PRODUCT MONOGRAPH

[Pr]ratio-GABAPENTIN

(Gabapentin Capsules 100 mg, 300 mg and 400 mg)
and
(Gabapentin Tablets 600 mg and 800 mg)

Antiepileptic Agent

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Date of Preparation:
November 9, 2004

Control #: 095105

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(Gabapentin Capsules 100 mg, 300 mg and 400 mg)
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THERAPEUTIC CLASSIFICATION

Antiepileptic

ACTION AND CLINICAL PHARMACOLOGY

Gabapentin exhibits anti-seizure 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 radiolabeled 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

Adults:

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.

Gabapentin 600 mg and 800 mg tablets are bioequivalent to two 300 mg capsules and two 400 mg capsules, respectively. The results of a single-dose, two-way crossover, comparative bioavailability study in the fasted state comparing gabapentin 600 mg tablets and 2 x 300 mg gabapentin capsules are summarized below.

TABLE 1. Summary Table of the Comparative Bioavailability Data
Gabapentin 600 mg tablets and gabapentin 2 x 300 mg capsules

Parameter	Gabapentin				% Ratio of Geometric Means
	600 mg tablets		2 x 300 mg capsules		
	Arithmetic (CV%)	Geometric	Arithmetic (CV%)	Geometric	
	Mean values from measured data				
AUC_T (μg·hr/mL)	51.3 (31.8)	48.9	46.8 (28.4)	45.2	108
AUC_I (μg·hr/mL)	52.5 (30.2)	50.4	47.7 (27.1)	46.1	109
C_{max} (μg/mL)	4.94 (30.9)	4.71	4.48 (25.9)	4.35	108
T_{max} (h)	3.2 (27.3)	-	3.5 (34.1)	-	-
$T_{1/2}$ (h)	15.6 (88.2)	-	15.4 (90.5)	-	-

Gabapentin elimination from plasma is best described by linear pharmacokinetics. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours in subjects with normal renal function.

Plasma gabapentin concentrations are dose-proportional at doses of 300 to 400 mg q8h, ranging between 1 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 is not appreciably metabolized in humans, 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 creatine clearance.

Gabapentin does not induce or inhibit hepatic mixed function oxidase enzymes responsible for drug metabolism, does not interfere with the metabolism of commonly coadministered antiepileptic drugs, and is minimally bound to plasma proteins.

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

A comparative bioavailability study of GABAPENTIN 400 mg capsules was performed. Pharmacokinetic and bioavailability data were measured in 30 volunteers in the fasting state. The results are summarized as follows in Table 2.

TABLE 2 - Summary Table of the Comparative Bioavailability Data of GABAPENTIN 400 mg capsules versus NEURONTIN 400 mg capsules

A single 400 mg (1 × 400 mg capsule) oral administration in the fasting state

Measured Data Parameter	Geometric Mean Arithmetic Mean (C.V.%)		Ratio of Geometric Mean
	Test	Reference-1	
AUC_T (ng.h/mL)	32426.2 33544.1(26.46)	33541.8 34319.8 (21.99)	97
AUC_∞ (ng.h/mL)	32960.1 34023.1 (25.82)	34051.7 34818.4 (21.65)	97
C_{max} (ng/mL)	3189.8 3297.1 (25.13)	3284.9 3357.5 (20.66)	97
T_{max} (h)	3.42 (32.84)	3.10	---
$T_{1/2el}$ (h)	6.67 (23.11)	6.65 (23.43)	---

⁂Neurontin™ is manufactured by Parke-Davis, Division of Warner-Lambert Canada Inc. and purchased in Canada.
For T_{max} and $T_{1/2el}$, the arithmetic mean only is presented.

The test formulation (GABAPENTIN 600 mg tablets) is judged to be bioequivalent to the Canadian Reference Product (Neurontin™ 600 mg tablets, Parke-Davis, Division of Warner-Lambert Company Canada Inc., Scarborough, Ontario, Canada) on the basis of the C_{max} and AUC parameters.

