

GABAPENTIN TEVA

CAPSULES

Composition

Gabapentin Teva 300 mg

Each capsule contains

Active Ingredient

Gabapentin 300 mg

Other Ingredients

Talc, pregelatinized starch (from corn origin).

Capsule Shell

FD&C Red No.3, FD&C Yellow No.6, titanium dioxide, gelatin.

Gabapentin Teva 400 mg

Each capsules contains

Active Ingredient

Gabapentin 400 mg

Other Ingredients

Talc, pregelatinized starch (from corn origin).

Capsule Shell

Red iron oxide, yellow iron oxide, black iron oxide, titanium dioxide, gelatin.

Mechanism of Action

Gabapentin is an oral anticonvulsant agent structurally related to the inhibitory CNS neurotransmitter gamma-amino-butyric acid (GABA). Although Gabapentin was developed as a structural analog of GABA, it 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 does not exhibit affinity for a number of other common receptor sites. *In vitro* studies have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. The identity and function of this binding site remain to be elucidated.

The mechanism by which gabapentin exerts its anticonvulsant action is unknown but in animals it has properties in common with other anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy). The relevance of these models to human epilepsy is not known.

Analgesic activity has been shown in animal models of inflammatory and neuropathic pain.

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized.

Pharmacokinetics

Absorption

Gabapentin bioavailability is not dose-proportional (i.e., as dose is increased, bioavailability decreases). A 400 mg dose, for example, is about 25% less bioavailable than a 100 mg dose. Over the recommended dose range of 300 to 600 mg 3 times daily, however, the differences in bioavailability are not large, and bioavailability is about 60%. Food has no effect on the rate and extent of absorption.

Distribution

Gabapentin circulates largely unbound (less than 3%) to plasma protein.

The apparent volume of distribution after 1 mg I.V. administration is $58 \pm 6L$. In patients with epilepsy, steady-state pre-dose (C_{min}) concentrations of gabapentin in cerebrospinal fluid (CSF) were approximately equal to 20% of the corresponding plasma concentrations.

Metabolism/Excretion

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug; it is not appreciably metabolized.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Elimination rate constant, plasma clearance and renal clearance are directly proportional to creatinine clearance (C_{cr}). In elderly patients and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Pharmacokinetics in Patients with Renal Insufficiency

When subjects with renal insufficiency were administered single 400 mg oral doses, the mean half-life ranged from about 6.5 hours (patients with C_{cr} less than 60 ml/min) to 52 hours (C_{cr} less than 30 ml/min) and renal clearance from about 90 ml/min to about 10 ml/min. Mean plasma clearance decreased from about 190 to 20 ml/min. Therefore dosage adjustment is necessary in patients with compromised renal function (see Dosage and Administration).

Hemodialysis

In a study in anuric subjects, the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; dialysis 3 times a week (4 hours duration) lowered the apparent half-life of gabapentin by about 60% from 132 to 51 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects. Dosage adjustment in patients undergoing hemodialysis is necessary (see Administration and Dosage).

Effect of Age

The effect of age was studied in subjects 20 to 80 years of age. Apparent oral clearance of gabapentin decreased as age increased, from approximately equal to 225 ml/min in those less than 30 years of age to approximately equal to 125 ml/min in those more than 70 years of age. Renal clearance also declined with age; however, the decline in the renal clearance of gabapentin with age 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 Administration and Dosage).

Indications

Epilepsy

Gabapentin Teva is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy.

Neuropathic Pain

Gabapentin Teva is also indicated for the treatment of neuropathic pain in diabetic neuropathy or postherpetic neuropathy (neuralgia).

Contraindications

Known hypersensitivity to gabapentin or to any other ingredient of the preparation.

Warnings

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

Patients with epilepsy can be the subject of mood and behavioral disturbances. Such reports have been noted in patients on gabapentin although a causal link has not been established.

Withdrawal-precipitated seizure

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency and the precipitation of status epilepticus.

