PRODUCT MONOGRAPH

Pr *Sig*-GABAPENTIN

(Gabapentin USP)

100 mg, 300 mg and 400 mg Capsules

Antiepileptic Agent

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Control No. 128255

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Sig-GABAPENTIN

(Gabapentin USP)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules 100 mg, 300 mg, and 400 mg	Lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Sig-Gabapentin (Gabapentin) is indicated:

- as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

Geriatrics (> 65 years of age):
Systematic studies in geriatrics patients have not been conducted. (See **WARNINGS AND PRECAUTIONS, Special Populations**)

Pediatrics (< 18 years of age):
The safety and efficacy in patients under the age of 18 have not been established. (See **WARNINGS AND PRECAUTIONS, Special Populations**)

CONTRAINDICATIONS

Hypersensitivity
Sig-Gabapentin (Gabapentin) is contraindicated in patients who have demonstrated hypersensitivity to the drug or to any of the components of the formulation.

WARNINGS AND PRECAUTIONS

General

Sig-Gabapentin (gabapentin) is not considered effective in the treatment of absence seizures and should therefore be used with caution in patients who have mixed seizure disorders that include absence seizures.

Discontinuation of Treatment with *Sig*-GABAPENTIN

As with other anticonvulsant agents, abrupt withdrawal is not recommended because of the possibility of increased seizure frequency. There have been post-marketing reports of adverse events such as anxiety, insomnia, nausea, pain and sweating following abrupt discontinuation of treatment (See **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**). When in the judgement of the clinician there is a need for dose reduction, discontinuation or substitution with an alternative medication, this should be done gradually over a minimum of 1 week (a longer period may be needed at the discretion of the prescriber).

Concomitant Use With Morphine

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs and symptoms of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately (See **DRUG INTERACTIONS**).

Psychomotor Impairment

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

Carcinogenesis and Mutagenesis

Gabapentin produced an increased incidence of acinar cell adenomas and carcinomas in the pancreas of male rats, but not female rats or in mice, in oncogenic studies with doses of 2000 mg/kg which resulted in plasma concentrations 14 times higher than those occurring in humans at a dose of 2400 mg/day. The relevance of these pancreatic acinar cell tumours in male rats to humans is unknown, particularly since tumours of ductal rather than acinar cell origin are the predominant form of human pancreatic cancer (See **TOXICOLOGY, Carcinogenicity Studies**).

Dependence/Tolerance

The abuse and dependence potential of gabapentin has not been evaluated in human studies. As with any CNS active drug, however, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of abuse or misuse of gabapentin.

Special Populations

Pregnant Women: No evidence of impaired fertility or harm to the fetus due to gabapentin administration was revealed in reproduction studies in mice at doses up to 62 times, and in rats and rabbits at doses up to 31 times the human dose of 2400 mg/day.

There are no adequate and well-controlled studies to establish the safety of gabapentin in pregnant women. Gabapentin should only be used during pregnancy if the potential benefit to the mother outweighs the potential risk to the fetus.

Nursing Women: Gabapentin is excreted in human milk. Because the effect on the nursing infant is unknown, caution should be exercised when gabapentin is administered to a nursing mother. Gabapentin should be used in nursing mothers only if the potential benefit to the mother outweighs the potential risks to the fetus.

Pediatrics: The safety and efficacy in patients under the age of 18 have not been established. Data in 39 patients between the ages of 12 and 18 years included in the double-blind, placebo-controlled trials showed that, at doses of 900-1200 mg/day, gabapentin was superior to placebo in reducing seizure frequency. Doses above 1200 mg/day have not been investigated. Safety data showed that the incidence of adverse events in this group of patients was similar to that observed in older individuals.

In controlled clinical trial involving patients, 3-12 years of age (N = 323), psychiatric adverse events such as emotional lability, hostility, hyperkinesia and thought disorder were reported at a higher frequency in patients treated with gabapentin compared to placebo.

Geriatrics: Systematic studies in geriatric patients have not been conducted. Adverse clinical events reported among 59 patients over the age of 65 years treated with gabapentin did not differ from those reported for younger individuals. The small number of individuals evaluated and the limited duration of exposure limits the strength of any conclusions reached about the influence of age, if any, on the kind and incidence of adverse events associated with the use of gabapentin.

As gabapentin is eliminated primarily by renal excretion, dosage adjustment may be required in elderly patients because of declining renal function (See **DOSAGE AND ADMINISTRATION, Dosing Considerations; ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Monitoring and Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of gabapentin. Gabapentin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or other antiepileptic drugs.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Commonly Observed Adverse Events
The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs, not seen at an equivalent frequency in placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, nystagmus and tremor (see Table 1).

