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เอกสารกำกับยา

NEUGABA™
(Capsules)

1 NAME OF THE MEDICINAL PRODUCT

NEUGABA™

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NEUGABA™ is supplied as capsules containing 300 mg of active drug substance for oral administration.

Gabapentin is a white to off-white crystalline solid. It is freely soluble in water and both basic and acidic aqueous solutions.

3 PHARMACEUTICAL FORM

Capsules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy

NEUGABA™ is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 12 years and older. Safety and effectiveness for monotherapy in children younger than 12 years have not been established (see Section **4.2 Posology and method of administration - Epilepsy: Adults and pediatric patients older than 12 years of age**).

NEUGABA™ is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 3 years and older. Safety and effectiveness for adjunctive therapy in pediatric patients younger than 3 years have not been established (see Section **4.2 Posology and method of administration - Epilepsy: Pediatric patients aged 3 to 12 years**).

Neuropathic pain

NEUGABA™ is indicated for the treatment of neuropathic pain in adults aged 18 years and older. Safety and effectiveness in patients younger than 18 years have not been established.

4.2 Posology and method of administration

General

NEUGABA™ is given orally with or without food.

When, in the judgment 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.

Epilepsy

Adults and pediatric patients older than 12 years of age

In clinical trials, the effective dosing range was 900 mg/day to 3,600 mg/day. Therapy may be initiated by administering 300 mg three times a day on Day 1, or by titrating the dose (TABLE 1). Thereafter, the dose can be increased in three equally divided doses up to a maximum dose of 3,600 mg/day. Doses up to 4,800 mg/day have been well tolerated in long-term open-label clinical studies. The maximum time between doses in the three times a day schedule should not exceed 12 hours to prevent breakthrough convulsions.

TABLE 1

Dosing Chart: Initial Titration

Dose	Day 1	Day 2	Day 3
900 mg	300 mg QD[a]	300 mg BID[b]	300 mg TID[c]

[a] QD = once a day

[b] BID = two times a day

[c] TID = three times a day

Pediatric patients aged 3 to 12 years

The starting dose should range from 10 to 15 mg/kg/day given in equally divided doses (three times a day), and the effective dose reached by upward titration over a period of

approximately 3 days. The effective dose of NEUGABA™ in pediatric patients aged 5 years and older is 25 to 35 mg/kg/day given in equally divided doses (three times a day). The effective dose in pediatric patients aged 3 to less than 5 years is 40 mg/kg/day given in equally divided doses (three times a day). Doses up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize NEUGABA™ therapy. Further, NEUGABA™ may be used in combination with other antiepileptic drugs without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic drugs.

Neuropathic pain in adults

The starting dose is 900 mg/day given in three equally divided doses, and increased if necessary, based on response, up to a maximum dose of 3,600 mg/day. Therapy should be initiated by titrating the dose (TABLE 1).

Dose adjustment in impaired renal function in patients with neuropathic pain or epilepsy

Dose adjustment is recommended in patients with compromised renal function (TABLE 2) and/or in those undergoing hemodialysis.

TABLE 2

Dosage of NEUGABA™ in Adults Based on Renal Function

Creatinine Clearance (mL/min)	Total Daily Doses[a] (mg/day)
≥80	900-3,600
50-79	600-1,800
30-49	300-900
15-29	150[b]-600
<15	150[b]-300

[a] Total daily dose should be administered as a three times a day regimen. Doses used to treat patients with normal renal function (creatinine clearance ≥80 mL/min) range from 900 mg/day to 3,600 mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance <79 mL/min).

[b] To be administered as 300 mg every other day.

Dose adjustment in patients undergoing hemodialysis

For patients undergoing hemodialysis who have never received gabapentin, a loading dose of 300 mg to 400 mg is recommended, and then 200 mg to 300 mg of gabapentin following each 4 hours of hemodialysis.

4.3 Contraindications

NEUGABA™ is contraindicated in patients who are hypersensitive to gabapentin or the product's components.

