Topiramate is a white crystalline powder having a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate with a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3.

ii) Composition

TOPAMAX (topiramate) contains the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80 and may contain synthetic iron oxide.

iii) Stability and Storage Recommendations

TOPAMAX Tablets should be stored in tightly closed containers at controlled room temperature (15 to 30°C). Protect from moisture.

AVAILABILITY OF DOSAGE FORMS

TOPAMAX (topiramate) is available as embossed tablets in the following strengths as described below:

25 mg:	white, round, coated tablets containing 25 mg topiramate.
100 mg:	yellow, round, coated tablets containing 100 mg topiramate.
200 mg:	salmon-coloured, round, coated tablets containing 200 mg topiramate.
Supplied:	Bottles of 60 tablets with desiccant.

Product Monograph available on request

REFERENCES:

1. Faught E et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. *Neurology* 1996; 46:1684-90. **2.** TOPAMAX (topiramate) Product Monograph. Janssen-Ortho Inc., 1997. **3.** Walker MC and Sander JWAS. Topiramate: a new antiepileptic drug for refractory epilepsy. *Seizure* 1996; 5: 199-203. **4.** Shorvan SD. Safety of topiramate: adverse events and relationships to dosing. *Epilepsia* 1996; 37(Suppl) 2): S18-22.

JANSSEN-ORTHO Inc.
19 Green Belt Drive
North York, Ontario M3C 1L9

TOPAMAX® topiramate

See pages xi, vii, xxii, xxiii

Table 3: Percentage of patients with headache relief at 2 hours

Study	Placebo (n)	5 mg (n)	10 mg (n)	20 mg (n)
Study 6*	35% (100)	–	54%$^{\vee}$ (106)	63%$^{\vee}$ (202)
Study 7*	29% (112)	–	43% (109)	62%$^{\vee}$ (215)
Total	208/695	232/494	482/985	722/1195
Weighted Average	**30%**	**47%**	**49%**	**60%**
Range	**25-42%**	**44-67%**	**43-67%**	**55-78%**

Headache relief was defined as a decrease in headache severity from severe or moderate to mild or none. n = total number of patients who received treatment. *comparisons between sumatriptan doses not conducted $^{\vee}$ $p \leq 0.05$ versus placebo $^{\uparrow}$ $p \leq 0.05$ versus lower sumatriptan doses ▲ $p \leq 0.05$ vs 5 mg – not evaluated

As shown in the table above, optimal rates of headache relief were seen with the 20 mg dose. Single doses above 20 mg should not be used due to limited safety data and lack of increased efficacy relative to the 20 mg single dose.

Within the range of 5-20 mg, an increase in dose was not associated with any significant increase in the incidence or severity of adverse events other than taste disturbance (See Adverse Reactions).

The nasal spray should be administered into one nostril **only**. The device is a ready to use single dose unit and **must not** be primed before administration. Patients should be advised to read the patient instruction leaflet regarding the use of the nasal spray device before administration.

STABILITY AND STORAGE RECOMMENDATIONS IMITREX Tablets should be stored at 2°C to 30°C. IMITREX Injection and Nasal Spray should be stored between 2°C to 30°C and protected from light.

COMPOSITION IMITREX TABLETS contain 100 mg or 50 mg sumatriptan (base) as the succinate salt. Imitrex Tablets also contain lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

IMITREX INJECTION contains 6 mg sumatriptan (base) as the succinate salt in an isotonic sodium chloride solution.

IMITREX Nasal Spray contains 5 mg, 10 mg or 20 mg of sumatriptan base (as the hemisulphate salt formed *in situ*) in an aqueous buffered solution containing monobasic potassium phosphate, anhydrous dibasic sodium phosphate, sulphuric acid, sodium hydroxide, and purified water.

AVAILABILITY OF DOSAGE FORMS IMITREX TABLETS 100 mg are pink film-coated tablets available in blister packs containing 6 tablets, packed in a cardboard carton.

IMITREX TABLETS 50 mg are white film-coated tablets available in blister packs containing 6 tablets.

Each tablet contains 100 mg or 50 mg sumatriptan (base) as the succinate salt.

IMITREX INJECTION is available in pre-filled syringes containing 6 mg of sumatriptan base, as the succinate salt, in an isotonic solution (total volume = 0.5 mL). Syringes are placed in a tamper-evident carrying/disposal case. Two pre-filled syringes plus an autoinjector are packed in a patient starter kit. A refill pack is available containing 2 x 2 pre-filled syringes in a carton.

IMITREX INJECTION is also available to physicians or hospitals in a single dose vial (total volume = 0.5 mL) containing 6 mg of sumatriptan base, as the succinate salt.

IMITREX Nasal Spray 5 mg and 20 mg are each supplied in boxes of 6 nasal spray devices (3 X 2 devices). Each unit dose spray supplies 5 and 20 mg, respectively, of sumatriptan (base) as the hemisulphate salt.

Product Monograph available to physicians and pharmacists upon request. Please contact Glaxo Wellcome Inc., 7333 Mississauga Road N, Mississauga, Ontario, L5N 6L4.

REFERENCES:

1. Product Monograph of IMITREX®, Glaxo Wellcome Inc., 1996. 2. Ryan R et al. The efficacy and tolerability of sumatriptan 5, 10 and 20 mg nasal sprays in the acute treatment of repeated attacks of migraine. Presented at the 7th International Headache Congress. Sept. 16-20, 1995. Toronto, Canada. 3. Becker WJ et al. A placebo-controlled, dose-defining study of sumatriptan nasal spray in the acute treatment of migraine. Presented at the 7th International Headache Congress. Sept. 16-20, 1995. Toronto, Canada.

PAAB CCPP GlaxoWellcome

℞IMITREX®
SUMATRIPTAN NASAL SPRAY

See pages xiv, xv.