When in the judgment of the clinician there is a need for dose reduction, discontinuation or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of one week.

Status Epilepticus

In the placebo controlled studies, the incidence of status epilepticus in patients receiving gabapentin was 0.6% vs. 0.5% with placebo. Among the patients treated with gabapentin, 1.5% of the patients had status epilepticus. 45% of these patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with gabapentin is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with gabapentin.

Sudden and Unexplained Deaths

During the course of premarketing development of gabapentin, 8 sudden and unexplained deaths were recorded among 2203 patients. Some of these could represent seizure-related deaths in which the seizure was not observed (e.g., at night). This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving gabapentin.

Mutagenicity

Gabapentin did not demonstrate mutagenic or genotoxic potential in 3 *in vitro* and 2 *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow.

Carcinogenicity

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 adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day.

Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg per day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. Studies to attempt to define a mechanism by which this relatively rare tumor type is occurring are in progress. The relevance of this finding to carcinogenic risk in humans is unclear.

Teratogenicity

Gabapentin is fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to approximately 1 to 5 times the maximum human dose. There was an increased incidence of hydronephrosis in rats. The doses at which the effects occurred are approximately equal to 1 to 5 times the maximum human dose of 3600 mg/day.

In rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately equal to 1/4 to 8 times the maximum human dose.

Effect on Fertility and Reproduction

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m² basis).

Use in Pregnancy

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

Use during Lactation

It is not known whether gabapentin is secreted in human milk and the effect on the nursing infant is unknown. However, because many drugs are excreted in human milk, gabapentin should be used in women who are nursing only if the benefits clearly outweigh the risks.

Use in Pediatrics

Safety and effectiveness in pediatric patients below the age of 12 years in epilepsy have not been established.

Use in the indication for neuropathic pain is for adults over the age of 18 years.

Use in the Elderly

Safety and efficacy of gabapentin in geriatric patients have not been evaluated systematically and clinical trials did not include sufficient number of patients older than 65 years of age to determine whether they respond differently than do younger patients. However, in clinical studies of the drug in patients ranging from 20-80 years of age, gabapentin plasma clearance, renal clearance, and renal clearance adjusted for body surface area declined with age. If gabapentin is used in geriatric patients, the initial dosage may need to be reduced and caution should be exercised since renal, hepatic and cardiovascular dysfunction and concomitant disease or other drug therapy is more common in this age group than in younger patients.

Use in Patients with Impairment of Renal Function or those undergoing Hemodialysis.

Mean plasma clearance of gabapentin decreases when administered to patients with impaired renal function. Therefore dosage adjustment is recommended in patients with compromised renal function or those undergoing hemodialysis

Adverse Reactions

Epilepsy

The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus.

Approximately 7% of the 2074 individuals who received gabapentin in premarketing clinical trials discontinued because of an adverse event. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%).

Incidence in Controlled Clinical Trials

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin-treated patients with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when gabapentin was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

Table 1. Treatment-Emergent Adverse Event Incidence in 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	Gabapentin* N=543%	Placebo* N=378%
<i>Body as a Whole</i>		
Fatigue	11.0	5.0
Weight Increase	2.9	1.6
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
<i>Cardiovascular System</i>		
Vasodilation	1.1	0.3
<i>Digestive System</i>		
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
<i>Hematologic and Lymphatic Systems</i>		
Leukopenia	1.1	0.5
<i>Musculoskeletal System</i>		
Myalgia	2.0	1.9
Fracture	1.1	0.8

Body System/Adverse Event	Gabapentin* N=543%	Placebo* N=378%
<i>Central Nervous System</i>		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3
Twitching	1.3	0.5
Coordination Abnormal	1.1	0.3
<i>Respiratory System</i>		
Rhinitis	4.1	3.7
Pharyngitis	2.8	1.6
Coughing	1.8	1.3
<i>Skin and Appendages</i>		
Abrasion	1.3	0.0
Pruritus	1.3	0.5
<i>Urogenital System</i>		
Impotence	1.5	1.1
<i>Special Senses</i>		
Diplopia	5.9	1.9
Amblyopia**	4.2	1.1
<i>Laboratory Deviations</i>		
WBC Decreased	1.1	0.5

* Plus background antiepileptic drug therapy.