4.4 Special warnings and precautions for use

General

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus (see Section **4.2 Posology and method of administration - General**).

Gabapentin is generally not considered effective in the treatment of absence seizures.

Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall). There have also been post-marketing reports of confusion, loss of consciousness and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Concomitant use with opioids and other CNS depressants

Patients who require concomitant treatment with opioids may experience increases in gabapentin concentrations. Patients who require concomitant treatment with CNS (central nervous system) depressants, including opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or concomitant treatment with CNS depressants including opioids should be reduced appropriately (see Section **4.5 Interaction with other medicinal products and other forms of interaction**).

Caution is advised when prescribing gabapentin concomitantly with opioids due to risk of CNS depression. In a population-based, observational, nested case-control study of opioid

users, co-prescription of opioids and gabapentin was associated with an increased risk for opioid-related death compared to opioid prescription use alone (adjusted odds ratio [aOR], 1.49 [95% CI, 1.18 to 1.88, p<0.001]).

Drug rash with eosinophilia and systemic symptoms

Severe, life-threatening, systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) 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.

Anaphylaxis

Gabapentin can cause anaphylaxis. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue gabapentin and seek immediate medical care should they experience signs or symptoms of anaphylaxis.

Abuse and Dependence

Cases of abuse and dependence have been reported in the post-marketing database. As with any CNS active drug, carefully evaluate patients for a history of drug abuse and/or psychiatric disorders.

Caution should be applied when considering gabapentin use in patients with current substance abuse or a history of substance abuse, who may be at higher risk for gabapentin abuse (see Section **5.1 Pharmacodynamic properties**).

Patients treated with gabapentin should be monitored for signs and symptoms of gabapentin abuse or dependence, such as the development of tolerance, dose escalation and drug-seeking behavior.

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with gabapentin, withdrawal

symptoms have been observed in some patients. Withdrawal symptoms may occur shortly after the discontinuation, usually within 48 hours. Most frequently reported symptoms include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise.

Women of childbearing potential/Contraception

Gabapentin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Gabapentin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Women of childbearing potential must use effective contraception during treatment (see Section **4.6 Fertility, pregnancy and lactation - Pregnancy**).

Information for patients

To assure safe and effective use of gabapentin, the following information and instructions should be given to patients:

1. You should inform your physician about any prescription or non-prescription medications, alcohol or drugs you are now taking or are planning to take during your treatment with gabapentin.
2. You should inform your physician if you are pregnant, or if you are planning to become pregnant, or if you become pregnant while you are taking gabapentin.
3. Gabapentin is excreted in human milk, and the effect on the nursing infant is unknown. You should inform your physician if you are breast feeding an infant (see Section **4.6 Fertility, pregnancy and lactation - Lactation**).
4. Gabapentin may impair your ability to drive a car or operate potentially dangerous machinery. Until it is known that this medication does not affect your ability to engage in these activities, do not drive a car or operate potentially dangerous machinery.
5. You should not allow more than 12 hours between gabapentin doses to prevent breakthrough convulsions.
6. 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.

4.5 Interaction with other medicinal products and other forms of interaction

There are spontaneous and literature case reports of respiratory depression, sedation, and

death associated with gabapentin when coadministered with CNS depressants, including opioids. In some of these reports, the authors considered the combination of gabapentin with opioids to be a particular concern in frail patients, in the elderly, in patients with serious underlying respiratory disease, with polypharmacy, and in those patients with substance abuse disorders.

Morphine

In a study involving healthy volunteers (N=12), when a 60-mg controlled-release morphine capsule was administered 2 hours prior to a 600-mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. This was associated with an increased pain threshold (cold pressor test). The clinical significance of such changes has not been defined. Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The observed opioid-mediated side effects associated with morphine plus gabapentin did not differ significantly from morphine plus placebo. The magnitude of interaction at other doses is not known (see Section **4.4 Special warnings and precautions for use - General**).

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed. Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic agents.

Co-administration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol does not influence the steady-state pharmacokinetics of either component.

