PRODUCT MONOGRAPH

BCI GABAPENTIN

(gabapentin)

300 mg Capsules

Antiepileptic Agent

Baker Cummins Inc.
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Montreal, Quebec
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Date of Preparation:
April 1, 2005

Control#: 097812

PRODUCT MONOGRAPH

BCI GABAPENTIN

(gabapentin)

300 mg Capsules

THERAPEUTIC CLASSIFICATION

Antiepileptic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

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

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 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, and can be removed from plasma by hemodialysis.

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.

Table 1 summarizes the mean steady-state pharmacokinetic parameters of gabapentin capsules.

Table 1. 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 $_{(0-\infty)}$ (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 5 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; dialysis three times a week (4 hours duration) lowered the apparent half-life of gabapentin by about 60%, from 132 hours to 51 hours. Hemodialysis, thus, has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (See Table 5 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 3600 mg/day did not result in anything unusual in the type or frequency of adverse events.

A comparative, two-way, single-dose, bioavailability study was performed under fasted conditions on BCI GABAPENTIN (gabapentin) 100 mg capsules and Neurontin® 100 mg capsules by Parke-Davis division of Warner-Lambert Canada. The pharmacokinetic data calculated for the two gabapentin formulations are tabulated below:

Single-Dose Pharmacokinetic Parameters for Gabapentin (Fasted Conditions)

PARAMETER	**From Measured Data Geometric Mean Arithmetic Mean (C.V.%)**		
	BCI Gabapentin 1 x 100 mg	**Neurontin®** 1 x 100 mg**	**% RATIO OF GEOMETRIC MEANS**
AUC_T (µg.h/mL)	9.008 9.221 (21.4%)	8.937 9.071 (17.7%)	101%
AUC_I (µg.h/mL)	9.349 9.535 (20.1%)	9.183 9.314 (17.3%)	102%
C_{MAX} (µg/mL)	1.013 1.055 (29.9%)	1.002 1.031 (24.9%)	101%
T_{MAX}* (h)	2.958 (43.7%)	2.875 (42.1%)	--
$T_{½}$* (h)	5.563 (13.8%)	5.479 (13.8%)	--

* expressed as arithmetic mean (CV%) only.
** Neurontin® manufactured by Parke-Davis division of Warner-Lambert Canada and purchased in Canada..

A comparative, two-way, single-dose, bioavailability study was performed under fed conditions on BCI GABAPENTIN (gabapentin) 100 mg capsules and Neurontin® 100 mg capsules by Parke-Davis division of Warner-Lambert Canada. The pharmacokinetic data calculated for the two gabapentin formulations are tabulated below:

Single-Dose Pharmacokinetic Parameters for Gabapentin (Fed Conditions)

PARAMETER	**From Measured Data Geometric Mean Arithmetic Mean (C.V. %)**		
	BCI Gabapentin 1 x 100 mg	**Neurontin®** 1 x 100 mg**	**% RATIO OF GEOMETRIC MEANS**
AUC_T (µg.h/mL)	8.492 8.619 (18.1%)	8.539 8.658 (17.4%)	99%
AUC_I (µg.h/mL)	8.769 8.901 (18.1%)	8.826 8.950 (17.5%)	99%
C_{MAX} (µg/mL)	0.938 0.947 (13.6%)	0.948 0.959 (15.1%)	99%
T_{MAX}* (h)	3.438 (22.4%)	3.354 (20.8%)	--
$T_{½}$* (h)	5.618 (14.6%)	5.611 (13.9%)	--

* expressed as arithmetic mean (CV%) only.
** Neurontin® manufactured by Parke-Davis division of Warner-Lambert Canada and purchased in Canada..

