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La Société Canadienne de Neurologie

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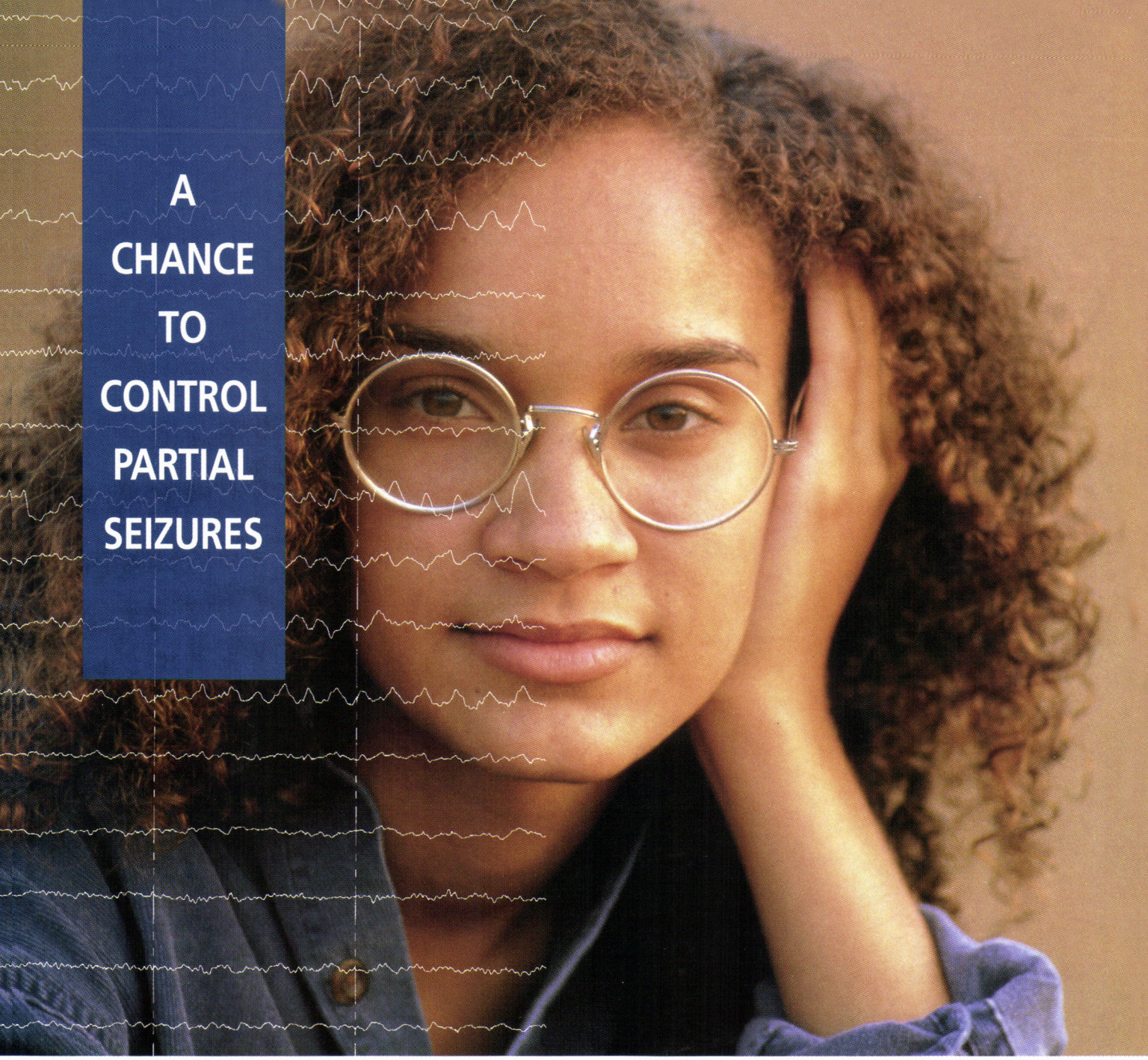

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IMPRESSIVE EFFICACY[1] WHEN SABRIL® IS ADDED TO FIRST LINE TREATMENT

- Almost 50% of patients (n=333)†, with mild to moderate partial epilepsy, became seizure-free[2]
- Significant increase in seizure control‡ in 66% of patients[3]
- No negative effects on cognitive function to impair job performance or quality of life[4]

Winner of the 1996 Prix Galien Canada for Innovative Product

† Of the 333 patients who completed > 100 days of treatment (mean dose 2.6 ± 0.5 g/day)

‡ ≥ 50% reduction in seizure frequency; N=31, at doses of 1-2 gm per day, duration of 8 weeks, as part of an initial, open phase study. However in clinical trials, Sabril reduced seizure frequency by 50% or more in approximately half of the patients studied.