Co-administration of gabapentin with antacids containing aluminum and magnesium reduces gabapentin bioavailability by about 20%. It is recommended that gabapentin be taken about 2 hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin that is observed when it is co-administered with cimetidine is not expected to be of clinical importance.

Laboratory Tests

False positive readings were reported with the Ames N-Multistix SG® dipstick test when gabapentin was added to other anticonvulsant drugs. To determine urinary protein, the more specific sulfosalicylic acid precipitation procedure is recommended.

4.6 Fertility, pregnancy and lactation

Fertility

There is no effect on fertility in animal studies (see Section **5.3 Preclinical safety data - Impairment of fertility**).

Pregnancy

Gabapentin crosses the human placenta.

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product.

Data from an observational study, which included more than 1,700 pregnancies exposed to gabapentin based on routinely collected data from administrative and medical registers in Denmark, Finland, Norway, and Sweden, do not suggest substantially increased risks of major congenital malformations, adverse birth outcomes, or abnormal postnatal neurodevelopmental outcomes in gabapentin-exposed pregnancies.

For major congenital malformations, the adjusted prevalence ratios (aPRs) and 95% confidence intervals (CI) in the standard meta-analysis for first trimester gabapentin exposed vs. unexposed to antiepileptic drugs was 0.99 (0.80-1.23).

Overall, there were no statistically significant findings for stillbirth, small for gestational age, low Apgar score, and microcephaly. The aPRs were 1.21 (1.02-1.44) for low birth weight, 1.16 (1.00-1.35) for preterm birth.

In pediatric population exposed in utero, the study did not provide evidence of an increased risk for neurodevelopmental outcomes, such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and intellectual disabilities.

Neonatal withdrawal syndrome has been reported in newborns exposed in utero to gabapentin. Co-exposure to gabapentin and opioids during pregnancy may increase the risk

of neonatal withdrawal syndrome.

Studies in animals have shown reproductive toxicity (see Section **5.3 Preclinical safety data - Teratogenesis**). Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the fetus.

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 benefits clearly outweigh the risks.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive a car or operate potentially dangerous machinery until it is known that this medication does not affect their ability to engage in these activities.

4.8 Undesirable effects

Epilepsy

Gabapentin has been evaluated for safety in more than 2,000 subjects and patients in adjunctive therapy studies and was well tolerated. Of these, 543 patients participated in controlled clinical trials. Since gabapentin was most often administered in combination with other antiepileptic agents, it was not possible to determine which agent(s), if any, was associated with adverse events.

Gabapentin has also been evaluated as monotherapy in more than 600 patients. Adverse events were usually mild to moderate in intensity.

Incidence in controlled adjunctive therapy clinical trials

TABLE 3 lists the treatment-emergent signs and symptoms that occurred in at least 1% of patients with partial seizures participating in placebo-controlled adjunctive therapy studies. In these studies, either gabapentin or placebo was added to the patient’s current antiepileptic drug therapy. Adverse events were usually reported as mild to moderate.

TABLE 3

Summary of Treatment-emergent Signs and Symptoms in ≥1% of Gabapentin-treated Patients in Placebo-controlled Adjunctive Therapy Studies

COSTART Body System Adverse Event	Gabapentin[a] N=543		Placebo[a] N=378	
	n of Pts	(%)	n of Pts	(%)
Body as a Whole				
Abdominal pain	10	1.8	9	2.4
Back pain	10	1.8	2	0.5
Fatigue	60	11.0	19	5.0
Fever	7	1.3	5	1.3
Headache	44	8.1	34	9.0
Viral infection	7	1.3	8	2.1
Cardiovascular				
Vasodilation	6	1.1	1	0.3
Digestive System				
Constipation	8	1.5	3	0.8
Dental abnormalities	8	1.5	1	0.3
Diarrhea	7	1.3	8	2.1
Dyspepsia	12	2.2	2	0.5
Increased appetite	6	1.1	3	0.8
Mouth or throat dry	9	1.7	2	0.5
Nausea and/or vomiting	33	6.1	27	7.1
Hematologic and Lymphatic				
Leukopenia	6	1.1	2	0.5
WBC decreased	6	1.1	2	0.5
Metabolic and Nutritional				
Peripheral edema	9	1.7	2	0.5
Weight increase	16	2.9	6	1.6
Musculoskeletal System				
Fracture	6	1.1	3	0.8
Myalgia	11	2.0	7	1.9
Nervous System				
Amnesia	12	2.2	0	0.0