A comparative bioavailability study comparing GABAPENTIN 600 mg tablets with Neurontin™ 600 mg tablets manufactured by Parke-Davis, Division of Warner-Lambert Canada Inc. was conducted in healthy male adults under fasting and fed conditions. Bioavailability data were measured and the results are summarized in tables 3A and 3B.

TABLE 3A - SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA FOR A SINGLE DOSE STUDY UNDER FASTED CONDITIONS

Gabapentin
(A single 600 mg dose - 1 X 600 mg)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	GABAPENTIN	Neurontin™ ⧗	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	39450 40567 (25.9)	40076 41692 (27.8)	98.44	88.80-109.11
AUCI (ng.h/mL)	41148 42243 (25.1)	41981 43589 (27.2)	98.02	88.77-108.23
CMAX (ng/mL)	4062 41.78 (24.8)	4307 4443 (22.7)	94.31	86.42-102.91
TMAX* (h)	3.30 (38.8)	3.20 (30.0)		
T½* (h)	6.14 (18.9)	6.05 (16.3)		

⧗NeurontinTM is manufactured by Parke-Davis, Division of Warner-Lambert Canada Inc. and purchased in Canada.

*expressed as arithmetic mean (CV%) only.

TABLE 3B - SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA FOR A SINGLE DOSE STUDY UNDER FED CONDITIONS

Gabapentin
(A single 600 mg dose - 1 X 600 mg)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	GABAPENTIN	NeurontinTM	% Ratio of Geometric Means	90% Confidence Interval
AUCT (ng.h/mL)	48516 50013 (23.1)	48198 49191 (20.6)	100.66	96.20-105.33
AUCI (ng.h/mL)	50386 51828 (22.3)	50132 51098 (19.9)	100.51	96.19-105.02
CMAX (ng/mL)	4955 5091 (22.1)	5050 5137 (18.1)	98.12	93.76-102.69
TMAX* (h)	2.98 (23.9)	3.06 (23.5)		
T½* (h)	5.87 (14.2)	5.94 (19.01)		

⁑NeurontinTM is manufactured by Parke-Davis, Division of Warner-Lambert Canada Inc. and purchased in Canada.
*expressed as arithmetic mean (CV%) only.

The test formulation (GABAPENTIN 600 mg tablets) is judged to be bioequivalent to the Canadian Reference Product (NeurontinTM 600 mg tablets, Parke-Davis, Division of Warner-Lambert Company Canada Inc., Scarborough, Ontario, Canada) on the basis of the Cmax and AUC parameters.

Table 4 summarizes the mean steady-state pharmacokinetic parameters of gabapentin capsules.

TABLE 4 - Summary of Gabapentin Capsules 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
T½ (hr)	5.2	6.1
$AUC_{(o-\alpha)}$ (μg •hr/mL)	24.8	33.3
AE%[1]	NA	63.6

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

In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid are approximately 20% of corresponding steady-state trough plasma concentrations.

Elderly:

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).

Renal Impairment:

In patients with impaired renal function, gabapentin clearance is markedly reduced and dosage adjustment is necessary (see Table 8 in DOSAGE AND ADMINISTRATION).

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 Table 8 in DOSAGE AND ADMINISTRATION).

Pediatric:

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

Hepatic Impairment:
Because gabapentin is not appreciably metabolized in humans, no study was performed in patients with hepatic impairment.

CLINICAL TRIALS
In placebo-controlled trials 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 3 600 mg/day did not result in anything unusual in the type or frequency of adverse events.

INDICATIONS AND CLINICAL USE

ratio-GABAPENTIN (gabapentin) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

CONTRAINDICATIONS

Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or to any of the components of the formulation.

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.

Tumorigenic Potential:

Gabapentin produced an increased incidence of acinar cell adenomas and carcinomas in the pancreas of male rates, 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 tumors in male rats to humans is unknown, particularly since tumors of ductal rather than acinar cell origin are the predominant form of human pancreatic cancer.

