

PRODUCT MONOGRAPH

Pr APO-GABAPENTIN

**Gabapentin Capsules
Apotex Standard
100 mg, 300 mg and 400 mg**

**Gabapentin Tablets USP
600 mg and 800 mg**

Antiepileptic Agent

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Control #: 164269**

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Pr **APO-GABAPENTIN**
(gabapentin)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Capsules 100 mg, 300 mg and 400 mg	magnesium stearate, croscarmellose sodium, talc, edible blue ink, gelatin, red iron oxide (400 mg capsules only), silicon dioxide, sodium lauryl sulphate, titanium dioxide, and yellow iron oxide (300 and 400 mg capsules only).
Oral	Tablets 600 mg and 800 mg	copovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, purified water and titanium dioxide.

INDICATIONS AND CLINICAL USE

Adults

APO-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 geriatric 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

APO-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

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 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.

Serious Dermatological Reactions

There have been post-marketing reports of Stevens-Johnson syndrome (SJS) and Erythema multiforme (EM) in patients during treatment with gabapentin. Should signs and symptoms suggest SJS or ER, gabapentin should be discontinued immediately. (see Post-Marketing Adverse Drug Reactions)

Hypersensitivity

There have been reports in the post-marketing experience of hypersensitivity including systemic reactions and cases of urticaria and angioedema. (see Post-Marketing Adverse Drug Reactions)

Severe, life-threatening, systemic hypersensitivity reactions such as Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported in patients taking antiepileptic drugs including gabapentin.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Gabapentin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Prior to initiation of treatment with gabapentin, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity such as fever or lymphadenopathy may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

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.

Safety 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 to 1200 mg/day, the incidence of adverse events in this group of patients was similar to that observed in older individuals.

In controlled clinical trials involving patients, 3 to 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; ACTION 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.

Psychiatric

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

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 %
<u>Body as a Whole</u>		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
<u>Cardiovascular</u>		
Vasodilatation	1.1	0.3
<u>Digestive System</u>		
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
<u>Hematologic and Lymphatic Systems</u>		
Leukopenia	1.1	0.5
<u>Musculoskeletal</u>		
Myalgia	2.0	1.9
Fracture	1.1	0.8
<u>Nervous System</u>		
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
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3

	GABAPENTIN^a n = 543 %	PLACEBO^a n = 378 %
<u>Respiratory System</u>		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
<u>Skin and Appendages</u>		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
<u>Urogenital System</u>		
Impotence	1.5	1.1
<u>Special Senses</u>		
Diplopia	5.9	1.9
Amblyopia	4.2	1.1
<u>Laboratory Deviations</u>		
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, face 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, suicide attempt, 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.

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.

Table 2 presents estimated reporting rates of adverse events not described elsewhere in the label, based on post-market spontaneous adverse event reports. The percentages shown are calculated as the number of adverse events reported per 100 patient-years exposure to gabapentin. It should be noted that a causal relationship between gabapentin and the emergence of these events has not been clearly established. Furthermore, because these adverse events are reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency. Due to variations in the methods of estimation of patient exposure, and differences in potential biases

associated with voluntary reporting, these estimates should not be used to compare safety profiles between drugs.

Table 2. Number of Reported Gabapentin Cases from 01 January 2000 - 30 September 2011

<i>Adverse Event</i>	<i>Estimated Reporting Rate</i>			
	<i>Reported Commonly ≥1 %</i>	<i>Reported Uncommonly <1% and ≥0.1%</i>	<i>Reported Rarely <0.1% and ≥0.01%</i>	<i>Reported Very Rarely <0.01%</i>
Gastrointestinal Disorders:				
Pancreatitis				X
Hepatobiliary Disorders:				
Hepatitis				X
Hepatic function abnormal				X
Hepatitis cholestatic				X
Hepatitis fulminant				X
Jaundice				X
Immune System Disorders:				
Anaphylactic reaction				X
Hypersensitivity				X
Investigations:				
Blood creatine phosphokinase increased				X
Blood glucose abnormal				X
Musculoskeletal and Connective Tissue Disorders:				
Rhabdomyolysis				X
Renal and Urinary Disorders:				
Renal failure acute				X
Reproductive system and breast disorders:				
Gynaecomastia				X
Respiratory Thoracic and Mediastinal Disorders:				
Pulmonary oedema				X
Skin and Subcutaneous Tissue Disorders:				
Angioedema				X
Drug rash with eosinophilia and systemic symptoms				X
Stevens-Johnson syndrome				X

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 P₄₅₀ 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 P₄₅₀ enzymes.