TABLE 3

Summary of Treatment-emergent Signs and Symptoms in ≥1% of Gabapentin-treated Patients in Placebo-controlled Adjunctive Therapy Studies

COSTART Body System Adverse Event	Gabapentin[a] N=543		Placebo[a] N=378	
	n of Pts	(%)	n of Pts	(%)
Ataxia	68	12.5	21	5.6
Confusion	9	1.7	7	1.9
Coordination abnormal	6	1.1	1	0.3
Depression	10	1.8	4	1.1
Dizziness	93	17.1	26	6.9
Dysarthria	13	2.4	2	0.5
Emotional lability	6	1.1	5	1.3
Insomnia	6	1.1	7	1.9
Nervousness	13	2.4	7	1.9
Nystagmus	45	8.3	15	4.0
Somnolence	105	19.3	33	8.7
Thinking abnormal	9	1.7	5	1.3
Tremor	37	6.8	12	3.2
Twitching	7	1.3	2	0.5
Respiratory System				
Coughing	10	1.8	5	1.3
Pharyngitis	15	2.8	6	1.6
Rhinitis	22	4.1	14	3.7
Skin and Appendages				
Abrasion	7	1.3	0	0.0
Acne	6	1.1	5	1.3
Pruritus	7	1.3	2	0.5
Rash	8	1.5	6	1.6
Special Senses				
Amblyopia	23	4.2	4	1.1
Diplopia	32	5.9	7	1.9
Urogenital System				
Impotence	8	1.5	4	1.1

TABLE 3				
Summary of Treatment-emergent Signs and Symptoms in ≥1% of Gabapentin-treated Patients in Placebo-controlled Adjunctive Therapy Studies				
COSTART Body System Adverse Event	**Gabapentin[a] N=543**		**Placebo[a] N=378**	
	n of Pts	**(%)**	**n of Pts**	**(%)**

[a] Includes concomitant antiepileptic drug therapy

Pts - patients

Other adverse events observed during all clinical trials

Adjunctive therapy

Those events that occurred in at least 1% of the study participants with epilepsy who received gabapentin as adjunctive therapy in any clinical study and that are not described in the previous section as frequently occurring treatment-emergent signs and symptoms during placebo-controlled studies are summarized below.

Body as a Whole: asthenia, malaise, facial edema.

Cardiovascular System: hypertension.

Digestive System: flatulence, anorexia, gingivitis.

Hematologic and Lymphatic Systems: purpura, most often described as bruises resulting from physical trauma.

Musculoskeletal System: arthralgia.

Nervous System: vertigo; hyperkinesia; increased, decreased, or absent reflexes, paresthesia; anxiety; hostility.

Respiratory System: pneumonia.

Urogenital System: urinary tract infection.

Special Senses: abnormal vision most often described as a visual disturbance.

Monotherapy

No new and unexpected adverse events were reported during the clinical trials for monotherapy. Dizziness, ataxia, somnolence, paresthesia, and nystagmus showed a dose relationship when comparing 300 mg/day to 3,600 mg/day.

Geriatric use:

Fifty-nine individuals aged 65 years or older received gabapentin in pre-marketing clinical trials. Side effects reported among these patients did not differ in kind from those reported in younger individuals. For patients with compromised renal function, the dose should be adjusted (see Section **4.2 Posology and method of administration - Dose adjustment in impaired renal function in patients with neuropathic pain or epilepsy** and **Dose adjustment in patients undergoing hemodialysis**).