Neurological function/visual disturbances should be monitored; used with caution in patients with a history of psychosis, in the elderly, in the renally impaired; there could be occupational hazards due to drowsiness; there may be a possible increase in seizures in some patients.

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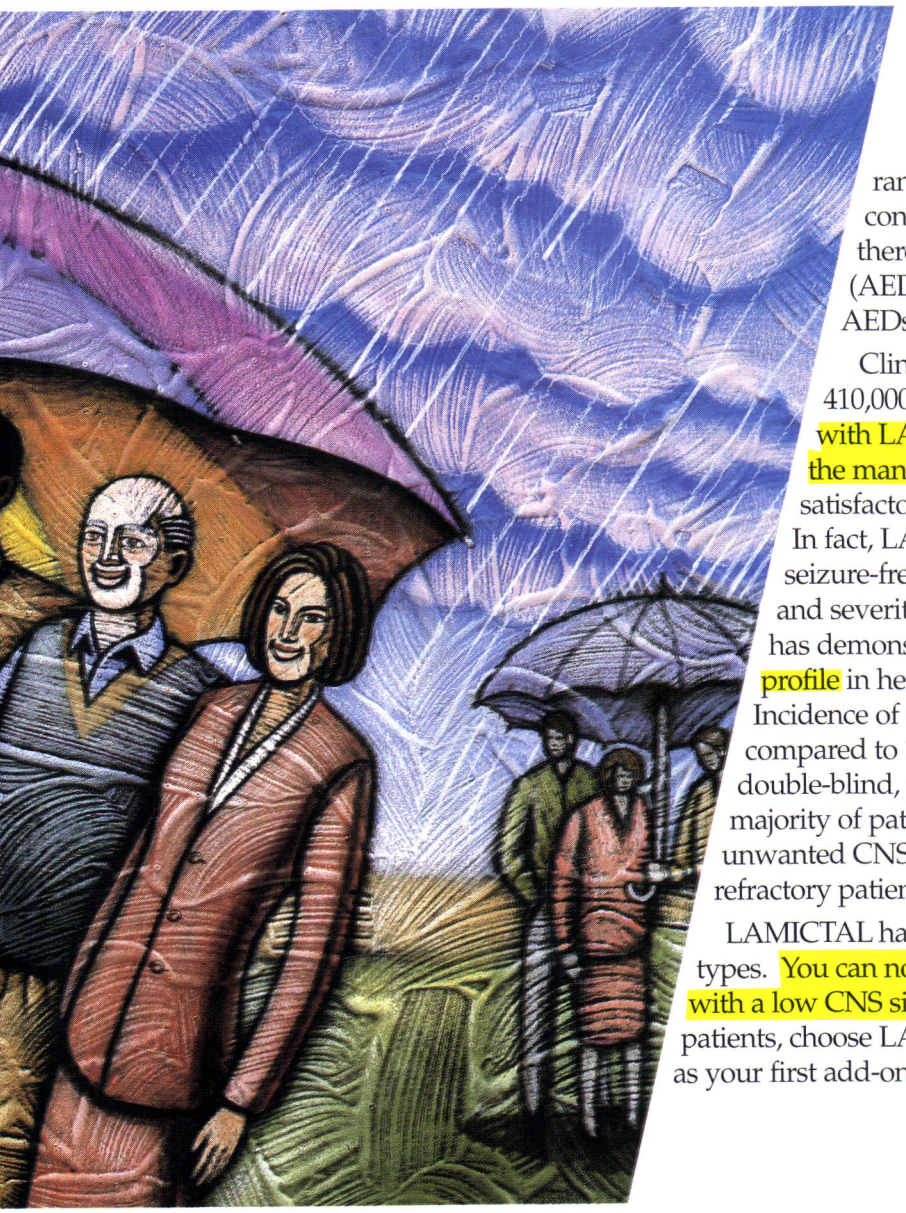
range of seizure types, side-effect profile



Many patients with epilepsy – across a wide range of seizure types – are unsatisfactorily controlled with conventional therapies.[1] Now there's LAMICTAL, a novel antiepileptic drug (AED) that is chemically unrelated to all other AEDs in current use.[1,2]