Adverse Events Leading to Discontinuation of Treatment
Approximately 6.4% of the 543 patients who received gabapentin in the placebo-controlled studies withdrew due to adverse events. In comparison, approximately 4.5% of the 378 placebo-controlled participants withdrew due to adverse events during these studies. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue, nausea, and/or vomiting and dizziness (all at 0.6%).

Clinical Trial Adverse Drug Reactions

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

Incidence in Controlled Clinical Trials
Adults
Multiple doses of gabapentin were administered to 543 subjects with partial seizures in placebo controlled clinical trials of 12 weeks duration. In these studies, either gabapentin (at doses of 600, 900, 1200 or 1800 mg/day) or placebo was added to the patient's current antiepileptic drug therapy. Treatment-emergent signs and symptoms that occurred in at least 1% of patients participating in these studies are listed in Table 1.

TABLE 1: Treatment-Emergent Adverse Event Incidence In Placebo-Controlled Add-On Trials (Events in at Least 1% of Gabapentin Patients and Numerically More Frequent than in the Placebo Group)

	GABAPENTIN[a] N=543 %	PLACEBO[a] N=378 %
BODY AS A WHOLE		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
CARDIOVASCULAR		
Vasodilatation	1.1	0.3
DIGESTIVE SYSTEM		
Dyspepsia	2.2	0.5
Mouth or Throat Dry	1.7	0.5
Constipation	1.5	0.8
Dental Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
HEMATOLOGIC AND LYMPHATIC SYSTEM		
Leukopenia	1.1	0.5
MUSCULOSKELETAL		
Myalgia	2.0	1.9
Fracture	1.1	0.8
NERVOUS SYSTEM		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5

	GABAPENTIN[a] N=543 %	PLACEBO[a] N=378 %
Amnesia	2.2	0.0
Depression	1.8	1.8
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
RESPIRATORY SYSTEM		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
SKIN AND APPENDAGES		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
UROGENITAL SYSTEM		
Impotence	1.5	1.1
SPECIAL SENSES		
Diplopia	5.9	1.9
Amblyopia	4.2	1.1
LABORATORY DEVIATIONS		
WBC Decreased	1.1	0.5

[a] Plus background antiepileptic drug therapy.

Since gabapentin was administered most often in combination with other antiepileptic agents, it was not possible to determine which agent(s) was associated with adverse events.

Dose-Related Treatment Emergent Adverse Events

Among the treatment-emergent adverse events occurring in gabapentin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship. Patients treated with 1800 mg/day (n=54, from one controlled study) experienced approximately a two-fold increase, as compared to patients on lower doses of 600 to 1200 mg/day (n=489, from several controlled studies), in the incidence of nystagmus (20.4%), tremor (14.8%), rhinitis (13%), peripheral edema (7.4%), coordination abnormal, depression and myalgia (all at 5.6%). Adverse events were usually mild to moderate in intensity, with a median time to resolution of 2 weeks.

Data from long-term, open, uncontrolled studies shows that gabapentin treatment does not result in any new or unusual adverse events.

Other Adverse Events Observed in All Clinical Trials

Adverse events that occurred in at least 1% of the 2074 individuals who participated in all clinical trials, only some of which were placebo-controlled, are described below. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients exposed to gabapentin who experienced an event of the type cited on at least one occasion while receiving gabapentin. All reported events are included except those already listed in Table 1, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body As a Whole: *Frequent:* asthenia, malaise, facial edema; *Infrequent:* allergy, generalized edema, weight decrease, chill; *Rare:* strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System: *Frequent:* hypertension; *Infrequent:* hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; *Rare:* atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System: *Frequent:* anorexia, flatulence, gingivitis; *Infrequent:* glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; *Rare*: dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perlèche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: *Rare:* hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: *Frequent:* purpura most often described as bruises resulting from physical trauma; *Infrequent:* anemia, thrombocytopenia, lymphadenopathy; *Rare:* WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased.

Musculoskeletal System: *Frequent:* arthralgia; *Infrequent:* tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; *Rare:* costochondritis, osteoporosis, bursitis, contracture.

Nervous System: *Frequent:* vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; *Infrequent:* CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; *Rare:* choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: *Frequent:* pneumonia; *Infrequent:* epistaxis, dyspnea, apnea; *Rare:* mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: *Infrequent:* alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; *Rare:* herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: *Infrequent:* hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; *Rare:* kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain.

Special Senses: *Frequent:* abnormal vision; *Infrequent:* cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; *Rare:* eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

Post-Market Adverse Drug Reactions

Sudden, unexplained deaths in patients with epilepsy have been reported where a causal relationship to treatment with gabapentin has not been established.