A comparative, two-way, single-dose, bioavailability study was performed under fasted conditions on BCI GABAPENTIN (gabapentin) 800 mg tablets and Neurontin® 800 mg tablets by Parke-Davis division of Warner-Lambert Canada. The pharmacokinetic data calculated for the two gabapentin formulations are tabulated below:

Single-Dose Pharmacokinetic Parameters for Gabapentin (Fasted Conditions)

PARAMETER	**From Measured Data Geometric Mean Arithmetic Mean (C.V. %)**		
	BCI Gabapentin 1 x 800 mg	**Neurontin®** 1 x 800 mg**	**% RATIO OF GEOMETRIC MEANS**
AUC_T (ng.h/mL)	48493 49759 (25.0%)	47522 48599 (22.0%)	102%
AUC_I (ng.h/mL)	49778 51010 (24.5%)	48810 49874 (21.6%)	102%
C_{MAX} (ng/mL)	4601.6 4873.6 (30.3%)	4468.7 4614.4 (25.6%)	103%
T_{MAX}^{*} (h)	3.24 (29.0%)	3.67 (25.8%)	--
$T_{½}^{*}$ (h)	8.16 (35.6%)	8.01 (20.8%)	--

* expressed as arithmetic mean (CV%) only.
** Neurontin® manufactured by Parke-Davis division of Warner-Lambert Canada and purchased in Canada..

A comparative, two-way, single-dose, bioavailability study was performed under fed conditions on BCI GABAPENTIN (gabapentin) 800 mg tablets and Neurontin® 800 mg tablets by Parke-Davis division of Warner-Lambert Canada. The pharmacokinetic data calculated for the two gabapentin formulations are tabulated below:

Single-Dose Pharmacokinetic Parameters for Gabapentin (Fed Conditions)

PARAMETER	**From Measured Data Geometric Mean Arithmetic Mean (C.V. %)**		
	BCI Gabapentin 1 x 800 mg	**Neurontin®** 1 x 800 mg**	**% RATIO OF GEOMETRIC MEANS**
AUC_T (ng.h/mL)	47312 48044 (18.0%)	49254 49916 (16.9%)	96%
AUC_I (ng.h/mL)	48392 49106 (17.6%)	50285 50937 (16.5%)	96%
C_{MAX} (ng/mL)	4939.4 5009.9 (17.3%)	5160.8 5236.7 (17.3%)	96%
T_{MAX}^{*} (h)	2.935 (26.8%)	3.326 (24.7%)	--
$T_{½}^{*}$ (h)	7.762 (18.7%)	7.351 (17.6%)	--

* expressed as arithmetic mean (CV%) only.
** Neurontin® manufactured by Parke-Davis division of Warner-Lambert Canada and purchased in Canada..

A comparative, two-way, single-dose, bioavailability study was performed under fasting conditions on BCI GABAPENTIN (gabapentin) 600 mg tablets and Neurontin® 600 mg tablets by Parke-Davis division of Warner-Lambert Canada. The pharmacokinetic data calculated for the two gabapentin formulations are tabulated below:

Single-Dose Pharmacokinetic Parameters for Gabapentin (Fasted Conditions)

PARAMETER	**From Measured Data Geometric Mean Arithmetic Mean (C.V. %)**		
	BCI Gabapentin 1 x 600 mg	**Neurontin®** 1 x 600 mg**	**% RATIO OF GEOMETRIC MEANS**
AUC_T (ng.h/mL)	46095.7 47522.2 (26)	44491.3 46759.5 (31)	103.61
AUC_I (ng.h/mL)	46606.2 48011.1 (26)	45095.5 47319.2 (31)	103.35
C_{MAX} (ng/mL)	4433.3 4576.2 (25)	4254.6 4460.8 (28)	104.20
T_{MAX}* (h)	3.29 (29)	3.64 (23)	--
$T_{½}$* (h)	7.26 (31)	7.73 (31)	--

* expressed as arithmetic mean (CV%) only.

** Neurontin® manufactured by Parke-Davis division of Warner-Lambert Canada and purchased in Canada.

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

BCI GABAPENTIN (gabapentin) is contraindicated in patients who have demonstrated hypersensitivity to the drug or to any of the components of the formulation.

PRECAUTIONS

General

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

Tumorigenic Potential

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 tumors 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.