At plasma concentrations associated with doses up to 3600 mg/day (C_{max} 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 C_{max} and AUC values of hydrocodone in a dose-dependent manner relative to administration of hydrocodone alone. The C_{max} 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, co-administration 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 sulfosalicylic 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 APO-GABAPENTIN (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 3**).

Adults:

APO-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, or 600 or 800 mg tablets 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, or 600 mg or 800 mg tablets. 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 APO-GABAPENTIN therapy. Further, as there are no drug interactions with commonly used antiepileptic drugs, APO-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 APO-GABAPENTIN dose is reduced, discontinued or substituted with an alternate anticonvulsant or an alternate anticonvulsant is added to APO-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 3 Dosage of APO-GABAPENTIN in Adults Based on Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose Range¹ (mg/day)	Dose Regimen²
≥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)		
Hemo-dialysis	125-350	Patients on hemodialysis should receive maintenance doses as indicated and an additional post-hemodialysis dose administered after each 4 hours of hemodialysis.
<p>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.</p> <p>2 Physician should administer the dose regimen according to the response and tolerance of the patient.</p>		

Pediatrics: APO-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 overdoses 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.

In managing overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of overdose.

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 1 $\mu\text{g}/\text{mL}$ and 10 $\mu\text{g}/\text{mL}$, 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 \pm 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 4 summarizes the mean steady-state pharmacokinetic parameters of gabapentin capsules.

Table 4. 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 _½ (hr)	5.2	6.1
AUC _(0-∞) (µg•hr/mL)	24.8	33.3
AE% ¹	N/A	63.6

¹ Amount excreted in urine (% of dose)
N/A = 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 (CL_r) 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 3**).

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 3**).

STORAGE AND STABILITY

Capsules: Store at room temperature 15-30°C (59-86°F), in tightly closed and light resistant containers.

Tablets: Store at room temperature 15-30°C (59-86°F). Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-GABAPENTIN Capsules 100 mg: Each white opaque cap with white opaque body hard gelatin capsule, with white to off-white powder fill, imprinted "APO 100", contains 100 mg of gabapentin. Available in unit dose blister packages of 100 (10x10) capsules and in HDPE bottles of 100 and 500 capsules

APO-GABAPENTIN Capsules 300 mg: Each yellow opaque cap with yellow opaque body hard gelatin capsule, with white to off-white powder fill, imprinted "APO 300", contains 300 mg of gabapentin. Available in unit dose blister packages of 100 (10x10) capsules and in HDPE bottles of 100 and 500 capsules.

APO-GABAPENTIN Capsules 400 mg: Each orange opaque cap with orange opaque body hard gelatin capsule, with white to off-white powder fill, imprinted "APO 400", contains 400 mg of gabapentin. Available in unit dose blister packages of 100 (10x10) capsules and in HDPE bottles of 100 and 500 capsules.

APO-GABAPENTIN Tablets 600 mg: Each white, oval film-coated tablet, scored and engraved "GAB 600" on one side, "APO" on the other side contains 600 mg of gabapentin. Available in bottles of 100.

APO-GABAPENTIN Tablets 800 mg: Each white, oval film-coated tablets, scored and engraved "GAB 800" on one side, "APO" on the other side contains 800 mg of gabapentin. Available in bottles of 100.

Composition:

Capsules: In addition to gabapentin, each hard gelatin capsule contains the non-medicinal ingredients: magnesium stearate, croscarmellose sodium and talc. The hard gelatin capsule shells contain edible blue ink, gelatin, red iron oxide (400 mg capsules only), silicon dioxide, sodium lauryl sulphate, titanium dioxide, and yellow iron oxide (300 and 400 mg capsules only).