Post-marketing adverse events that have been reported, which may have no causal relationship to gabapentin, include:

Blood and Lymphatic System Disorders: thromobocytopenia

Cardiac Disorders: palpitation

Ear and Labyrinth Disorders: tinnitus

Gastrointestinal Disorders: abdominal pain, diarrhea, nausea and/or vomiting, pancreatitis

General Disorders: chest pain, fever, peripheral edema

Hepatobiliary Disorders: rare or very rare cases of hepatic events including hepatitis sometimes associated with elevated liver function tests (LFTs) and jaundice. Isolated reports have been received for hepatic function abnormal, hepatitis cholestatic, liver failure, and hepatitis fulminant. In most of these reports, patients taking multiple medications, including those known to be potentially hepatotoxic, while being treated with gabapentin.

Immune System Disorders: allergic reaction including anaphylactic reaction and urticaria

Infections and Infestations: viral infection

Investigations: blood glucose fluctuations in patients with diabetes

Metabolism and Nutrition Disorders: hyponatremia

Nervous System Disorders: headache, movement disorders such as choreoathetosis, dyskinesia, dystonia

Psychiatric Disorders: confusion, emotional lability, hallucinations, insomnia

Renal and Urinary Disorders: acute kidney failure, urinary incontinence

Respiratory, Thoracic and Mediastinal Disorders: pulmonary edema

Skin and Subcutaneous Tissue Disorders: acne, alopecia, angioedema, erythema multiforme, rash, Stevens-Johnson syndrome

Adverse events following the abrupt discontinuation of gabapentin have also been reported during postmarketing experience. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

DRUG INTERACTIONS

Overview

In vitro studies were performed to investigate the potential of gabapentin to inhibit the major cytochrome P_{450} enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism, using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 μg/mL; 1 mM) was a slight degree of inhibition (14% to 30%) observed with isoform CYP2A6. No inhibition was observed with any of the other isoforms tested at gabapentin concentrations up to 171 μg/mL (approximately 15 times the C_{max} at 3600 mg/day). Gabapentin is not an inducer of cytochrome P_{450} enzymes.

At plasma concentrations associated with doses up to 3600 mg/day (Cmax 11.6 μg/mL), the highest recommended daily dose, a metabolically-based interaction between gabapentin and a drug whose clearance is dependent upon the major cytochrome P450 enzymes is unlikely.

Gabapentin is not metabolized to a significant extent in humans and does not interfere with the metabolism of commonly administered antiepileptic drugs (See **DRUG INTERACTIONS, Drug-Drug-Interactions - Antiepileptic agents**). Gabapentin also shows a low level of binding to plasma proteins (approximately 3%) and is eliminated solely by renal excretion as unchanged drug (See **ACTION AND CLINICAL PHARMACOLOGY**). Consequently, there have been few drug interactions described in which the pharmacokinetics of gabapentin or other co-administered drugs were affected to an appreciable extent.

Drug-Drug Interactions

The drug interaction data described in this subsection were obtained from studies involving healthy adults and adult patients with epilepsy:

Antiepileptic Agents

There is no interaction between gabapentin and phenytoin, valproic acid, carbamazepine, or phenobarbital. Consequently, gabapentin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the plasma concentrations of gabapentin or the other antiepileptic drugs.

Hydrocodone

Co-administration of single doses of gabapentin (125 mg to 500 mg; N= 48) and hydrocodone (10 mg; N= 50) decreased the Cmax and AUC values of hydrocodone in a dose-dependent manner relative to administration of hydrocodone alone; The Cmax and AUC values for hydrocodone were 2% and 4% lower, respectively, after administration of 125 mg gabapentin and 16% and 22% lower, respectively, after administration of 500 mg gabapentin. The mechanism for this interaction is unknown. Hydrocodone increased gabapentin AUC values by 14%. The magnitude of interaction with higher doses of gabapentin is not known.

Morphine
A literature article reported that when a 60 mg controlled release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule in healthy volunteers (N= 12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine in this study. Because this was a single dose study, the magnitude of the interaction at steady state and at higher doses of gabapentin are not known.

Naproxen
In healthy adult volunteers (N= 18), the co-administration of single doses of naproxen sodium capsules (250 mg) and gabapentin (125 mg) increased the amount of gabapentin absorbed by 12% to 15%. Gabapentin did not affect naproxen pharmacokinetic parameters in this study. These doses are lower than the therapeutic doses for both drugs. Therefore, the magnitude of interaction at steady state and within the recommended dose ranges of either drug is not known.

Oral Contraceptives
Coadministration of gabapentin with the oral contraceptive Norlestrin® does not influence the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Antacids
Coadministration of gabapentin with an aluminum and magnesium-based antacid reduces gabapentin bioavailability by up to 20%. Although the clinical significance of this decrease is not known, coadministration of similar antacids and gabapentin is not recommended.

Cimetidine
A slight decrease in renal excretion of gabapentin observed when it is coadministered with cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine has not been evaluated.

Probenecid
Renal excretion of gabapentin is unaltered by probenecid.