Drug Discontinuation:

As with other anticonvulsant agents, abrupt withdrawal is not recommended because of the possibility of increased seizure frequency. When in the judgment of the clinician there is a need for dose reduction, discontinuation or substitution with alternative medication, this should be done gradually over a minimum of one week.

Occupational Hazards:

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.

Drug Interactions

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.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving antiepileptic agents.

Cytochrome P_{450} Enzymes:

A metabolically-based interaction between gabapentin and a drug whose clearance is dependent upon the major cytochrome P_{450} enzymes is unlikely at plasma concentrations associated with doses up to 3600 mg/day (C_{max} 11.6 µg/mL), the highest recommended daily dose.

This was demonstrated through *in vitro* studies investigating 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 indicer of cytochrome P_{450} enzymes.

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

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.

Probenecid:
Renal excretion of gabapentin is unaltered by probenecid.

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.

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.

Hydrocodone:

Co-administration of single doses of gabapentin (125 mg to 500 mg; N= 48) decreases hydrocodone (10 mg; N= 50) C_{max} and AUC values 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 increases 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.

Use in Pregnancy

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, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus.

Use in Lactation

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 outweighs the potential risks.

Use in Children

Systematic studies to establish safety and efficacy in children have not been performed. Data in 39 patients between the ages of 12 and 18 years included in the double-blind, placebo-controlled trials showed that gabapentin was superior to placebo in reducing seizure frequency. Safety data

showed that the incidence of adverse events in this group of patients were similar to those observed in older individuals.

Use in the Elderly

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).

Use in Renal Impairment

Gabapentin clearance is markedly reduced in this patient population and dosage reduction is necessary (See Table 6 in DOSAGE AND ADMINISTRATION).

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.

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.

ADVERSE REACTIONS

Incidence in Controlled Clinical Trials

Table 5 lists treatment-emergent signs and symptoms that occurred in at least 1% of patients with partial seizures participating in placebo-controlled studies. In these studies, either gabapentin (at doses of 600, 900, 1200 or 1800 mg/day) or placebo were added to the patient's current antiepileptic drug therapy.

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.

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 2-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.

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.

TABLE 5 - Treament-Emergernt Averse 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)

BODY AS A SYSTEM/ ADVERSE EVENT (AE)	GABAPENTIN* N = 543 %	PLACEBO* 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:		
Vasodilation	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 systems:		
Leukopenia	1.1	0.5
Musculaskeletal system:		
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
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

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

Withdrawal from Treatment Due to Adverse Events:

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%).

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 4, 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 discolour, perleche, 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 apperance.

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, anxiety, hostility, decreased or absent reflexes, increased reflexes; *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: p*neumonia; *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-marketing Experience:

Sudden, unexplained deaths have been reported where a casual relationship to treatment with gabapentin has not been established. Additional post-marketing adverse events reported include acute kidney failure, allergic reaction including anaphylactic reaction and urticaria, alopecia, angioedema, blood glucose fluctuations in patients with diabetes, chest pain, elevated liver function tests (LFTs), erythema multiforme, hallucinations, movement disorders such as

choreoathetosis, dyskinesia, and dystonia, palpitation, pancreatitis, Stevens-Johnson syndrome, thrombocytopenia, tinnitus, urinary incontinence.

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

Post-marketing adverse events that may have no causal relationship to gabapentin include acne, angioedema, abdominal pain, blood glucose fluctuations in patients with diabetes, confusion, diarrhea, elevated liver function tests, emotional lability, erytheme multiforme, fever, headache, hyponatremia, insomnia, jaundice, nausea and/or vomiting, pancreatitis, rash, Stevens-Johnson syndrome, sudden unexplained deaths in patients with epilepsy, urinary incontinence, and viral infection.

SYMPTOMS AND TREATMENT 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.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patients 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.

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, labored breathing, ptosis, hypoactivity, or excitation.