Drug Discontinuation

As with other anticonvulsant agents, abrupt withdrawal is not recommended because of the possibility of increased seizure frequency. When, in the judgement 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.

Oral Contraceptives:

Co-administration of gabapentin with the oral contraceptive Norlestrin does not influence the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Antacids:

Co-administration 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 co-administered with cimetidine is not expected to be of clinical importance.

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 was 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 5 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 2 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 was 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 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. 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 2. 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)

BODY SYSTEM/ADVERSE EVENT (AE)	Gabapentin[a] N = 543 %	PLACEBO[a] N = 378 %
BODY AS A WHOLE:		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
CARDIOVASCULAR:		
Vasodilatation	1.1	0.3
DIGESTIVE SYSTEM:		
Dyspepsia	2.2	0.5
Dry Mouth or Throat	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
MUSCULOSKELETAL SYSTEM:		
Myalgia	2.0	1.9
Fracture	1.1	0.8

BODY SYSTEM/ADVERSE EVENT (AE)	Gabapentin[a] N = 543 %	PLACEBO[a] N = 378 %
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 Decrease	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 are described below, except those already listed in the previous table:

Body As a Whole:	aesthenia, malaise, facial edema
Cardiovascular System:	hypertension
Digestive System:	anorexia, flatulence, gingivitis
Hematologic and Lymphatic System:	purpura; most often described as bruises resulting from physical trauma
Musculoskeletal System:	arthralgia
Nervous System:	vertigo, hyperkinesia, paresthesia, anxiety, hostility, and increased, decreased or absent reflexes
Respiratory System:	pneumonia
Urogenital System:	urinary tract infection
Special senses:	abnormal vision

Post-marketing Experience

Post-marketing adverse events that may have no causal relationship to gabapentin include sudden unexplained deaths, elevated liver function tests, blood-glucose fluctuations in patients

with diabetes, urinary incontinence, pancreatitis, erythema multiforme and Stevens-Johnson syndrome.

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 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 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.

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.

DOSAGE AND ADMINISTRATION

Adult

In clinical trials, the effective dosage range was 900 to 1800 mg/day. Therapy may be initiated by administering 300 mg three times a day (TID) on Day 1, or by titrating the dose as described below (see Table 3). Thereafter, the dose can be increased in three equally divided doses up to a clinically effective and tolerated dose. 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. BCI GABAPENTIN (gabapentin) is given orally with or without food.

Table 3. Titration Schedule

DOSE	Day 1	Day 2	Day 3
900 mg/day	300 mg OD	300 mg BID	300 mg TID
1200 mg/day	400 mg OD	400 mg BID	400 mg TID

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 (See Table 4), and the maximum time between doses in a three times daily schedule should not exceed 12 hours. It is not necessary to monitor gabapentin plasma concentrations in order to optimize BCI GABAPENTIN (gabapentin) therapy. Furthermore, as there are no drug interactions with commonly used antiepileptic drugs, BCI GABAPENTIN may be used in combination with these drugs without concern for alteration of plasma concentrations of either gabapentin or other antiepileptic drugs.

Table 4. Maintenance Dosage Schedule

Total Daily Dose (mg/day)	Schedule
900	300 mg TID
1200	400 mg TID
1800	2 x 300 mg TID or 600 mg TID
2400	2 x 400 mg TID or 800 mg TID

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

Table 5. Maintenance Dosage of BCI GABAPENTIN in Adults With Reduced Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)	Dosage Regimen
>60	1200	400 mg three times a day
30-60	600	300 mg twice a day
15-30	300	300 mg once a day
<15	150	300 mg once daily every other day
Hemodialysis[a]	-	200-300 mg [b]

[a]Loading dose of 300 to 400 mg
[b]Maintenance dose of 200 to 300 mg gabapentin following each 4 hours of hemodialysis

Children Over 12 Years of Age

The dosage used in a limited number of patients in this age group was 900-1200 mg/day.

Doses above 1200 mg/day have not been investigated.