Pediatric use

The most commonly observed adverse events reported with the use of gabapentin in combination with other antiepileptic drugs in children aged 3 to 12 years, not seen in equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting and somnolence.

TABLE 4

Incidence of Treatment-emergent Adverse Events Children Aged 3 to 12 Years in Controlled Add-on Trials (Events in at least 2% of Gabapentin patients and numerically more frequent than in the placebo group)

COSTART Body System **Adverse Event**	**Gabapentin[a]** **N=119** **%**	**Placebo[a]** **N=128** **%**
Body as a Whole		
Viral infection	10.9	3.1
Fever	10.1	3.1
Weight increase	3.4	0.8
Fatigue	3.4	1.6
Digestive System		
Nausea and/or vomiting	8.4	7.0
Nervous System		
Somnolence	8.4	4.7
Hostility	7.6	2.3
Emotional lability	4.2	1.6
Dizziness	2.5	1.6
Hyperkinesia	2.5	0.8
Respiratory System		

TABLE 4		
Incidence of Treatment-emergent Adverse Events Children Aged 3 to 12 Years in Controlled Add-on Trials (Events in at least 2% of Gabapentin patients and numerically more frequent than in the placebo group)		
COSTART Body System **Adverse Event**	**Gabapentin[a]** **N=119** **%**	**Placebo[a]** **N=128** **%**
Bronchitis	3.4	0.8
Respiratory infection	2.5	0.8

[a] Includes concomitant antiepileptic drug therapy

Other events in more than 2% of children that occurred equally or more frequent in the placebo group included pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

Withdrawal from treatment due to adverse events

Adjunctive therapy

Approximately 7% of the more than 2,000 healthy volunteers and patients with epilepsy, spasticity, or migraine who received gabapentin in clinical studies withdrew due to adverse events.

In all clinical studies, the most frequently occurring events that contributed to discontinuation of gabapentin included somnolence, ataxia, dizziness, fatigue, and nausea and/or vomiting. Almost all participants had multiple complaints, none of which could be characterized as primary.

Monotherapy

Approximately 8% of the 659 patients who received gabapentin as monotherapy or conversion to monotherapy in pre-marketing trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were dizziness, nervousness, weight gain, nausea and/or vomiting and somnolence.

Pediatric

Approximately 8% of the 292 children aged 3 to 12 years who received gabapentin in

clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in children were somnolence, hyperkinesia, and hostility.

Neuropathic pain

TABLE 5

Summary of Treatment-emergent Signs and Symptoms in ≥1% of Gabapentin-treated Patients in Neuropathic Pain Placebo-controlled Studies

COSTART Body System Adverse Event	Gabapentin N=821		Placebo N=537	
	n of Pts	(%)	n of Pts	(%)
Body as a Whole				
Abdominal pain	23	2.8	17	3.2
Accidental injury	32	3.9	17	3.2
Asthenia	41	5.0	25	4.7
Back pain	19	2.3	8	1.5
Flu syndrome	21	2.6	14	2.6
Headache	45	5.5	33	6.1
Infection	38	4.6	40	7.4
Pain	30	3.7	36	6.7
Digestive System				
Constipation	19	2.3	9	1.7
Diarrhea	46	5.6	24	4.5
Dry mouth	27	3.3	5	0.9
Dyspepsia	16	1.9	10	1.9
Flatulence	14	1.7	6	1.1
Nausea	45	5.5	29	5.4
Vomiting	16	1.9	13	2.4
Metabolic and Nutritional				
Peripheral edema	44	5.4	14	2.6
Weight gain	14	1.7	0	0.0
Nervous System				
Abnormal gait	9	1.1	0	0.0
Amnesia	15	1.8	3	0.6

TABLE 5

Summary of Treatment-emergent Signs and Symptoms in ≥1% of Gabapentin-treated Patients in Neuropathic Pain Placebo-controlled Studies