DOSAGE AND ADMINISTRATION

Adults

In clinical trials, the effective dosage range was 900 to 1800 mg per day, given 3 times a day using 300 mg or 400 mg capsules, or 600 mg or 800 mg tablets. The starting dose is 300 mg

three times a day. If necessary, the dose may be increased using 300 or 400 mg capsules, or 600 or 800 mg tablets 3 times a day up to 1800 mg/day. Dosages up to 2400 mg per day have been well tolerated in long-term open label clinical studies. Doses of 3600 mg per day have also been administered to a small number of patients for a relatively short duration and have been well tolerated. ratio-GABAPENTIN (gabapentin) is given orally with or without food.

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

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 ratio-GABAPENTIN therapy. Further, as there are no drug interactions with commonly used antiepileptic drugs, ratio-GABAPENTIN may be used in combination with these drugs without concern for alteration of plasma concentrations of either gabapentin or other antiepileptic drugs.

Dosage adjustment in elderly patients due to declining renal function and in patients with renal impairment or undergoing hemodialysis is recommended as follows:

TABLE 6. Dosage of Gabapentin in Adults

Based on Reduced Renal Function

Renal Function Creatinine Clearance (mL/min)	**Total Daily Dose[1] (mg/day)**					**Dose Regimen**
>60	900	1200 3600	1800	2400		Total daily dose (mg/day) should be divided by 3 and administered three times daily (TID)
>30-59	400	600 1400	800	1000		Total daily dose (mg/day) should be divided by 2 and administered twice daily (BID)
>15-29	200	300	400	500	700	Total daily dose (mg/day) should be administered once daily (QD)
15	100	125	150	200	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 Dose (mg)						
Hemo-dialysis	125	150	200	250	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.

Children Over 12 Years of Age

The dosage used in a limited number of patients in this age group was 900 to 1200 mg/day. Doses above 1200 mg/day have not been investigated.

PHARMACEUTICAL INFORMATION

Drug Substance

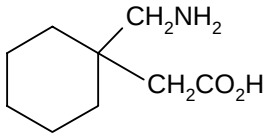
Common Name: Gabapentin

Chemical Name: 1-(aminomethyl)cyclohexaneacetic acid

Molecular formula: $C_9H_{17}NO_2$

Molecular weight: 171.24 g/mol

Molecular structure:



Description: A white to off-white crystalline solid.

Solubility: Freely soluble in water and both basic and acidic aqueous solutions.

pH and pK values: $pK_{a1} = 3.68$; $pK_{a2} = 10.70$; partition coefficient at pH 7.4 = 1.25 (Log P)

Composition

Capsules:

Active ingredient: gabapentin

Non-medicinal ingredients *(alphabetically)*: corn starch, lactose, and talc. Capsule shells contain gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and may contain red iron oxide and yellow iron oxide.

Tablets:

Active ingredient: gabapentin

Non-medicinal ingredients *(alphabetically)*: carnauba wax, copovidone, dehydrated alcohol, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and talc.

Stability and Storage Recommendations

Capsules: Store at controlled room temperature (15° to 30°C).

Tablets: Store at controlled room temperature (15° to 30°C).

AVAILABILITY OF DOSAGE FORMS

ratio-GABAPENTIN capsules and tablets are supplied as follows:

100 mg capsules: Hard gelatin Coni-Snap capsules with white opaque body and cap. Printed "rph" on one side and "G43" on the other in blue ink. Bottles of 100 capsules

300 mg capsules: Hard gelatin Coni-Snap capsules with yellow opaque body and cap Printed "rph" on one side and "G42" on the other in blue ink. Bottles of 100 capsules

400 mg capsules: Hard gelatin Coni-Snap capsules with orange opaque body and cap. Printed "rph" on one side and "G41" on the other in blue ink. Bottles of 100 capsules

600 mg tablets: White to off-white, elliptical in shape, film-coated and embossed "rph" on one side, and "G32" on the other side. Bottles of 100 and 500 tablets.