Tablets: In addition to gabapentin, each tablet contains the non-medicinal ingredients: copovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, purified water and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

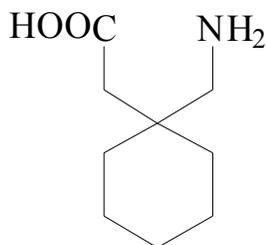
Drug Substance

Proper Name: Gabapentin

Chemical Name: 1) Cyclohexaneacetic acid, 1-(aminomethyl)-
2) 1-(Amino-methyl)cyclohexaneacetic acid

Molecular formula and molecular weight: $C_9H_{17}NO_2$, 171.24

Structural Formula:



Physicochemical properties: A white to off-white crystalline powder, that is odorless, non-hygroscopic and free of foreign particulate matter. Freely soluble in water, glacial acid, 0.1N HCl and 0.1N NaOH, soluble in chloroform, slightly soluble in dimethylacetamide and methanol, very slightly soluble in acetone, ethanol and 2-propanol, practically insoluble in ether, and insoluble in toluene. Solubility in water at pH 7.4 exceeds 10%, and at pH 3.7 and 10.7 far exceeds 20 mg/mL. Therefore, the minimum solubility within the physiological pH range is approximately 100 mg/mL. The melting point range is 162 to 167°C. The isoelectric point is 7.14, where it exists as a zwitterion together with the un-ionized form. The $pK_{a1} = 3.68$ and $pK_{a2} = 10.70$, the $K_d = -1.10$ (log P between n-octanol and aqueous pH 7.4 buffer), and the pH = 6.8 to 7.4 (in 2% aqueous solution).

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of gabapentin was measured and compared following oral administration of a single 400 mg dose of APO-GABAPENTIN (gabapentin) 400 mg capsules or Neurontin (gabapentin) 400 mg capsules, under fasting conditions. The results from measured data are summarized in Table 4 as follows:

Table 4: Summary Table of the Comparative Bioavailability Data Gabapentin (Dose: 1 x 400 mg) From Measured Data			
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Test#	Reference† Capsules	
AUC _T (ng•hr/mL)	27255 27797 (20)	27750 28208 (18)	98.2
AUC _I (ng•hr/mL)	27945 28483 (19)	28453 28923 (18)	98.3
C _{max} (ng/mL)	3014 3086 (22)	3153 3202 (18)	95.6
T _{max} (hr)*	2.54 (37)	3.06 (31)	-
t _{1/2} (hr)*	5.57 (19)	5.60 (22)	-
#	Apo-Gabapentin Capsules		
*	Arithmetic means (CV%).		
**	Based on the least squares estimate.		
†	Neurontin® is manufactured by Parke-Davis (a Division of Warner-Lambert Company, Morris Plains, New Jersey, U.S.A.), and was purchased in the U.S.A.		

A randomized, single-dose, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on nine healthy male and eleven healthy female volunteers (range 21 to 52 years of age). The rate and extent of absorption of gabapentin was measured and compared following a single oral dose of APO-GABAPENTIN 600 mg tablets and NEURONTIN[®] 600 mg tablets. The results from measured data are summarized in the following table.

Table 5: Summary Table of the Comparative Bioavailability Data Gabapentin (1 x 600 mg Tablets) From Measured Data -- Fasting Conditions Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test**	Reference†	Ratio of Geometric Means (%)##	90% Confidence Interval (%)##
AUC _T (mcg x hr/mL)	47.1521 48.580 (25.2%)	47.8967 49.763 (27.3%)	98.4	91.1 – 106
AUC _I (mcg x hr/mL)	47.9694 49.441 (25.3%)	48.7768 50.567 (26.7%)	98.3	91.3 – 106
C _{max} (mcg/mL)	4.8749 5.128 (38.3%)	4.9323 5.245 (38.0%)	98.8	90.1 - 108
T _{max} # (hrs)	2.975 (39.9)	2.978 (32.3)		
T _½ # (hrs)	8.684 (34.9)	8.185 (38.4)		
** Apo-Gabapentin Tablets # Arithmetic means (CV%). ## Based on the least squares estimate. † Neurontin* Tablets are manufactured by Pfizer Canada Inc., Licensee, and were purchased in Canada. * T.M. Warner-Lambert Company				