COSTART Body System Adverse Event	Gabapentin N=821		Placebo N=537	
	n of Pts	(%)	n of Pts	(%)
Ataxia	19	2.3	0	0.0
Confusion	15	1.8	5	0.9
Dizziness	173	21.1	35	6.5
Hypesthesia	11	1.3	3	0.6
Somnolence	132	16.1	27	5.0
Thinking abnormal	12	1.5	0	0.0
Tremor	9	1.1	6	1.1
Vertigo	8	1.0	2	0.4
Respiratory System				
Dyspnea	9	1.1	3	0.6
Pharyngitis	15	1.8	7	1.3
Skin and Appendages				
Rash	14	1.7	4	0.7
Special Senses				
Amblyopia	15	1.8	2	0.4

Post-marketing experience

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

Additional post-marketing adverse events reported include blood creatine phosphokinase increased, rhabdomyolysis, acute kidney failure, agitation, allergic reaction including urticaria, alopecia, anaphylaxis, angioedema, hyperglycemia and hypoglycemia (most often observed in patients with diabetes), breast hypertrophy, chest pain, drug rash with eosinophilia and systemic symptoms, elevated liver function tests (LFTs), erythema multiforme, fall, generalized edema, gynecomastia, hallucinations, hepatitis, hypersensitivity including systemic reactions, hyponatremia, jaundice, loss of consciousness, movement disorders, such as choreoathetosis, dyskinesia, and dystonia,

myoclonus, palpitation, pancreatitis, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia), Stevens-Johnson syndrome, thrombocytopenia, tinnitus, and urinary incontinence.

After discontinuation of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed in some patients. Most frequently reported symptoms include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise (see Section **4.4 Special warnings and precautions for use – Withdrawal symptoms**).

4.9 Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 g. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, loss of consciousness, lethargy, and mild diarrhea. All patients recovered fully with supportive care.

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

Although gabapentin can be removed by hemodialysis, based on prior experience, it is usually not required. However, in patients with severe renal impairment, hemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8,000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, hypoactivity, or excitation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, ATC code: N02BF01.

Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin does not possess affinity for either GABAA or GABAB receptor nor does it alter the metabolism of GABA. It does not bind to other neurotransmitter receptors of the brain and does not interact with sodium channels. Gabapentin binds with

high affinity to the α2δ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the α2δ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug target other than α2δ.

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to α2δ through a reduction in release of excitatory neurotransmitters in regions of the central nervous system. Such activity may underlie gabapentin's anti-seizure activity. The relevance of these actions of gabapentin to the anticonvulsant effects in humans remains to be established.

Gabapentin also displays efficacy in several pre-clinical animal pain models. Specific binding of gabapentin to the α2δ subunit is proposed to result in several different actions that may be responsible for analgesic activity in animal models. The analgesic activities of gabapentin may occur in the spinal cord as well as at higher brain centers through interactions with descending pain inhibitory pathways. The relevance of these pre-clinical properties to clinical action in humans is unknown.

5.2 Pharmacokinetic properties

Gabapentin bioavailability is not dose proportional. That is, as the dose is increased, bioavailability decreases. Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours. Absolute bioavailability of gabapentin capsules is approximately 60%. Food, including a high-fat diet, has no effect on gabapentin pharmacokinetics.

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.

Gabapentin pharmacokinetics are not affected by repeated administration and steady-state plasma concentrations are predictable from single-dose data. Although plasma gabapentin concentrations were generally between 2 µg/mL and 20 µg/mL in clinical studies, such concentrations were not predictive of safety or efficacy. Plasma gabapentin concentrations are dose proportional at doses of 300 mg or 400 mg given every 8 hours. Pharmacokinetic parameters are given in TABLE 6.