800 mg tablets: White to off-white, elliptical in shape, film-coated and embossed "rph" on one side, and "G31" on the other side. Bottles of 100 and 500 tablets.

INFORMATION TO BE PROVIDED TO THE PATIENT (CONSUMER)
BY THE DISPENSING PROFESSIONAL

PLEASE READ THIS INFORMATION CAREFULLY BEFORE YOU START TO TAKE YOUR MEDECINE, EVEN IF YOU HAVE TAKEN THIS DRUG BEFORE. DO NOT THROW AWAY THIS LEAFLET UNTIL YOU HAVE FINISHED YOUR MEDECINE AS YOU MAY NEED TO READ IT AGAIN. FOR FURTHER INFORMATION OR ADVICE, PLEASE ASK YOUR DOCTOR OR PHARMACIST.

What is ratio-GABAPENTIN?

- ratio-GABAPENTIN belongs to the family of medicines called antiepileptic drugs for treating epilepsy.
- ratio-GABAPENTIN has been prescribed for you by your doctor to reduce your number of seizures or for treating other related conditions considered appropriate by your doctor.

Important Points You Must Tell Your Doctor <u>Before</u> Taking ratio-GABAPENTIN

- Tell about all your medical conditions, especially if you have any kidney disease.
- If you are pregnant or thinking about becoming pregnant, or if you are breast-feeding.
- Any other medicines (prescription and nonprescription) you are taking.
- Inform you doctor of your usual alcohol consumption.

How To Take ratio-GABAPENTIN

- It is very important you take ratio-GABAPENTIN exactly as your doctor has instructed.
- Never increase or decrease the amount of ratio-GABAPENTIN you are taking unless your doctor tells you to.
- Do not stop taking it abruptly because your seizures may increase.
- 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. If that happens, consult you doctor as soon as possible.
- ratio-GABAPENTIN may be taken with or without food.

When Not To Use ratio-GABAPENTIN

- Do not use ratio-Gabapentin if you are allergic to it or any of the components in the formulation (see list of components at the end of this leaflet).

Precautions When Taking ratio-GABAPENTIN

- Call your doctor <u>immediately</u> if your seizures get worse.
- Contact you doctor <u>immediately</u> if you experience any severe, unusual or allergic reactions.
- When you first begin taking ratio-GABAPENTIN you may experience some side effects such as drowsiness, dizziness, 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 ratio-GABAPENTIN.

What To Do In Case of Overdose
- Contact your doctor or nearest hospital emergency department, even though you may not feel sick.

How To Store ratio-GABAPENTIN
- Store Capsules and Tablets at room temperature (15° to 30°).
- Keep out of reach of children.

What Does ratio-GABAPENTIN Contain?
- ratio-GABAPENTIN is available in:
  - Capsules containing 100 mg, 300 mg or 400 mg of gabapentin as the active medicinal ingredient. Non-medicinal ingredients include corn starch, gelatin, lactose, talc, titanium dioxide, silicon dioxide, sodium lauryl sulfate, yellow iron oxide and red iron oxide.

  - Tablets containing 600 mg or 800 mg of gabapentin as the active medicinal ingredient. Non-medicinal ingredients include: carnauba wax, copovidone, dehydrated alcohol, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and talc.

ratio-GABAPENTIN is a medicine of:
- ratio-GABAPENTIN capsules and tablets are manufactured for:
  ratiopharm inc.
  Canada, J7J 1P3

REMINDER: This medicine has been prescribed only for you. Do not give it to anybody else.
If you require any further information or advice please consult your doctor or pharmacist.

PHARMACOLOGY

In Vitro Studies - Preclinical

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 - Preclinical

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, picrotoxine, 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 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-weeks-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 tumors 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 concentration in humans given 1200 mg/day and are14 times higher than the therapeutic concentrations in humans given 2400 mg/day.

The pancreatic acinar cell tumors 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 tumors in male rats to carcinogenic risk in humans is unclear, as the biologic characteristics of the tumors 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 tumors 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 tumors 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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