A randomized, single-dose, 2-way crossover comparative bioavailability study, conducted under non-fasting (fed) conditions, was performed on seven healthy male and thirteen healthy female volunteers (range 19 to 55 years of age). The rate and extent of absorption of gabapentin was measured and compared following a single oral dose of APO-GABAPENTIN 600 mg tablets and NEURONTIN® 600 mg tablets. The results from measured data are summarized in the following table.

Table 6: Summary Table of the Comparative Bioavailability Data Gabapentin (1 x 600 mg Tablets) From Measured Data -- Non-Fasting Conditions Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test**	Reference†	Ratio of Geometric Means (%)##	90% Confidence Interval (%)##
AUC _T (mcg x hr/mL)	53.5333 54.299 (17.6)	52.6971 53.201 (14.1)	102	96.2 – 107
AUC _I (mcg x hr/mL)	54.1992 54.981 (17.6)	53.2750 53.785 (14.1)	102	96.4 – 107
C _{max} (mcg/mL)	5.3602 5.414 (14.7)	5.4863 5.557 (16.8)	97.7	93.5 – 102
T _{max} # (hrs)	3.631 (33.8)	3.303 (38.2)		
T _½ # (hrs)	8.536 (20.7)	7.978 (27.3)		
** Apo-Gabapentin Tablets # Arithmetic means (CV%). ## Based on the least squares estimate. † Neurontin* Tablets are manufactured by Pfizer Canada Inc., Licensee, and were purchased in Canada. * T.M. Warner-Lambert Company				

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.

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.

REFERENCES

- 1) Schmidt B. Potential antiepileptic drugs: Gabapentin. In: Levy R, Mattson R, Meldrum B, et al Eds. Antiepileptic Drugs. Raven Press Ltd, 3rd edition, 1989;925-35.
- 2) Chadwick D. Gabapentin: Profile of a new antiepileptic drug. In: McLean J, Ed. Antiepileptic drug research: the second fifty years. Proc Symp, Jerusalem, September 6, 1987. Princeton, Excerpta Medica 1988;24-28.
- 3) Bartoszyk G, Meyerson N, Reimann W et al. Gabapentin. In: Meldrum B, Porter R, Eds. New anticonvulsant drugs. John Libbey & Co., 1986;147-163.
- 4) UK Gabapentin Study Group. Gabapentin in partial epilepsy. Lancet 1990;335:1114-1117.
- 5) Bauer G, Bechinger D, Castell M, et al. Gabapentin in the treatment of drug-resistant epileptic patients. Advances in Epileptology 1989;17:219-221.
- 6) Crawford P, Ghadiali E, Lane R, et al. Gabapentin as an antiepileptic drug in man. J Neuro Neurosurg Psychiatry 1987;50:682-686.
- 7) Vollmer K, Anhut H, Thomann P, et al. Pharmacokinetic model and absolute bioavailability of the new anticonvulsant gabapentin. Advances in Epileptology 1989;17:209-211.
- 8) Kondo T, Fromm G, Schmidt B. Comparison of gabapentin with other antiepileptic and GABAergic drugs. Epilepsy Res 1991;8:226-231.
- 9) Reimann W. Inhibition by gaba, baclofen and gabapentin of dopamine release from rabbit caudate nucleus: Are there common or different sites of action? Eur J Pharmacol 1983;94:341-344.
- 10) Schlicker E, Reimann W, Gôthert M. Gabapentin decreases monoamine release without affecting acetylcholine release in the brain. Arzneim.-Forsch/Drug Res 1985;35:1347-1349.
- 11) New trends in epilepsy management: The role of gabapentin: edited by D. Chadwick, 1993; Royal Society of Medicine Services International Congress and Symposium Series No. 198, published by Royal Society of Medicine Services Limited, London, New York.
- 12) The US Gabapentin Study Group No. 5. Gabapentin as add-on therapy in refractory partial epilepsy: A double-blind, placebo-controlled, parallel-group study. Neurology 1993;2292-2298.
- 13) Chadwick, D. Drug Profile: Gabapentin. Lancet 1994;343:89-91.