Clinical trials and worldwide experience in over 410,000 patients[3] have shown that adjunctive therapy with LAMICTAL offers a wide range of activity in the management of epilepsy for patients who are not satisfactorily controlled by conventional therapies.[1-24] In fact, LAMICTAL has been shown to render patients seizure-free[4-6,25] or to reduce seizure frequency[1,6,10,15-17,23,25] and severity in up to 65% of patients.[1,6,16,23,25] LAMICTAL has demonstrated a more favourable CNS side-effect profile in healthy volunteers compared to phenytoin.[26] Incidence of somnolence was 13% for LAMICTAL compared to 12% for placebo in pooled results of four double-blind, placebo-controlled studies.[7] Moreover, the majority of patients taking LAMICTAL will not experience unwanted CNS-related side effects.[5†] More of your refractory patients will feel better on LAMICTAL.[6,23]

LAMICTAL has activity across a wide range of seizure types. You can now offer your patients proven tolerability with a low CNS side-effect profile.[†] When faced with refractory patients, choose LAMICTAL – in 25- , 100- or 150-mg strengths – as your first add-on therapy.[‡]

Lamotrigine

℗ Lamictal®

For brief prescribing information see pages xxiii, xxiv.

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PRESCRIBING INFORMATION

SABRIL®
VIGABATRIN
Tablets 500 mg
Antiepileptic

ACTION AND CLINICAL PHARMACOLOGY

SABRIL (vigabatrin) is an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the catabolism of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the brain. The mechanism of action of vigabatrin is attributed to irreversible enzyme inhibition of GABA-T, and consequent increased levels of the inhibitory neurotransmitter, GABA.

Decreased serum levels of SGOT (ALT) and SGPT (AST) have been observed during treatment with vigabatrin and may be the result of inhibition of these transaminases by vigabatrin. The clinical significance of these findings is unknown.

The duration of effect of vigabatrin is thought to be dependent on the rate of GABA-T resynthesis rather than on the plasma concentration of vigabatrin.

Clinical Trials

In clinical trials, including double-blind, placebo-controlled studies involving 354 patients with drug-resistant complex partial seizures, vigabatrin reduced seizure frequency by 50% or more in approximately half of the patients studied.

In clinical trials involving children, the efficacy of vigabatrin was similar to that seen in adult patients with refractory partial seizures. In one study of 70 children with intractable infantile spasms, approximately 70% of the patients had a greater than 50% reduction in spasms. In this study, long-term response was observed in 75% of the children with symptomatic infantile spasms and 36% of the children with cryptogenic infantile spasms.

Pharmacokinetics

Vigabatrin is rapidly absorbed following oral administration and peak plasma concentrations are reached within two hours. Vigabatrin is widely distributed with an apparent volume of distribution slightly greater than total body water. The primary route of elimination is via the kidney, with little metabolic transformation occurring. Following a single dose, approximately 70% is excreted in the urine as unchanged drug within the first 24 hours post-dose. The plasma elimination half-life is approximately 5-8 hours in young adults and 12-13 hours in the elderly. In renal impairment the elimination is prolonged and the rate of renal clearance is directly related to creatinine clearance (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Vigabatrin does not induce the hepatic cytochrome P450 system nor is it extensively metabolized or plasma-protein bound. Administration of vigabatrin with food slightly reduces the rate, but not the extent of absorption.

INDICATIONS AND CLINICAL USE

SABRIL (vigabatrin) is indicated for the adjunctive management of epilepsy which is not satisfactorily controlled by conventional therapy.

There is insufficient data on the usefulness of vigabatrin in monotherapy at this time.

Vigabatrin should be used under close monitoring by a neurologist.

CONTRAINDICATIONS

SABRIL (vigabatrin) is contraindicated in pregnancy and lactation (see WARNINGS) and in patients with a known hypersensitivity to vigabatrin or to any components of the product.

WARNINGS

Neurotoxicity in Animals

Rat, Mouse and Dog: Safety studies carried out in the rat, mouse and dog at doses of 30 to 50 mg/kg/day and higher, caused dose-and time-dependent microvacuolation within certain white matter tracts of the brain (the cerebellum, reticular formation and thalamus in rodents and the columns of the fornix and optic tracts in dogs were most affected). The microvacuolation was caused by the separation of the outer lamellar sheath of myelinated fibres, a change characteristic of non-inflammatory intramyelinic edema.

In both the rat and dog (mouse was not tested), the intramyelinic edema was reversible after stopping the administration of vigabatrin; however, in the mouse and rat, residual changes consisting of swollen axons and mineralised microbodies were observed.