Drug-Food Interactions
Gabapentin is given orally with or without food.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
For urinary protein determination the sulfosalicyclic acid precipitation procedure is recommended, as false positive readings were reported with the Ames N-Multistix SG® dipstick test, when gabapentin or placebo was added to other anticonvulsant drugs.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Because gabapentin is eliminated solely by renal excretion, dosage adjustments are recommended for patients with renal impairment (including elderly patients with declining renal function) and patients undergoing hemodialysis (see **DOSAGE AND ADMINISTRATION, Special Patient Populations, Table 2**).

Adults:
Sig-Gabapentin (Gabapentin) is given orally with or without food.

Initial dose: The starting dose is 300 mg three times a day.

Dose Range: The dose may be increased, depending on the response and tolerance of the patient, using 300 or 400 mg capsules, 3 times a day up to 1800 mg/ day. In clinical trials, the effective dosage range was 900 to 1800 mg/day, given 3 times a day using 300 mg or 400 mg capsules. Dosages up to 2400 mg/day have been well tolerated in long-term open-label clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration and have been well tolerated.

Although, data from clinical trials suggest that doses higher than 1200 mg/day may have increased efficacy in some patients, higher doses may also increase the incidence of adverse events (see **ADVERSE REACTIONS**).

Maintenance: Daily maintenance doses should be given in three equally divided doses, and the maximum time between doses in a three times daily schedule should not exceed 12 hours to prevent breakthrough convulsions. It is not necessary to monitor gabapentin plasma concentrations in order to optimize gabapentin therapy. Further, as there are no drug interactions with commonly used antiepileptic drugs, gabapentin may be used in combination with these drugs without concern for alteration of plasma concentrations of either gabapentin or other antiepileptic drugs.

Discontinuation of Treatment, Dose Reduction or Initiation of Adjunctive Antiepileptic Therapy:
If gabapentin dose is reduced, discontinued or substituted with an alternate anticonvulsant or an alternate anticonvulsant is added to gabapentin therapy, this should be done gradually over a minimum of 1 week (a longer period may be needed at the discretion of the prescriber (see **WARNINGS AND PRECAUTIONS**).

Special Patient Populations:

Geriatrics and Renal Impairment: Due to the primarily renal excretion of gabapentin, the following dosage adjustments are recommended for elderly patients with declining renal function, patients with renal impairment and patients undergoing hemodialysis (see **DOSAGE AND ADMINISTRATION, Dosing Considerations; ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).

TABLE 2. Dosage of Gabapentin in Adults Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	**Total Daily Dose Range[1] (mg/day)**	**Dose Regimen[2]**
≥60	900-3600	Total daily dose (mg/day) should be divided by 3 and administered three times daily (TID)
>30-59	400-1400	Total daily dose (mg/day) should be divided by 2 and administered twice daily (BID)
>15-29	200-700	Total daily dose (mg/day) should be administered once daily (QD)
15	100-300	Total daily dose (mg/day) should be administered once daily (QD). For patients with creatinine clearance < 15 mL/min, reduce daily dose in proportion to creatinine clearance (eg, patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive)
Post-hemodialysis Supplemental Dose (mg)		
Hemodialysis	125-350	Patients on hemodialysis should receive maintenance doses as indicated and an additional post-hemodialysis dose administered after each 4 hours of hemodialysis.

[1] The table lists the recommended dose to be administered. When the recommended dose is unobtainable with the available dosage strengths, in these cases, dose selection should be based on available dosage strengths, clinical judgement and tolerability.

[2] Physician should administer the dose regimen according to the response and tolerance of the patient.

Pediatrics: Gabapentin is not indicated for use in children under 18 years of age (see **INDICATIONS; WARNINGS AND PRECAUTIONS, Special Populations**).

Hepatic Impairment: Because gabapentin is not metabolized to a significant extent in humans, no studies have been performed in patients with hepatic impairment.

Missed Dose

Physicians should instruct their patients that if a dose is missed, the next one should be taken as soon as possible. However, if it is within 4 hours of the next dose, the missed dose is not to be taken and the patient should return to the regular dosing schedule. To avoid breakthrough convulsions the maximum time between doses should not exceed 12 hours.

OVERDOSAGE

Symptoms of Overdosage

Acute, life-threatening toxicity has not been observed with gabapentin overdosages of up to 49 grams ingested at one time. In these cases, dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhea were observed. All patients recovered with supportive care.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

Treatment of Overdosage

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, reduce toxicity from overdoses.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Gabapentin exhibits antiseizure activity in mice and rats both in the maximal electroshock and in the pentylenetetrazol seizure models.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but does not interact with GABA receptors, it is not metabolized to GABA or to GABA agonists, and it is not an inhibitor of GABA uptake or degradation. Gabapentin at concentrations up to 100 μM

did not demonstrate affinity for other receptor sites such as benzodiazepine, glutamate, glycine or N-methyl-D-aspartate receptors nor does it interact with neuronal sodium channels or L-type calcium channels.