** Amblyopia was often described as blurred vision.

Other events in more than 1% of patients but equally or more frequent in the placebo group included: headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne.

Among the treatment-emergent adverse events occurring at an incidence of at least 10% of gabapentin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with gabapentin. The incidence of adverse events increased slightly with increasing age in patients treated with either gabapentin or placebo. Because only 3% of patients (28/291) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race.

Other Adverse Events Observed During All Clinical Trials

Gabapentin has been administered to 2074 individuals during all clinical trials, only some of which were placebo-controlled. 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 individuals 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 the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

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

Body as a Whole

Frequent

Asthenia, malaise, face edema.

Infrequent

Allergy, generalized edema, weight decrease, chill.

Rare

Strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System

Frequent

Hypertension.

Infrequent

Hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur.

Rare

Atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System

Frequent

Anorexia, flatulence, gingivitis.

Infrequent

Glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly.

Rare

Dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, 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 appearance.

*Hematologic and Lymphatic Systems***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.

*Central Nervous System***Frequent**

Vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility.

Infrequent

CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis.

Rare

Choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reactions, suicide gesture.

*Respiratory System***Frequent**

Pneumonia.

Infrequent

Epistaxis, dyspnea, apnea.

Rare

Mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

*Dermatological***Infrequent**

Alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex.

Rare

Herpes zoster, skin discolor skin papules photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System**Infrequent**

Hematuria, dysuria, urination frequency, cystitis urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal.

Rare

Kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicule 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, chorioetinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

Postmarketing and Other Experience

In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. These adverse reactions include: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, jaundice, Stevens-Johnson syndrome.

Neuropathic Pain

Based on placebo-controlled studies, the most common possible side-effects (>1/10) associated with treating neuropathic pain with gabapentin are: dizziness and somnolence.

Common possible side-effects (between 1/10 and 1/100) are: diarrhoea, dry mouth, peripheral edema, weight gain, abnormal gait, amnesia, ataxia, abnormal thinking, rash and amblyopia.

Uncommon possible side-effects (between 1/100 and 1/1000) are: accidental injury, asthenia, back pain, constipation, flatulence, nausea, confusion, hypesthesia, vertigo, dyspnea and pharyngitis.

Precautions

(See also Warnings)

Because of the possibility of increased seizure frequency, anticonvulsant drugs, including gabapentin, should not be discontinued suddenly. In controlled studies, the incidence of status epilepticus was 0.6% in patients receiving gabapentin and 0.5% in those receiving placebo. In all (uncontrolled and controlled) clinical studies of gabapentin therapy, the incidence of status epilepticus was 1.5%. Because adequate historical data are unavailable for comparison, it has not been established whether the incidence of status epilepticus in patients treated with gabapentin is higher or lower than would be expected in a similar population of patients not treated with the drug. Discontinuance of gabapentin and/or addition of an alternative anticonvulsant drug to existing therapy should be done gradually over a minimum of 1 week.

Effect on Ability to Drive and Operate Machinery

Gabapentin can produce drowsiness and dizziness, as well as possible blurred or double vision. Therefore patients should be cautioned that the drug may impair their ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle).

Drug Abuse and Dependence

The abuse and dependence potential of gabapentin has not been evaluated in human studies.

Drug Interactions

Note

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs. Thus gabapentin may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs

Gabapentin/Phenytoin/Carbamazepine/Valproic Acid/Phenobarbital: There is no interaction between gabapentin and phenytoin, valproic acid, carbamazepine or phenobarbital. Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving antiepileptic agents.

Gabapentin/Central Nervous System Depressants/Alcohol: Concomitant administration may lead to increased CNS depression.

Gabapentin/Oral Contraceptives: Co-administration of gabapentin with oral contraceptives including norethisterone and/or ethinyl estradiol does not influence the steady-state pharmacokinetics of either component.