Monkey: In monkeys, the oral administration of 300 mg/ kg/day for 16 months produced minimal microvacuolation with equivocal differences between treated and control animals. Low oral absorption of vigabatrin in the monkey resulted in an actual absorbed dose of 75 mg/kg/day. In spite of the poor absorption, cerebrospinal fluid (CSF) levels of vigabatrin in the monkeys were comparable to those seen in rats treated with 300 mg/kg/day; however, GABA levels in the CSF and the brain cortex in treated monkeys were not significantly different from untreated monkeys. This finding may explain the reason for the equivocal effects, since the intramyelinic edema associated with vigabatrin treatment appears to be to increased brain GABA levels.

Evoked Potentials

Evoked potentials in animals: In the dog, studies indicate that intramyelinic edema is associated with increased latencies in somatosensory and visual evoked potentials. Magnetic resonance imaging (MRI) changes also correlated with intramyelinic edema in the fornix, thalamus and hypothalamus.

Evoked potentials in man: No increased evoked potential latencies have been observed in man. Two hundred and twenty-one patients treated for 4-5 months showed no significant evoked potential latency changes at the end of treatment as compared to baseline. MRI results in man did not show the changes observed in dogs who had intramyelinic edema.

Postmortem neuropathological changes seen in 11 patients who were treated with vigabatrin (mean duration of treatment was 28 months, and the longest treatment was 6 years) showed no myelin vacuolation in the white matter that was considered to be outside of the control range.

Although clinical trials have not revealed the type of neurotoxicity seen in animal studies, because of increased CSF GABA levels observed in humans, it is recommended that patients treated with vigabatrin be closely observed for adverse effects on neurological function, with special attention to visual disturbance.

Use in Pregnancy and Lactation: In a teratology study in the rabbit a dose-related incidence, 2% and 9%, of cleft palate was observed at doses of 150 and 200 mg/kg/day, respectively.

In animal reproductive studies neurohistopathology was not performed on the fetuses, therefore it is not known whether micro-vacuolation occurred in utero.The possibility that microvacuolation or other neurotoxicity may occur in human fetuses cannot be discarded.

PRECAUTIONS

Use in Patients with a History of Psychosis Behavioural disturbances such as aggression and psychotic episodes have been reported following initiation of vigabatrin therapy. A history of abnormal behaviour or psychosis appears to be a predisposing factor for such reactions, therefore treatment in such patients should be initiated cautiously at low doses and with frequent monitoring.

Use in the Elderly and in Patients with Renal Impairment Vigabatrin is eliminated via the kidney and caution should be exercised when administering the drug to elderly patients and to patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Use in Patients with Myoclonic Seizures As with other antiepileptic drugs, some patients may experience an increase in seizure frequency with vigabatrin. Patients with myoclonic seizures may be particularly liable to this effect.

Discontinuation of Therapy As with other antiepileptic drugs, abrupt discontinuation may lead to rebound seizures. If a patient is to be withdrawn from vigabatrin treatment, it is recommended that this be done gradually by reducing the dose over a 2 to 4 week period if possible.

Drug Interactions A gradual reduction of about 20% in plasma phenytoin concentration has been observed following add-on therapy with vigabatrin. The mechanism whereby this occurs is unknown. Limited data from clinical trials suggest that increasing the phenytoin dose to compensate may not be necessary.

Occupational Hazards Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials, the most common adverse reactions observed were drowsiness and fatigue. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that vigabatrin does not affect them adversely.

ADVERSE REACTIONS

SABRIL (vigabatrin) is generally well tolerated in epileptic patients. Adverse events are mainly CNS-related and probably a secondary consequence of increased GABA levels caused by vigabatrin. The safety of vigabatrin was evaluated in 2081 epileptic patients treated in clinical trials. The relationship of adverse events to vigabatrin therapy was not clearly established as patients were taking other antiepileptic drugs concomitantly. The most frequently reported adverse events were somnolence (12.5%), fatigue (9.2%), and weight gain (5.0%).

The following adverse events were observed in more than 1% of patients:

Adverse Events Reported By More Than 1% of Patients

Body System/ Adverse Event	Number of Patients	Incidence n=2081
Nervous		
somnolence	261	12.5
headache	80	3.8
dizziness	79	3.8
nervousness	56	2.7
depression	52	2.5
memory disturbances	47	2.3
diplopia	46	2.2
aggression	42	2.0
ataxia	39	1.9
vertigo	39	1.9
hyperactivity	37	1.8
vision abnormal	34	1.6
confusion	29	1.4
insomnia	26	1.3
impaired concentration	25	1.2
personality disorder	23	1.1
agitation	21	1.0
Digestive		
abdominal pain	34	1.6
constipation	29	1.4
vomiting	28	1.4
nausea	28	1.4
Body as a Whole		
fatigue	192	9.2
weight gain	104	5.0
asthenia	23	1.1

Adverse events reported with a frequency of less than 1% include: anxiety, emotional lability, behavioural disturbances including psychosis, irritability, tremor, abnormal gait, speech disorder, increased appetite, and dyspepsia.