The mechanism of action of gabapentin has not yet been established, however, it is unlike that of the commonly used anticonvulsant drugs.

In vitro studies with radiolabelled gabapentin have revealed a gabapentin binding site in rat brain tissues including neocortex and hippocampus. The identity and function of this binding site remain to be elucidated.

Pharmacokinetics

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not metabolized to a significant extent in humans.

Plasma gabapentin concentrations are dose-proportional at doses of 300 to 400 mg q8h, ranging between l µg/mL and 10 µg/mL, but are less than dose-proportional above the clinical range (>600 mg q8h). There is no correlation between plasma levels and efficacy.

Gabapentin pharmacokinetics are not affected by repeated administration, and steady state plasma concentrations are predictable from single dose data. Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving antiepileptic agents.

Absorption: Following oral administration of gabapentin, peak plasma concentrations are observed within 2 to 3 hours. Absolute bioavailability of a 300 mg dose of gabapentin capsules is approximately 59%. At doses of 300 and 400 mg, gabapentin bioavailability is unchanged following multiple dose administration.

Food has no effect on the rate or extent of absorption of gabapentin.

Distribution: Less than 3% of gabapentin is bound to plasma proteins. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58+6 L (Mean ± SD). In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid are approximately 20% of corresponding steady-state trough plasma concentrations.

Metabolism: Gabapentin is not metabolized to a significant extent in humans. Gabapentin does not induce or inhibit hepatic mixed function oxidase enzymes responsible for drug metabolism and does not interfere with the metabolism of commonly coadministered antiepileptic drugs.

Excretion: Gabapentin is eliminated solely by renal excretion as unchanged drug, and can be removed from plasma by hemodialysis. Gabapentin elimination rate constant, plasma clearance and renal clearance are directly proportional to creatinine clearance. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours in subjects with normal renal function.

Table 3 summarizes the mean steady-state pharmacokinetic parameters of gabapentin capsules.

TABLE 3. Summary of Gabapentin Mean Steady-State Pharmacokinetic Parameters in Adults Following Q8H Administration

Pharmacokinetic Parameter	300 mg (N = 7)	400 mg (N=11)
C_{max} (µg/mL)	4.02	5.50
t_{max} (hr)	2.7	2.1
$t_{1/2}$ (hr)	5.2	6.1
$AUC_{(0-\infty)}$ (µg • hr/mL)	24.8	33.3
AE%[1]	NA	63.6

[1]Amount excreted in urine (% of dose)
NA = Not available

Special Populations and Conditions

Pediatrics
There are no pharmacokinetic data available in children under 18 years of age.

Geriatrics
Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL /min in subjects under 30 years of age to about 125 mL/min in subjects over 70 years of age. Renal clearance (CLr) of gabapentin also declined with age; however, this decrease can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age-related compromised renal function (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

Hepatic Insufficiency
Because gabapentin is not metabolized to a significant extent in humans, no study was performed in patients with hepatic impairment

Renal Insufficiency
In patients with impaired renal function, gabapentin clearance is markedly reduced and dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION, Dosing Considerations and Special Patient Populations, Table 2**).

Hemodialysis
In a study in anuric subjects (N=11), the apparent elimination half-life of gabapentin on non-dialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (see **DOSAGE AND ADMINISTRATION, Dosing Considerations and Special Patient Populations, Table 2**).

STORAGE AND STABILITY

Store at controlled room temperature, 15-30˚C.

SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form:
Sig-Gabapentin are available in 3 strengths, namely 100 mg, 300 mg, and 400 mg capsules.

100-mg capsules:
Hard gelatin CONI-SNAP® capsules with white opaque body and cap printed with "GA100" on one side and "> " on the other.

300-mg capsules:
Hard gelatin CONI-SNAP® capsules with yellow opaque body and cap printed with "GA300" on one side and "> " on the other.

400-mg capsules:
Hard gelatin CONI-SNAP® capsules with orange opaque body and cap printed with "GA400" on one side and "> "on the other.

Composition:

Sig-Gabapentin capsules contain:
- Gabapentin

Non-medicinal ingredients:
- Lactose
- Maize starch
- Talc

Capsule shells may contain:
- Gelatin
- Titanium dioxide
- Yellow iron oxide
- Red iron oxide.