TABLE 6

Summary of Gabapentin Mean (%RSD) Steady-state Pharmacokinetic Parameters Following Q8H Administration

Pharmacokinetic Parameter	300 mg (n = 7)		400 mg (n = 11)	
C_{max} (µg/mL)	4.02	(24)	5.50	(21)
t_{max} (h)	2.7	(18)	2.1	(47)
$t_{1/2}$ (h)	5.2	(12)	6.1	ND
$AUC_{(0-\infty)}$ (µg•h/mL)	24.8	(24)	33.3	(20)
Ae%	NA	NA	63.6	(14)

ND = Not determined

NA = Not available

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 L. In patients with epilepsy, gabapentin concentrations in the cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is eliminated solely by renal excretion. There is no evidence of metabolism in man. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

Gabapentin is removed from plasma by hemodialysis. Dose adjustment in patients with compromised renal function or in those undergoing hemodialysis is recommended (see Section **4.2 Posology and method of administration - Dose adjustment in impaired renal function in patients with neuropathic pain or epilepsy** and **Dose adjustment in patients undergoing hemodialysis**).

Gabapentin pharmacokinetics in children were determined in 24 healthy subjects between the ages of 4 and 12 years. In general, gabapentin plasma concentrations in children are similar to those in adults.

In a pharmacokinetic study in 24 healthy infants and children, pediatric subjects between 1 and 48 months of age achieved approximately 30% lower exposure (AUC) than that observed in pediatric subjects older than 5 years of age; C_{max} was lower and the clearance per body weight was higher in infants and younger children.

5.3 Preclinical safety data

Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2,000 mg/kg/day and to rats at 250, 1,000, and 2,000 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. Peak plasma drug concentrations in rats at 2,000 mg/kg/day were 10 times higher than plasma concentrations in humans given at 3,600 mg/day. The pancreatic acinar cell tumors in male rats were low-grade malignancies, which did not affect survival, did not metastasize or invade surrounding tissue and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumors in male rats to carcinogenic risk in humans is unclear.

Mutagenesis

Gabapentin demonstrated no genotoxic potential. It was not mutagenic *in vitro* in standard assays using bacterial or mammalian cells. 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.

Impairment of fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2,000 mg/kg (approximately 5 times the maximum daily human dose, on a mg/m^2 basis).

Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offsprings of mice, rats, or rabbits at doses up to 50, 30, and 25 times, respectively, the daily human dose of 3,600 mg (4, 5 or 8 times, respectively, the human daily dose, on a mg/m^2 basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs and hindlimbs in

rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1,000 or 3,000 mg/kg/day during organogenesis and in rats given 2,000 mg/kg/day prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3,600 mg, on a mg/m^2 basis.

No effects were observed in pregnant mice given 500 mg/kg/day (approximately half of the daily human dose, on a mg/m^2 basis).

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2,000 mg/kg/day in a fertility and general reproduction study; 1,500 mg/kg/day in a teratology study; and 500, 1,000, and 2,000 mg/kg/day in a peri-natal and post-natal study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3,600 mg, on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of post-implantation fetal loss occurred in female rabbits given 60, 300, and 1,500 mg/kg/day during organogenesis. These doses are approximately 1/4 to 8 times the daily human dose of 3,600 mg, on a mg/m^2 basis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each capsule also contains lactose, corn starch, and talc.

6.2 Incompatibilities

None known

6.3 Shelf-life

Please see detail on carton.

6.4 Special precautions for storage

Capsule: Do not store above 30°C

6.5 Dosage form and available pack sizes

Capsule

Alu/PVC/PVDC Blister of 10 capsules. 1, 3 and 6 blisters per unit box

7 MARKETING AUTHORIZATION HOLDER

Viatris Healthcare (Thailand) Limited

Manufactured by: Viatris Pharmaceuticals LLC, Vega Baja, Puerto Rico

Packed and released by: Pfizer Manufacturing Deutschland GmbH, Freiburg, GERMANY

Warnings (based on the Ministry of Public Health's Announcement)

1. The drug may cause drowsiness, should not drive a car or operate machinery or drink alcoholic beverages while taking the drug.
2. The drug may cause hematologic disorder.
3. Do not use the drug in pregnant women because it may cause infant's morbidity.
4. Use the drug with caution in patients with liver and kidney disease.