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency with vigabatrin treatment (see PRECAUTIONS).

Laboratory data indicate that vigabatrin treatment does not lead to renal or hepatic toxicity. Chronic treatment with vigabatrin may be associated with a slight decrease in hemoglobin, which rarely attains clinical significance.

Pediatric Safety Safety data is available in 299 children, aged 2 months to 16 years (1 patient was 18 years of age), participating in clinical trials with vigabatrin. Relationship of adverse events to vigabatrin therapy was not clearly established as children were taking other antiepileptic drugs concomitantly.

The most frequent adverse event observed in children was "hyperactivity" (reported as hyperkinesia 7.7%, agitation 2.3%, excitation 0.3% or restlessness 0.7%), which was observed in 11.0% of children, an incidence higher than that seen in adults. Other commonly reported adverse events were somnolence (8.0%) and weight gain (3.0%).

The following adverse events were reported in children with a frequency greater than 1%:

Adverse Events Reported By More Than 1% of Pediatric Patients

Body System/ Adverse Event	Number of Patients	Incidence n=299
Nervous		
somnolence	24	8.0
hyperkinesia	23	7.7
aggression	8	2.7
insomnia	8	2.7
agitation	7	2.3
ataxia	7	2.3
emotional lability	3	1.0
headache	3	1.0
increased seizures	3	1.0
Digestive		
vomiting	6	2.0
nausea	3	1.0
increased saliva	3	1.0
Body as a Whole		
weight gain	9	3.0
fatigue	8	2.7
hypotonia	3	1.0

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific antidote. The usual supportive measures should be employed.

Two cases of SABRIL (vigabatrin) overdose have been reported. In the first case, the patient accidentally took a dose of 14 g daily for 3 days and transient vertigo and tremor were reported. In the second case, an 18-year old female took 30 g of vigabatrin and 250 mg of chlorazepate in a suicide attempt. The patient was admitted to hospital in a state of coma which lasted four days; however, the coma was considered to be due to the chlorazepate rather than vigabatrin. The patient recovered without sequelae.

DOSAGE AND ADMINISTRATION

SABRIL (vigabatrin) is intended for oral administration once or twice daily and may be taken with or without food. Sabril should be added to the patient's current antiepileptic therapy.

Instructions to the patient on the use of SABRIL are provided in the INFORMATION FOR THE CONSUMER section.

Adults The recommended starting dose is 1 g/day, although patients with severe seizure manifestations may require a starting dose of up to 2 g/day. The daily dose may be increased or decreased in increments of 0.5 g depending on clinical response and tolerability. The optimal dose range is between 2-4 g/day. Increasing the dose beyond 4 g/day does not usually result in improved efficacy and may increase the occurrence of adverse reactions.

Children The recommended starting dose in children is 40 mg/kg/day, increasing to 80 - 100 mg/kg/day depending on response. Therapy may be started at 0.5 g/day, and raised by increments of 0.5 g/day weekly depending on clinical response and tolerability.

Elderly and Renally Impaired Patients Vigabatrin is almost exclusively eliminated via the kidney and, therefore, caution should be exercised when administering the drug to the elderly, and more particularly to patients with creatinine clearance less than 60 mL/min. It is recommended that such patients be started on a lower dose of vigabatrin and observed closely for adverse events such as sedation and confusion.

Bodyweight	Daily Dose	No. Tablets / Day
10 - 15 kg	0.5 – 1 g/day	1 – 2 tablets/day
16 - 30 kg	1 – 1.5 g/day	2 – 3 tablets/day
31 - 50 kg	1.5 – 3 g/day	3 – 6 tablets/day
> 50 kg	2 – 4 g/day	4 – 8 tablets/day

AVAILABILITY OF DOSAGE FORMS

Tablets

Each SABRIL (vigabatrin) 500 mg tablet is white to off-white film-coated, oval biconvex, and imprinted "SABRIL" on one side. SABRIL is available in HDPE bottles containing 100 tablets.

Product Monograph available on request.