Packaging:

100 mg:	Available in HDPE bottles of 100's and 500's. Available in blisters of 10's (cartons of 100's).
300 mg:	Available in HDPE bottles of 100's and 500's. Available in blisters of 10's (cartons of 100's).
400 mg:	Available in HDPE bottles of 100's and 500's. Available in blisters of 10's (cartons of 100's).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

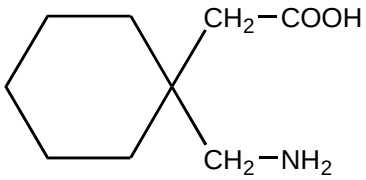
Proper name: Gabapentin USP

Chemical name: 1-(aminomethyl)cyclohexaneacetic acid

Molecular formula: $C_9H_{17}NO_2$

Molecular mass: 171.24

Structural formula:



Physicochemical properties: A white to off-white crystalline solid. Freely soluble in water and both basic and acidic and aqueous solutions. $PK_{a1} = 3.68$; $pK_{a2} = 10.70$; partition coefficient at pH 7.4 = 1.25 (Log P)

CLINICAL TRIALS

In placebo-controlled trials of 12 weeks duration in patients not satisfactorily controlled with current antiepileptic drugs, gabapentin, when added to current antiepileptic therapy, was superior to placebo in reducing the frequency of both simple and complex partial seizures and secondarily generalized tonic-clonic seizures. Further analysis of data indicated a higher efficacy for complex partial seizures and secondarily generalized tonic-clonic seizures as compared to all seizure types. Doses ranged from 900 to 1800 mg/day, with a median dose of 1200 mg/day.

Long-term, open uncontrolled studies in drug-resistant patients for periods of up to 18 months demonstrated that doses up to 3600 mg/day did not result in anything unusual in the type or frequency of adverse events.

A two-way, single-dose crossover comparative bioavailability study of *Sig*-Gabapentin Capsules 400 mg, and Neurontin™ Capsules 400 mg has been performed in healthy male volunteers in the fasting state. A summary of the bioavailability data is tabulated below.

TABLE 4: Summary Table of the Comparative Bioavailability Data
Fasted Study (1 x 400 mg)
Analyte: Gabapentin

Parameter	Geometric Mean Arithmetic Mean (%CV)		Ratio of Geometric Means (%)	90% Confidence Intervals
	Gabapentin Capsules 400 mg	Neurontin™* 400 mg		
AUC_t (ng.h/mL)	31075.5 32214.5 (26)	32520.0 33479.0 (24)	95.56	88.67 - 102.98
AUC_i (ng.h/mL)	31465.9 32607.1 (26)	32920.4 33886.1 (24)	95.58	88.73 - 102.96
Cmax (ng/mL)	3341.6 3483.1 (30)	3378.7 3501.5 (28)	98.90	92.00 - 106.32
Tmax[a] (h)	3.15 (32)	3.37 (27)	-	-
Kel[a] (h^{-1})	0.1286 (13)	0.1298 (12)	-	-
Thalf[a] (h)	5.47 (11)	5.41 (11)	-	-

* The reference product, Neurontin™ by Warner-Lambert Canada Inc., Parke-Davis div (currently Pfizer Canada Inc.) was purchased in Canada.
[a]Presented as arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

Animal Pharmacology

In Vitro Studies

The mechanism of the anticonvulsant action of gabapentin appears to be distinctly different from that of other antiepileptic drugs. Although structurally similar to GABA, gabapentin at concentrations up to 1000 µM, did not bind to GABA receptors, it was not metabolized to GABA or a GABA agonist, and it did not inhibit the uptake of GABA or its degradation by GABA-transaminase. Therefore, it does not appear to act through any known GABA mechanism, in contrast to the benzodiazepines, barbiturates, sodium valproate and other similar agents. Gabapentin (0.01-100 µM) did not interact with neuronal sodium channels or L-type calcium channels, in contrast to phenytoin, carbamazepine and sodium valproate which interact with these to promote the stability of excitable membranes. Finally, gabapentin (0.01-100 µM) did not interact with glutamate, glycine or N-methyl-D-aspartate (NMDA) receptors, in contrast to other drugs that have demonstrated anticonvulsant activity in animal models following interaction with these receptors. These neurophysiological findings indicate that gabapentin has a mechanism of action different from that of commonly used antiepileptic drugs.

Studies with purified synaptic plasma membranes from rat cerebral cortex have shown that gabapentin has high affinity for a novel peptide binding site which appears to be specific to the central nervous system. Autoradiographic studies have confirmed that there are high levels of gabapentin binding in the outer layers of the cerebral cortex and other regions of the brain with major excitatory input, such as the hippocampus and cerebellum, that are known to be associated with seizure activity.

***In Vivo* Studies**

Gabapentin has been shown to have anticonvulsant activity in animal models typically used to characterize anticonvulsant activity. Gabapentin prevented seizures induced by maximal electroshock in mice and rats in a dose-dependent manner (ED_{50}, 200 mg/kg and 9 mg/kg in mice and rats, respectively). Peak anticonvulsant effects were seen approximately 120-240 minutes post dose.

Gabapentin prevented threshold clonic convulsions induced by the convulsant pentylenetetrazol in mice (ED_{50} 450 mg/kg); the threshold dose of pentylenetetrazol needed to produce clonic seizures was significantly elevated by gabapentin.

