GABATA 300/400

Gabapentin Capsules USP 300 mg & 400 mg

Name and strength of active ingredient(s)
Gabapentin , 300 mg & 400 mg.

Description and composition:
GABATA 300:
White to off white, crystalline powder filled in size “1” yellow colour hard gelatin capsules imprinted “215” on body with blue ink.
Each hard gelatin capsule Contains.
Gabapentin USP …….. 300 mg

GABATA 400:
White to off white, crystalline powder filled in size “0” orange colour hard gelatin capsule imprinted “214” on body with blue ink.
Each hard gelatin capsule Contains.
Gabapentin USP …….. 400 mg

Pharmacodynamics
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.
It is proposed that this 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 has been shown to display efficacy in several 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 animal pain models properties to clinical action in humans is unknown.

Pharmacokinetics
Absorption
Gabapentin bioavailability is not dose-proportional. That is, as the dose is increased, bioavailability decreases.
Gabapentin is absorbed from the gastrointestinal tract by means of a saturable mechanism. After multiple dosing peak plasma concentrations usually occur within 2 to 3 hours of a dose and a steady state within 1 to 2 days.

Absolute bioavailability of gabapentin capsules is approximately 60%.

Distribution
Gabapentin is distributed into breast milk.

It is widely distributed throughout the body but binding to plasma proteins is minimal. It has a volume of distribution equal to 57.7 liters.

Metabolism
Gabapentin is excreted unchanged in the urine, and is not appreciably metabolized.

Excretion
The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

The renal clearance of gabapentin was 150 mL/min.
Fecal: 10% to 23%
Renal: 76% to 81%
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.

Indications
Epilepsy:
Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children age 3 years and above. Safety and effectiveness for adjunctive therapy in pediatric patients below the age of 3 years have not been established.

Neuropathic pain:
Gabapentin is indicated for the treatment of neuropathic pain which includes diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia in adults age 18 years and above. Safety and effectiveness in patients below the age of 18 years have not been established.

Mode of Administration
Oral

Dosage and Administration
General:
Gabapentin 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 one week.

Epilepsy:
Adults and pediatric patients over 12 years of age:
The effective dosing range was 900 to 3600 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 in Table 1. Thereafter, the dose can be increased in three equally divided doses up to a maximum dose of 3600 mg/day. Dosages up to 4800 mg/day have been well tolerated. The maximum time between doses in the three times a day (TID) schedule should not exceed 12 hours to prevent breakthrough convulsions.

Table 1. Dosing Chart – Initial Titration

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Dose	Day 1	Day 2	Day 3
900 mg	300mg 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 age 3-12 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 three days. The effective dose of gabapentin in pediatric patients age 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 ages 3 to less than 5 years is 40 mg/kg/day given in equally divided doses (three times a day). Dosages up to 50 mg/kg/day have been well tolerated. The maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, gabapentin 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 as three equally divided doses, and increased if necessary, based on response, up to a maximum dose of 3600 mg/day. Therapy should be initiated by titrating the dose as described in Table 1.

Dosage adjustment in impaired renal function for patients with neuropathic pain or epilepsy:
Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing hemodialysis.

Table 2. Dosage of Gabapentin in Adults based on Renal function

Creatinine Clearance (mL/min)	Total Daily Dosea mg/day
⩾80	900 - 3600
50-79	600 -1800
30-49	300 - 900
15-29	150[b] - 600
<15	150[b] - 300

[a]Total daily dose should be administered as a divided TID regimen. Doses used to treat patients with normal renal function (creatinine clearance >80 mL/min) range from 900 to 3600 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.

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

Contraindication
Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to gabapentin or the inactive ingredients in the capsules.

Warning and precautions
Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
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 (see section Undesirable effects).

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.

Suicidal ideation and behavior
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. It has been shown for a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Acute pancreatitis
If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered.

Seizures
Abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus (see section Posology and method of administration).

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

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
Patients who require concomitant treatment with opioids should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression. Patients who use gabapentin and morphine concomitantly may experience increases in gabapentin concentrations. The dose of gabapentin or opioids should be reduced appropriately.