References:

1 Grant SM, Heel RC, A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in Epilepsy and Disorders of Motor Control. Drugs. Adis International: June 1991, Vol. 41 No. 6, pg. 889-926.

2 Arzimanoglou AA, Dumas C, Chirardi L et al. Multicentre clinical evaluation of vigabatrin (Sabril) in mild to moderate partial epilepsies. Epilepsia 1995;36(S3)

3 Reynolds BH, Ring HA Farr IN et al. Open, double-blind and long term study of vigabatrin in long term epilepsy. Epilepsia 1991;32:(4):530-538.

4 Doddrill CB, Arnett JL, Sommerville KW, Sussman NM. Effects of differing dosages of vigabatrin (Sabril) on cognitive abilities and quality of life in epilepsy. Epilepsia 1995;36(2):164-173.

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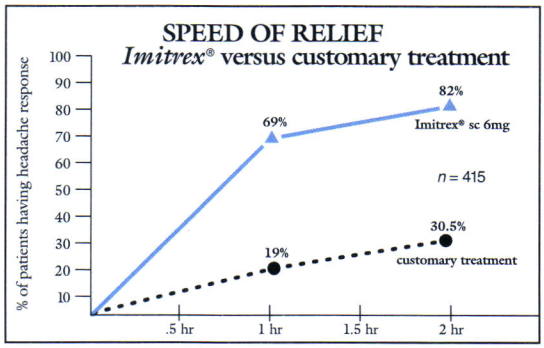
Sooner or later, every migra again. Imitrex® believes

A patient who complains about migraine is also complaining about a disrupted life. Indeed, research shows that in at least 31% of attacks, migraine sufferers cannot continue with their daily activities.[1]

That's where *Imitrex*® comes in. For most patients, *Imitrex*® can bring complete relief between 90 minutes and 2 hours, versus up to 9 hours for the usual treatments.*[2,3] *Imitrex*® treats all the symptoms of migraine.**[3-5]



Adapted from *Cephalalgia*: Schoenen 1994.[2]

Unlike conventional remedies, it has not been shown to cause medication-induced headache.[3,6-8] Its adverse events are generally well tolerated, quickly resolved and usually non-threatening when explained to the patient.***[3,7,9] *Imitrex*® may be more expensive, but over 250,000 Canadian patients continue to choose it for migraine relief.[10]

The successful use of *Imitrex*® is most likely in patients who understand its common

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Ⓟ IMITREX®

(sumatriptan succinate)

50 and 100 mg Tablet
6 mg Subcutaneous Injection and Autoinjector

THERAPEUTIC CLASSIFICATION: Migraine Therapy

PHARMACOLOGIC CLASSIFICATION: 5-HT$_1$ Receptor Agonist

CLINICAL PHARMACOLOGY

IMITREX (sumatriptan succinate) is a selective 5-hydroxytryptamine1 (5-HT$_1$) receptor agonist which has been shown to be effective in relieving migraine headache. The activity of sumatriptan at the 5-HT$_1$ receptor mediates a selective vasoconstriction within the carotid arterial circulation supplying the intracranial and extracranial tissues such as the brain and meninges. The dilatation of cranial blood vessels is thought to play an important role in the underlying mechanism of migraine. Sumatriptan (0.01-100 μM) caused a dose-dependent vasoconstriction in human isolated perfused dura mater as judged by increases in perfusion pressure. The activation of 5-HT$_1$ receptors by sumatriptan suggests the possibility that the mechanism of the anti-migraine action of sumatriptan could involve vasoconstriction of dural blood vessels. Sumatriptan has no effect at either 5-HT$_2$ or 5-HT$_3$ receptor subtypes. Clinical response begins 10-15 minutes following subcutaneous injection and around 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, 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 and subcutaneous administration with a mean bioavailability of 96% after subcutaneous dosing and 14% after oral dosing. The low oral bioavailability is mainly due to hepatic metabolism and, to a lesser extent, 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). 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) 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) 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, 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.

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

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$_\infty$	181%	130 to 252%	0.009*
C_{max}	176%	129 to 240%	0.003*

* 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) 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 table lists the incidence of adverse reactions reported in clinical trials undertaken with the oral formulation and the subcutaneous injection. Most of the events were transient in nature and resolved within 45 minutes of subcutaneous administration and 2 hours of oral administration.