- 14) Bruni J. Outcome evaluation of gabapentin as add-on therapy for partial seizures. *Can J Neurol Sci* 1998;25:134-140.
- 15) McLean MJ, Morrell MH, Willmore LJ, et al. Safety and tolerability of gabapentin as adjunctive therapy in a large, multicenter study. *Epilepsia* 1999;40(7):965-972.
- 16) Product Monograph – Neurontin* (gabapentin) capsules and tablets. Pfizer Canada Inc. Date of revision: February 21, 2013, Control No.: 161668.

PART III: CONSUMER INFORMATION

**^{Pr}APO-GABAPENTIN
(gabapentin)**

This leaflet is part III of a three-part “Product Monograph” published when APO-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 APO-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:

APO-GABAPENTIN (gabapentin) belongs to the family of medicines called antiepileptic drugs and is used for treating epilepsy (seizures).

What it does:

APO-GABAPENTIN has been prescribed for you by your doctor to reduce your number of seizures.

When it should not be used:

Do not use APO-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

What the important nonmedicinal ingredients are:

APO-GABAPENTIN capsules contain the following non-medicinal ingredients: magnesium stearate, sodium croscarmellose and talc. The hard gelatin capsule shells contain edible blue ink, gelatin, red iron oxide (400 mg capsules only), silicon dioxide, sodium lauryl sulphate, titanium dioxide, and yellow iron oxide (300 and 400 mg capsules only).

APO-GABAPENTIN tablets contain the following non-medicinal ingredients: copovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, purified water and titanium dioxide.

What dosage forms it comes in:

APO-GABAPENTIN is available in both capsules (containing 100 mg, 300 mg and 400 mg of gabapentin) and in tablets (containing 600 mg or 800 mg of gabapentin).

WARNINGS AND PRECAUTIONS

BEFORE you use APO-GABAPENTIN tell 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 APO-GABAPENTIN in your blood. If you experience increased side effects such as drowsiness or slowed breathing while taking these drugs together, the dose of APO-GABAPENTIN or morphine may need to be adjusted.

PROPER USE OF THIS MEDICATION

Usual dose:

- It is very important that you take APO-GABAPENTIN exactly as your doctor has instructed.
- APO-GABAPENTIN may be taken with or without food.
- You should not increase or decrease the amount of APO-GABAPENTIN you are

IMPORTANT: PLEASE READ

- 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 tablets or 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 APO-GABAPENTIN, contact your doctor or pharmacist.

Like all medications, APO-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 APO-GABAPENTIN you may experience some side effects such as drowsiness, dizziness, lack of muscle 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 APO-GABAPENTIN.
- The following side effects have been reported since gabapentin has been marketed. At this time it is unknown whether or not 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.
- Please see your doctor immediately if you develop fever, rash, swollen lymph nodes, hives, sore mouth, sore eyes or swelling of lips or tongue, particularly in the first six weeks of therapy.
- 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 seek immediate medical attention
		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		*	

IMPORTANT: PLEASE READ

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

	tone; unexplained muscle pain or tenderness or weakness			
	Hallucinations			*
	Unusual changes in mood		*	
	Shortness of breath		*	
	Seizures			*
	Severe, unusual or allergic reactions (fever, rash, swollen lymph nodes, hives, sore mouth, sore eyes or swelling of lips or tongue)			*

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

HOW TO STORE IT

- Capsules: Store at room temperature 15-30°C (59-86°F), in tightly closed and light resistant containers.
- Tablets: Store at room temperature 15-30°C (59-86°F). Protect from moisture.
- Do not use this medicine after the expiry date, which is printed on the package label.
- If your doctor tells you to stop taking APO-GABAPENTIN, or if you find that they have passed their expiry data, please return any left over medicine to you pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at:
<http://www.apotex.ca/products>.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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