Respiratory depression
Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

Elderly (over 65 years of age)
It has been shown in patients with neuropathic pain & somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

Paediatric population
The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

Abuse and dependence
Cases of abuse and dependence have been reported. Carefully evaluate patients for a history of drug abuse and observe them for possible signs of gabapentin abuse e.g. drug-seeking behaviour, dose escalation, development of tolerance.

Laboratory tests
False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

Effects on the ability to drive and use machines
Gabapentin may impair the ability to drive a car or operate potentially dangerous machinery. Patients are advised not to drive or operate potentially dangerous machinery, until it is known that this medication does not affect their ability to engage in these activities.

Interactions with other medicaments
There are reports of respiratory depression and/or sedation associated with gabapentin and opioid use. In some of these reports, the authors considered this a particular concern with the combination of gabapentin and opioids, especially in elderly patients.

Patients who require concomitant treatment with opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or opioid should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

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 aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two 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.

Pregnancy and lactation
Pregnancy:
There is insufficient clinical experience with gabapentin in pregnancy to confirm its safety in this patient population. Since gabapentin is frequently prescribed with other anticonvulsants, a clear association between maternal gabapentin use and fetal adverse effects cannot be determined. Due to lack of adequate, well-controlled studies, hence it is recommended that gabapentin should be used during pregnancy only if the potential benefit 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.

Side effects
The adverse reactions observed (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency (very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) in italics in the list below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations
Very Common: Viral infection
Common: Pneumonia, respiratory infection, urinary tract infection, infection, otitis media

Blood and lymphatic system disorders
Common: leucopenia
Not known: *thrombocytopenia*

Immune system disorders
Uncommon: allergic reactions (e.g. urticaria)
Not known: hypersensitivity syndrome (a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms), anaphylaxis.

Metabolism and nutrition disorders
Common: anorexia, increased appetite
Uncommon hyperglycaemia (most often observed in patients with diabetes)
Rare hypoglycaemia (most often observed in patients with diabetes)
Not known hyponatraemia.

Psychiatric disorders
Common: hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal
Uncommon agitation
Not known: hallucinations

Nervous system disorders
Very common: somnolence, dizziness, ataxia,
Common: convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Uncommon: hypokinesia
Rare loss of consciousness
Not known: other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)

Eye disorders
Common: visual disturbances such as amblyopia, diplopia

Ear and labyrinth disorders
Common: vertigo
Not known: *tinnitus*

Cardiac disorders
Uncommon: palpitations

Vascular disorders
Common: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders
Common: dyspnoea, bronchitis, pharyngitis, cough, rhinitis
Rare respiratory depression

Gastrointestinal disorders
Common: vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence
Not known: pancreatitis

Hepatobiliary disorders
Not known: hepatitis, jaundice

Skin and subcutaneous tissue disorders
Common: facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne
Not known: Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia, drug rash with eosinophilia and systemic symptoms (see Special warnings and precautions for use)

Musculoskeletal and connective tissue disorders
Common: arthralgia, myalgia, back pain, twitching
Not known: rhabdomyolysis, myoclonus

Renal and urinary disorders
Not known: acute renal failure, incontinence

Reproductive system and breast disorders
Common: impotence
Not known: breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia).

General disorders and administration site conditions
Very common: fatigue, fever
Common: peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Uncommon: generalized oedema
Not known: withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.

Investigations
Common: WBC (white blood cell count) decreased, weight gain
Uncommon: elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin
Not known: blood creatine phosphokinase increased

Injury, poisoning and procedural complications
Common: accidental injury, fracture, abrasion
Uncommon fall

In patients on haemodialysis due to end-stage renal failure, myopathy with elevated creatine kinase levels has been reported.

Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in children. Additionally, in children, aggressive behaviour and hyperkinesias were reported commonly.

Symptoms and Treatment of over dose
Symptoms
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 diarrhoea. 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.

Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

Treatment
Treatment of gabapentin exposure is largely supportive in nature with careful attention to airway protection in severe cases.

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.

Storage condition
Store below 30°C.

Shelf life
36 months.

Presentation:
Each blister pack contains 10 Capsules. Available in pack sizes of 5 blister of 10's and 10 blister of 10's.

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