Gabapentin/Antacids: In a clinical study where gabapentin and an aluminium and magnesium containing antacid were given at the same time, gabapentin's bioavailability was reduced by up to 24%. It is therefore recommended that gabapentin be taken about two hours following any such antacid administration.

Gabapentin/Probenecid: Renal excretion of gabapentin is unaltered by probenecid.

Gabapentin/Cimetidine: The slight decrease in renal excretion of gabapentin observed when co-administered with cimetidine is not expected to be of clinical importance.

Drug/Food Interactions: Food has no effect on gabapentin pharmacokinetics.

Diagnostic Interference

Because false positive readings were reported with the Ames N-Multistix SG, dipstick test when gabapentin or placebo was added to other anticonvulsant drugs, the more specific sulphosalicylic acid precipitation procedure is recommended to determine urine protein.

Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of gabapentin. The value of monitoring blood concentrations has not been established..

Information for Patients

Patients should be instructed to take gabapentin only as prescribed.

Patients should be advised that gabapentin may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate machinery until they have gained sufficient experience on gabapentin to gauge whether or not it affects their mental and/or motor performance adversely.

Dosage and Administration

Gabapentin is given orally with or without food.

Epilepsy

Gabapentin Teva is recommended for add-on therapy in patients over 12 years of age. Evidence bearing on its safety and effectiveness in children is not available.

The effective dose of gabapentin is 900 to 1800 mg/day and may be given in divided doses (3 times a day) using 300 mg or 400-mg capsules. Titration to an effective dose can take place rapidly over a few days, giving 300 mg on Day 1, 300 mg twice a day on Day 2, and 300 mg three times a day on Day 3. To minimize potential side effects, especially somnolence, dizziness, fatigue, and ataxia, the first dose on Day 1 may be administered at bedtime. If necessary, the dose may be increased 3 times a day up to 1800 mg/day. Dosage up to 2400 mg/day have been well tolerated in long-term 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. The maximum time between doses in the t.i.d. schedule should not exceed 12 hours. It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, because there are no significant pharmacokinetic interactions among gabapentin and other commonly used antiepileptic drugs, the addition of gabapentin does not alter the plasma level of these drugs appreciably.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended as follows:

Gabapentin Teva Dosage Based on Renal Function		
Renal Function Creatinine Clearance (ml/min)	Total Daily Dose (mg/day)	Dose Regimen (mg)
>60	1200	400 t.i.d..
30-60	600	300 t.i.d..
15-30	300	300 O.D.
<15	150	300 Q.O.D.*
Hemodialysis		200-300**

* Every other day.

** Loading dose of 300 to 400 mg in patients who have never received gabapentin, then 200 to 300 mg gabapentin following each 4 hours of hemodialysis.

Neuropathic Pain*Adults (over the age of 18)*

Gabapentin should be titrated to a maximum dose of 1800 mg per day.

Titration to an effective dose can progress rapidly and can be accomplished over a few days by administering 300 mg once a day on day 1, 300mg twice a day on day 2 and 300 mg three times a day on day 3, as described in the following table.

DOSING CHART - INITIAL TITRATION			
Dose	Day 1	Day 2	Day 3
900mg	300mg once a day	300mg two times a day	300mg three times a day

Thereafter, the dose can be increased using increments of 300 mg per day given in three divided doses to a maximum of 1800 mg per day. It is not necessary to divide the doses equally when titrating gabapentin.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy.

The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin may be given orally with or without food.

If gabapentin is discontinued, or the dose reduced or substituted with an alternative medication, this should be done gradually over a minimum of one week.

Elderly

Elderly patients may require dosage adjustment because of declining renal function with age.

Overdosage

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg.

Manifestations

Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdose of gabapentin up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Treatment

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.

Presentation

Packs of 100 capsules.

Manufacturer

Teva Pharmaceuticals Industries Ltd.
P.O.Box 3190, Petach Tikva