Gabapentin treatment prevented tonic extensor seizures in mice from a variety of convulsant agents, including bicuculline, picrotoxin, strychnine and thiosemicarbazide.

Administration of gabapentin to kindled rats significantly reduced motor seizures from electrical stimulation of the brain, but had relatively little effect on the threshold for electrical after discharges at the site of stimulation.

Experiments with genetically-susceptible animals showed that gabapentin prevented generalized convulsive seizures. However, results with other genetic models indicated that gabapentin would be ineffective against photosensitive myoclonic seizures and absence seizures.

The anticonvulsant effects of gabapentin add to those of several other anticonvulsants against maximal electroshock in mice, thus suggesting that gabapentin would be useful as add-on therapy.

TOXICOLOGY

Acute Toxicity:

Gabapentin exhibited a very low order of acute toxicity in rodents and monkeys. In adult and 3 week old mice, no deaths occurred and median lethal doses (MLD's) were not identified, being greater than 8000, 2000, and 4000 mg/kg by the oral, intravenous, and subcutaneous routes, respectively. In adult and 3 week old rats, MLD's after single oral and intravenous doses were greater than 8000 and 2000 mg/kg respectively. No signs of toxicity were noted in monkeys given single oral doses of gabapentin up to 1250 mg/kg.

Chronic Toxicity:

Multidose oral administration of gabapentin was well tolerated in all species tested (mice, rats, dogs, monkeys). Decreased body weight gain was observed in rats; hypoactivity, emesis, and salivation were observed in dogs; and changes in fecal consistency were noted in all species except mice. Increased kidney weights in male rats correlated with the accumulation of hyaline droplets in renal proximal tubular epithelium. No changes were found in the kidneys of female rats. Reversible increases in liver weight were observed in rats administered gabapentin at 3000 mg/kg for 13 weeks or 1500 mg/kg for 26 weeks, and in dogs at 2000 mg/kg for 6 months. No pathologic findings were noted in mice given up to 2000 mg/kg gabapentin for 13 weeks or in monkeys given up to 500 mg/kg for 52 weeks.

In rats, plasma gabapentin concentrations increased with increasing dose. The increases were not dose proportional between 2000 and 3000 mg/kg, suggesting saturation of absorption at high doses.

Carcinogenesis and Mutagenesis:
Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell tumours was found only in male rats at the highest dose, but not in female rats or in mice of either sex. Peak plasma drug concentrations and areas under the concentration time curve in rats at 2000 mg/kg are 20 times higher than the therapeutic concentrations in humans given 1200 mg/day and are 14 times higher than the therapeutic concentrations in humans given 2400 mg/day.

The pancreatic acinar cell tumours in male rats are low grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. Furthermore, higher concentrations of gabapentin in pancreas relative to plasma have been observed in rats but not monkeys, which may account for the species-specific effects.

The relevance of these pancreatic acinar cell tumours in male rats to carcinogenic risk in humans is unclear, as the biologic characteristics of the tumours in rats are unlike those observed in humans. Ductal carcinoma comprise over 90% of all primary cancers of human exocrine pancreas, whereas acinar cell adenomas represent the primary pancreatic exocrine tumours in rats. In humans, pancreatic neoplasia exhibit local and distant tumour spread at the time of diagnosis. Metastasis occurs in 67% of cases, and survival is between 2 and 6 months after diagnosis. In contrast, pancreatic acinar cell tumours in male rats given gabapentin did not metastasize, exhibit aggressive behaviour or affect survival.

Gabapentin has no genotoxic potential. It was not mutagenic in the Ames bacterial plate incorporation assay or at the HGPRT locus in mammalian cells in the presence or absence of metabolic activation. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

Reproduction Studies:
In a fertility and general reproduction study in rats with dietary doses of gabapentin up to 2000 mg/kg, (i.e. 42 times the human dose of 2400 mg/day), no adverse effects were noted on fertility, precoital interval, pregnancy rate, gestation length, parturition, nesting/nursing behaviour, or lactation.

No teratogenicity was observed in mice given doses of gabapentin up to 3000 mg/kg, or in rats and rabbits given doses of gabapentin up to 1500 mg/kg. These doses are 62 times and 31 times, respectively, the human dose of 2400 mg/day.

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PART III: CONSUMER INFORMATION

***Sig*-Gabapentin**
(Gabapentin USP)

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

Please read this information carefully before you start to take your medicine, even if you have taken this drug before. Keep this information with your medicine in case you need to read it again. For further information or advice, please ask your doctor or pharmacist.

ABOUT THIS MEDICATION

What the medication is used for:
Sig-Gabapentin belongs to the family of medicines called antiepileptic drugs and is used for treating epilepsy (seizures).

What it does:
Gabapentin has been prescribed for you by your doctor to reduce your number of seizures.

When it should not be used:
Do not use *Sig*-Gabapentin if you are allergic to it or any of the components in the formulation (see list of components under nonmedicinal ingredients). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects while taking the drug.