Incidence of Related 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%

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). 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. 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) 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. Clinical response begins 10-15 minutes following subcutaneous injection and around 30 minutes following oral administration. Further doses of sumatriptan should not be taken if the patient shows no response to the initial treatment of a single attack. However, analgesic medication other than ergotamine-containing preparations may be used for further pain relief. Sumatriptan may be taken for subsequent attacks. Twenty-four hours should elapse before sumatriptan is taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations 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. If a patient has not responded within 4 hours, he/she is considered to be a non-responder. Rescue medication, excepting ergotamine-containing preparations may be used.

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.

Patients who have had a successful response (i.e. no pain or mild pain) may treat a later recurrence of headache with an additional 100 mg dose of sumatriptan. Not more than 300 mg should be taken in any 24 hour period.

Patients who do not respond to the first dose should not take a second dose of sumatriptan for the same attack. Sumatriptan may be taken for subsequent attacks.

Sumatriptan is equally effective when administered at any stage of a migraine attack, however, it is recommended that sumatriptan be given as early as possible after the onset of aura or headache.

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

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

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 patients continue to improve for at least 120 minutes after a single subcutaneous injection of sumatriptan. If a patient has not responded within 2 hours, he/she is considered to be a non-responder. Rescue medication excepting ergotamine-containing preparations may be used.

Patients who have had a successful response (i.e. no pain or mild pain) may treat a later recurrence of headache with one additional 6 mg dose of sumatriptan, provided 1 hour has elapsed since the first dose. This 1 hour interval is based on the knowledge of the pharmacokinetics of the drug. The maximum dose in 24 hours is two 6 mg injections (12 mg).

Patients who do not respond to the first dose should not take a second dose of sumatriptan for the same attack. But, sumatriptan may be taken for subsequent attacks.

For IMITREX injection, 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 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.

STABILITY AND STORAGE RECOMMENDATIONS IMITREX Tablets should be stored at 2°C to 30°C. IMITREX Injection 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.

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

Imitrex (sumatriptan succinate) 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.

References: 1. Edmeads J et al. Impact of migraine and tension-type headache on lifestyle, consulting behaviour, and medication use. A Canadian population survey. *Can J Neurol Sci* 1993;20:131-137. 2. Schoenen J et al. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device: Comparison with customary treatment in an open, longitudinal study. *Cephalalgia* 1994;14:55-63 3. Product Monograph of IMITREX®, Glaxo Wellcome Inc., 1993. 4. The Oral Sumatriptan International Multiple-Dose Study Group. Evaluation of a multiple-dose regimen of oral sumatriptan for the acute treatment of migraine. *Eur Neurol* 1991;31:306-313. 5. The Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. *N Engl J Med* 1991;325:316-321. 6. Sands GH. A protocol for butalbital, aspirin and caffeine (BAC) detoxification in headache patients. *Headache* 1990;30: 491-496. 7. Tansey MJB et al. Long-term experience with sumatriptan in the treatment of migraine. *Eur Neurol* 1993;33:310-315. 8. Sullivan JT et al. Psychoactivity and abuse potential of sumatriptan. *Clin Pharmacol Ther* 1992;52:635-642. 9. Salonen R. The time to onset and duration of adverse events reported after the acute treatment of migraine with sumatriptan. The 2nd International Conference European Headache Federation. June 15-18, 1994. Abstract from papers presented. Liege, Belgium. 10. Data on file. Glaxo Canada Inc., 1994. 11. Angus Reid Research, 1994. 12. Variation in Migraine Severity. Data on file. Glaxo Wellcome Inc., 1994.

