NEURAN CAPSULE

VINEU14-1 (SIN)

DESCRIPTION
Light yellow opaque / light yellow opaque with 'GP300' printed on one end and 'hovid' on the other end of the size 1 capsule filled with white to off-white powder.

COMPOSITION
Each capsule shell contains: Gabapentin 300 mg
Excipients: Gelatin, titanium dioxide, iron oxide yellow, partial pregelatinized starch, talc and magnesium stearate

ACTIONS AND PHARMACOLOGY
Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin does not possess affinity for either GABA A or GABA B 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.

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.

PHARMACOKINETICS
Absorption: Rapid. Gabapentin is absorbed in part by the L-amino acid transport system, which is a carrier-mediated, saturable transport system; as the dose increases, bioavailability decreases. Absolute bioavailability of a 300 mg capsule is approximately 60%.

Distribution: Volume of distribution (Vol_D) is approximately 50 to 60 L. Gabapentin penetrates the blood-brain barrier, yielding cerebrospinal fluid (CSF) concentrations approximately equal to 20% of corresponding steady-state plasma trough concentrations in patients with epilepsy. Brain tissue concentrations in one patient undergoing temporal lobectomy were approximately 80% of corresponding plasma concentrations.

Protein Binding: Very low (< 5%).

Biotransformation: Gabapentin is not metabolized.

Elimination:
- Renal - Entire absorbed dose, as unchanged drug. Gabapentin clearance is directly proportional to creatinine clearance.
- In dialysis - Gabapentin can be removed from plasma by hemodialysis. The elimination half-life of Gabapentin is independent of dose and averages 5 to 7 hours.

INDICATIONS
Epilepsy: Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 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.

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

PRECAUTIONS
- General: Although there is no evidence of rebound seizures with gabapentin abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus.
- Gabapentin is not generally considered effective in the treatment of absence seizures.
- Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.
- Inform your physician about any prescription or non- prescription medications, alcohol, or drugs you are now taking or plan to take during your treatment with gabapentin.
- 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.
- Gabapentin has potential for an increase of suicidal thoughts or behaviours.
- Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of central nervous system (CNS) depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

Neuropsychiatric adverse events - pediatric patients 3-12 years of age: Gabapentin use in pediatric patients with epilepsy 3–12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

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 observe them for possible signs of gabapentin abuse.

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 central nervous system (CNS) 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.

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]).

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.

PREGNANCY AND LACTATION
Use During Pregnancy:
- There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.
- 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.

Use During 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. You should inform your physician if you are breastfeeding an infant.
- Gabapentin should be used in nursing mothers only if the benefits clearly out-weigh the risks.

DRUG INTERACTION
- 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 anti-epileptic agents.
- Coadministration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.
- Coadministration 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 coadministered with cimetidine is not expected to be of clinical importance.
- False-positive readings were reported with the Ames N-Multistix SG® dipstick test when gabapentin was added to other anti-convulsant drugs. To determine urinary protein, the more specific sulfosalicylic acid precipitation procedure is recommended.
- There are spontaneous and literature case reports of respiratory depression, sedation and death associated with gabapentin when co-administered 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.

MAIN SIDE/ADVERSE EFFECTS

Epilepsy

Adverse events were usually reported as mild to moderate.

Below are the treatment-emergent signs and symptoms that occurred in at least 1% of patients with partial seizures:

- **Body as a whole:** Abdominal pain, back pain, fatigue, fever, headache and viral infection.
- **Cardiovascular:** Vasodilation.
- **Digestive system:** Constipation, dental abnormalities, diarrhea, dyspepsia, increased appetite, mouth or throat dry and nausea and/or vomiting.
- **Hematologic and lymphatic:** Leukopenia and WBC decreased
- **Metabolic and nutritional:** Peripheral edema and weight increase
- **Musculoskeletal system:** Fracture and myalgia
- **Nervous system:** Amnesia, ataxia, confusion, coordination abnormal, depression, dizziness, dysarthria, emotional lability, insomnia, nervousness, somnolence, thinking abnormal, tremor and twitching
- **Respiratory system:** Coughing, pharyngitis and rhinitis
- **Skin and appendages:** Abrasion, acne, pruritus and rash
- **Special senses:** Amblyopia and diplopia
- **Urogenital system:** Impotence

Other adverse events observed during all clinical trial

Those events that occurred in at least 1% of the study participants with epilepsy who received gabapentin as adjunctive therapy in any clinical trial are summarized below.

- **Body as a whole:** Asthenia, malaise, facial edema
- **Cardiovascular system:** Hypertension
- **Digestive system:** Flatulence, anorexia, gingivitis
- **Hematologic and lymphatic system:** 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

Geriatric use: Side effects reported among individual aged 65 years or older did not differ in kind from those reported in younger individuals.

Pediatric use: The most commonly observed adverse events reported with the use of gabapentin combination with other anti-epileptic drugs in children aged 3 to 12 years were viral infection, fever, nausea, vomiting and somnolence.

Treatment-emergent adverse events reported in at least 2% of gabapentin patients are as below:

- **Body as a whole:** Viral infection, fever, weight increase and fatigue
- **Digestive system:** Nausea and/or vomiting
- **Nervous system:** Somnolence, hostility, emotional lability, dizziness and hyperkinesia
- **Respiratory system:** Bronchitis and respiratory infection

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.

Neuropathic pain

Summary of treatment-emergent signs and symptoms in ≥1% of Gabapentin-treated Patients in Neuropathic Pain:

- **Body as a whole:** Abdominal pain, accidental injury, asthenia, back pain, flu syndrome, headache, infection and pain
- **Digestive system:** Constipation, diarrhea, dry mouth, dyspepsia, flatulence, nausea and vomiting
- **Metabolic and nutritional:** Peripheral edema and weight gain
- **Nervous system:** Abnormal gait, amnesia, ataxia, confusion, dizziness, hypesthesia, somnolence, thinking abnormal, tremor and vertigo
- **Respiratory system:** Dyspnea and pharyngitis
- **Skin and appendages:** Rash
- **Special senses:** Amblyopia

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, 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, urinary incontinence and respiratory depression.

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

OVERDOSE

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 grams. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, 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, minimise toxicity from overdoses. Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

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

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

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 1 week.

Epilepsy

Adults and pediatric patients older than 12 years of age:

In clinical trials, the effective dosing range was 900mg/day to 1800mg/day. Therapy may be initiated by administering 300mg 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 1800 mg/day. Doses up to 2400mg/day have been well tolerated in long-term open-label clinical studies. Doses up to 3600mg/day have 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 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
900mg	300mg once a day	300mg twice a day	300mg 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 gabapentin 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.

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 3600 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 GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION

Creatinine Clearance (ml/min)	Total Daily Dose[a] (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 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 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.

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.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage: Store below 30˚C. Protect from moisture.

Presentation/Packing:
PVC/PVDC-Aluminium Blister pack of 10 x10's.

Product Owner: HOVID Bhd.
121, Jalan Tunku Abdul Rahman, 30010 Ipoh, Malaysia.

Manufactured by: HOVID Bhd.
Lot 56442, 7 ½ Miles, Jalan Ipoh/Chemor,
31200 Chemor, Malaysia.

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