PHARMACEUTICAL INFORMATION

Drug Substance:

Proprietary Name: BCI GABAPENTIN

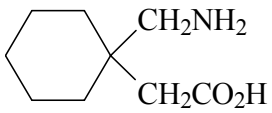
Proper Name: Gabapentin

Chemical Name: 1-(aminomethyl)cyclohexaneacetic acid

Molecular formula: $C_9H_{17}NO_2$

Molecular weight: 171.24

Molecular structure:



Description

A white to off-white crystalline solid. Freely soluble in water and both basic and acidic aqueous solutions. $pK_{a1} = 3.68$; $pK_{a2} = 10.70$.

Composition

Capsules contain gabapentin, colloidal silicon dioxide, lactose monohydrate, pregelatinized starch, and talc. Capsule shells may contain gelatin, titanium dioxide, silicon dioxide, sodium lauryl sulfate, yellow iron oxide (300 mg), red iron oxide (400 mg), and FD&C Blue No. 2.

Stability and Storage Recommendations

Store at bottles at room temperature between 15-30˚C.

AVAILABILITY OF DOSAGE FORMS

BCI GABAPENTIN (gabapentin) capsules are supplied as follows:

300 mg capsules: Yellow opaque cap and body hard gelatin capsules, size #1, with Novopharm logo and "300" printed in blue ink on opposing cap and body portions of the capsules.

300 mg capsules are supplied in white high density polyethylene bottles of 100.

INFORMATION FOR PATIENT (CONSUMER)

Please read this information carefully before you start to take your medicine, even if you have taken this drug before. Do not throw away this leaflet until you have finished your medicine as you may need to read it again. For further information or advice, please ask your doctor or pharmacist.

What is BCI GABAPENTIN:

- BCI GABAPENTIN (gabapentin) belongs to the family of medicines called antiepileptic drugs for treating epilepsy.
- BCI 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 BCI 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 breastfeeding.
- Any other medicines (prescription and nonprescription) you are taking.
- Inform your doctor of your usual alcohol consumption.

How To Take BCI GABAPENTIN:

- It is very important that you take BCI GABAPENTIN exactly as your doctor has instructed.
- Never increase or decrease the amount of BCI 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 but return to your regular dosing schedule. Do not allow more than 12 hours to go by between doses. If that happens, consult your doctor as soon as possible.
- BCI GABAPENTIN may be taken with or without food.

When Not To Use BCI GABAPENTIN:

- Do not use BCI 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 BCI GABAPENTIN:

- Call your doctor immediately if your seizures get worse.
- Contact your doctor immediately if you experience any severe, unusual or allergic reactions.
- When you first begin taking BCI 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 BCI 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 BCI GABAPENTIN:

- Store bottles at room temperature between 15 - 30˚C.
- Keep out of reach of children.

What Does BCI GABAPENTIN Contain:

- The active medicinal ingredient in BCI GABAPENTIN is gabapentin. BCI GABAPENTIN is available as capsules (containing 300 mg gabapentin).

  Capsules: Non-medicinal ingredients include lactose monohydrate, pregelatinized starch, talc, gelatin, titanium dioxide, colloidal silicon dioxide, sodium lauryl sulfate, FD&C Blue No. 2, and yellow iron oxide or red iron oxide.

Who Manufactures BCI GABAPENTIN:

- BCI GABAPENTIN capsules and tablets are manufactured by:
  Baker Cummins Inc.

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, 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 carcinomas comprise over 90% of all primary cancers of human exocrine pancreas, whereas acinar cell adenomas represent the primary pancreatic exocrine tumours in rats. In humans, pancreatic neoplasia exhibit local and distant tumour spread at the time of diagnosis. Metastasis occurs in 67% of cases, and survival is between 2 and 6 months after diagnosis. In contrast, pancreatic acinar cell tumours in male rats given gabapentin did not metastasize, exhibit aggressive behaviour or affect survival.

Gabapentin has no genotoxic potential. It was not mutagenic in the Ames bacterial plate incorporation assay or at the HGPRT locus in mammalian cells in the presence or absence of

metabolic activation. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

Reproduction Studies:

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

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

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