What the medicinal ingredient is:
Gabapentin USP

What the important nonmedicinal ingredients are:
Non-medicinal ingredients in the capsules include lactose, maize starch, talc, gelatin, titanium dioxide, yellow iron oxide and red iron oxide.

What dosage forms it comes in:
100 mg, 300 mg, and 400 mg capsules

WARNINGS AND PRECAUTIONS

BEFORE you use *Sig*-Gabapentin talk to your doctor or pharmacist:

- All your medical conditions, especially if you have any kidney disease
- If you are taking any other medicines (prescription and nonprescription).
- If you have ever had an allergic reaction to medication, food, etc.
- If you are pregnant or thinking about becoming pregnant.
- If you are breast-feeding.
- Your habits of alcohol consumption.
- If you drive a vehicle or perform hazardous tasks during your work.

It is important for your doctor to have all of the above information before prescribing treatment and dosage.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you start or stop taking morphine. Morphine may increase the levels of *Sig*-Gabapentin in your blood. If you experience increased side effects such as drowsiness or slowed breathing while taking these drugs together, the dose of *Sig*-Gabapentin or morphine may need to be adjusted.

PROPER USE OF THIS MEDICATION

Usual dose:
- It is very important that you take *Sig*-Gabapentin exactly as your doctor has instructed.
- *Sig*-Gabapentin may be taken with or without food.
- You should not increase or decrease the amount of *Sig*-Gabapentin you are taking unless your doctor tells you to.
- Do not stop taking it abruptly because your seizures may increase.

Overdose:
If you have taken a large number of capsules all at once, contact your doctor or nearest hospital emergency department, even though you may not feel sick. Show the doctor your bottle of medication.

Missed Dose:
If you miss a dose, take it as soon as possible. However, if it is within 4 hours of your next dose do not take the missed dose and return to your regular dosing schedule. Do not allow more than 12 hours to go by between doses because your seizures may increase. If that happens, consult your doctor as soon as possible.

REMINDER: This medicine has been prescribed only for you. Do not give it to anybody else, as they may experience undesirable effects, which may be serious.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

This is not a complete list of side effects. For any unexpected effects while taking Sig-Gabapentin*, contact your doctor or pharmacist.*

Like all medications, *Sig*-Gabapentin can cause some side effects. You may not experience any of them. For most patients these side effects are likely to be minor and temporary. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may need to be adjusted.

- Call your doctor immediately if your seizures get worse.

- Stop taking the drug and contact your doctor immediately if you experience any severe, unusual or allergic reactions (including skin rash or redness and/or breathing difficulties).
- When you first begin taking *Sig*-Gabapentin you may experience some side effects such as drowsiness, dizziness, lack of muscular coordination and fatigue. Consult your doctor if you experience any of these, as the dose may have to be adjusted.
- If your epilepsy is not controlled, it is very important not to perform any potentially hazardous tasks, such as driving a car or operating dangerous machines. If your epilepsy is controlled, it is important to refrain from potentially dangerous tasks until you are sure this medication does not affect your mental alertness or physical coordination.
- Avoid alcoholic drinks while taking *Sig*-Gabapentin.
- The following side effects have been reported since gabapentin has been marketed. At this time it is unknown if these side effects were caused by the use of gabapentin. If you develop any of the following side effects tell your doctor immediately: skin rash or redness, blood glucose fluctuations for patients suffering from diabetes, chest pain, shortness of breath, hallucinations, unusual muscle movement or tone, heart palpitations, ringing or whistling in the ear, unusual changes in mood, sleeplessness, jaundice (yellowing of skin), dark urine, nausea and/or vomiting, swelling of legs, ankles or feet, and inability to control urination.
- The following side effects have been reported when gabapentin is abruptly stopped: anxiety, sleeplessness, nausea, pain, and sweating.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	• Swelling of legs, ankles or feet	✓		
Uncommon	• Heart palpitations		✓	
	• Chest pains		✓	
	• Jaundice (yellowing of skin)		✓	
	• Dark urine		✓	
	• Unusual muscle movement or tone		✓	
	• Hallucinations		✓	
	• Unusual changes in mood		✓	
	• Shortness of breath		✓	

This is not a complete list of side effects. If you have any unexpected effects while taking Sig-Gabapentin, *contact your doctor or pharmacist.*

HOW TO STORE IT

- Keep all medicines out of the reach of children.
- Store *Sig*-Gabapentin capsules at room temperature (15°C to 30°C).
- Do not use this medicine after the expiry date, which is printed on the package label.
- If your doctor tells you to stop taking *Sig*-Gabapentin, or if you find that they have passed their expiry date, please return any left over medicine to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

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

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
On-line: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Health Products and Food Branch
Heath Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Sigmacon Lifesciences Inc., at: 1-800-898-7455.

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