PAAB CCPP **GlaxoWellcome**

Ⓟ IMITREX®
SUMATRIPTAN SUCCINATE

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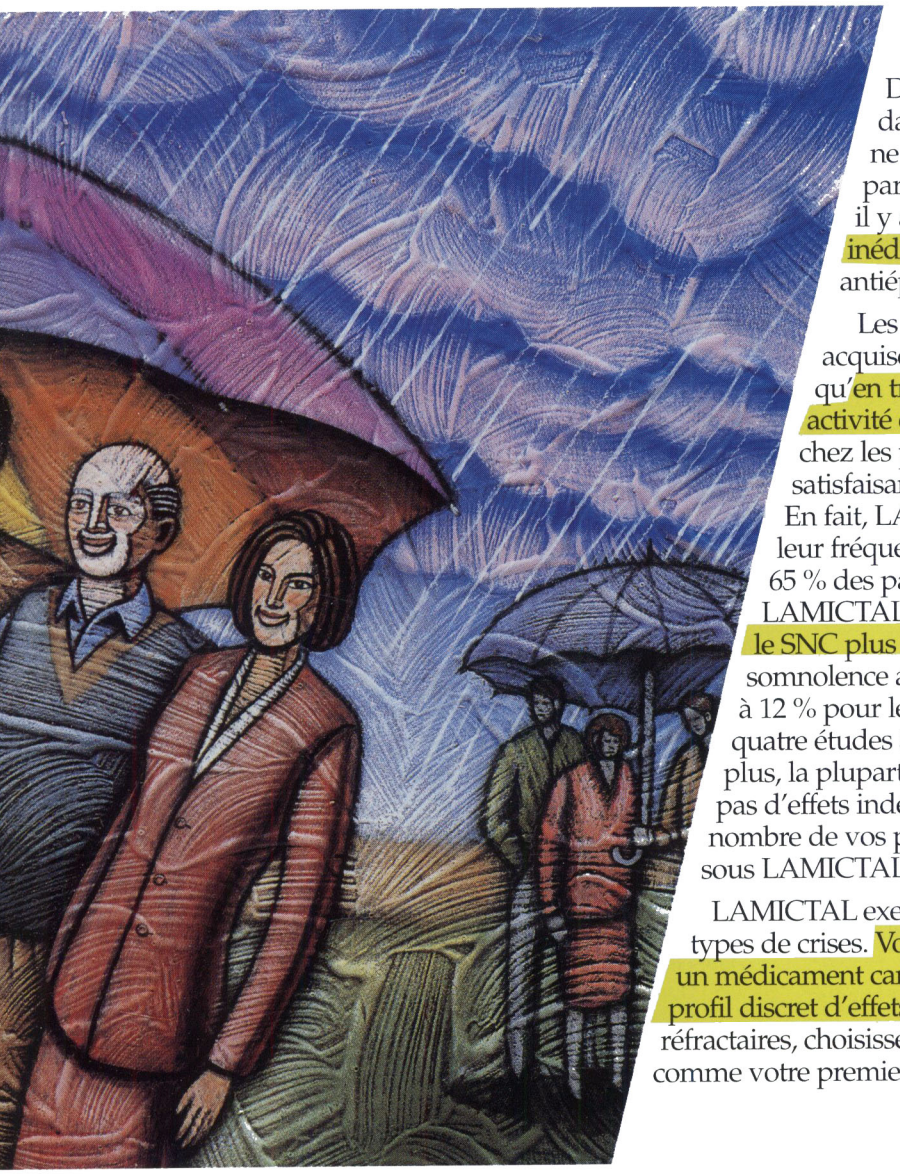
tail de types de crises avec secondaires sur le SNC



De nombreux patients souffrant d'épilepsie – dans un vaste éventail de types de crises – ne sont pas contrôlés de façon satisfaisante par les traitements conventionnels[1]. Maintenant, il y a LAMICTAL, un nouvel antiépileptique inédit sans parenté chimique avec aucun autre antiépileptique actuel[1,2].

Les essais cliniques et l'expérience mondiale acquise chez plus de 410 000 patients[3] ont montré qu'en traitement d'appoint, LAMICTAL offre une activité étendue dans le traitement de l'épilepsie chez les patients qui ne sont pas contrôlés de façon satisfaisante avec les traitements conventionnels[1-24]. En fait, LAMICTAL a supprimé les crises[4-6,25] ou diminué leur fréquence[1,6,10,15-17,23,25] et leur gravité chez jusqu'à 65 % des patients[1,6,16,23,25]. Chez des volontaires en santé, LAMICTAL a présenté un profil d'effets secondaires sur le SNC plus favorable que la phénytoïne[26]. L'incidence de somnolence a été de 13 % pour LAMICTAL par rapport à 12 % pour le placebo dans les résultats combinés de quatre études à double insu contrôlées par placebo[7]. De plus, la plupart des patients sous LAMICTAL n'éprouveront pas d'effets indésirables qui affectent le SNC[5†]. Un plus grand nombre de vos patients réfractaires se sentiront donc mieux sous LAMICTAL[6,23].

LAMICTAL exerce une activité dans un vaste éventail de types de crises. Vous pouvez maintenant offrir à vos patients un médicament caractérisé par une tolérabilité éprouvée et un profil discret d'effets indésirables sur le SNC[†]. Pour vos patients réfractaires, choisissez LAMICTAL – en 25, 100 ou 150 mg – comme votre premier traitement d'appoint[‡].

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Chapter in a book

McGeer PL, McGeer EG. Amino acid neurotransmitters. *In*: Siegel GJ, Albers RW, Agranoff BW, Katzman R, eds. Basic Neurochemistry. Boston: Little, Brown & Co., 1981: 233-254.

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