Neurovyx® Capsule 300mg

Active Ingredient:
Each capsule contains:
Gabapentin 300mg

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. 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.

Pharmacokinetics:
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 300mg or 400mg given every 8 hours. Pharmacokinetic parameters are given in Table 1.

Table 1: Summary of Gabapentin Mean (%RSD) Steady-state Pharmacokinetic Parameters Following Q8H Administration

Pharmacokinetic Parameter	300mg (n = 7)		400mg (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.
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.

Indication(s):
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 older. Safety and effectiveness for adjunctive therapy in paediatric patients younger than 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 aged 18 years and older. Safety and effectiveness in patients younger than 18 years have not been established.

Dosage and Administration(s):
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 paediatric patients older than 12 years of age
In clinical trials, the effective dosing range was 900mg/day to 3600mg/day. Therapy may be initiated by administering 300mg three times a day on Day 1 or by titrating the dose (Table 2). Thereafter, the dose can be increased in three equally divided doses up to a maximum dose of 3600mg/day. Doses up to 4800mg/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 2: 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

Paediatric patients aged 3 to 12 years
The starting dose should range from 10 to 15mg/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 paediatric patients aged 5 years and older is 25 to 35mg/kg/day given in equally divided doses (three times a day). The effective dose in paediatric patients aged 3 to less than 5 years is 40mg/kg/day given in equally divided doses (three times a day). Doses up to 50mg/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 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 900mg/day given in three equally divided doses, and increased if necessary, based on response, up to a maximum dose of 3600mg/day. Therapy should be initiated by titrating the dose (Table 2).

Dose adjustment in impaired renal function in patients with neuropathic pain or epilepsy
Dose adjustment is recommended in patients with compromised renal function (Table 3) and/or in those undergoing haemodialysis.

Table 3: Dosage of Gabapentin in Adults Based on Renal Function

Creatinine Clearance (mL/min)	Total Daily Doses[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 ≥ 80mL/min) range from 900mg/day to 3600mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance < 79mL/min).

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

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

Route of Administration(s):
For oral administration.

Contraindication(s):
Gabapentin is contraindicated in patients who are hypersensitive to gabapentin or any components of the product.

Warning and Precaution(s):
General
Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus.
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.

Caution is advised when prescribing gabapentin concomitantly with opioids due to risk of CNS depression.

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.

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 and observe them for possible signs of gabapentin abuse. Potential for an increased in risk of suicidal thoughts or behaviours.

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.

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.
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.

Interaction with Other Medicaments(s):

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 60mg controlled-release morphine capsule was administered 2 hours prior to a 600mg 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.

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.
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 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 coadministered 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.

Fertility, Pregnancy and Lactation:
Fertility
There is no effect on fertility in animal studies.
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 1700 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 paediatric 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. 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.

Side Effect(s):
The adverse reactions observed during clinical studies conducted in epilepsy (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 (≥ 1/10000 to < 1/1000); very rare (< 1/10000). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported. Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) 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 the 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: suicidal ideation, hallucinations, drug dependence
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, mental impairment
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 disorder
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
Uncommon: dysphagia
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
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*, chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.
Investigations
Common: white blood cell (WBC) 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

*After discontinuation of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed. Withdrawal symptoms may occur shortly after discontinuation, usually within 48 hours. Most frequently reported symptoms include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise. The occurrence of withdrawal symptoms following discontinuation of gabapentin may indicate drug dependence. The patient should be informed about this at the start of the treatment. If gabapentin should be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear.
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 clinical studies in children. Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.

Post-marketing experience: Dysphagia

Effects on Ability to Drive and Use Machine:
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.

Symptoms and Treatment of Overdose(s):
Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49g. 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.
Although gabapentin can be removed by haemodialysis, based on prior experience, it is usually not 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.

Storage Condition:
Store below 30°C.

Shelf Life(s):
30 months.

Product Description and Packing(s):
A size #1 yellow colour cap and body hard gelatin capsule, containing white powder.
Alu-alu blister packing of 10's x 10.

Y. S. P.®

Manufacturer and Product Registration Holder:
Y.S.P. INDUSTRIES (M) SDN. BHD. (199001001034)
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