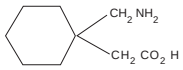
GABAPENTIN

GABIX®

100mg and 300mg Capsule
Neuropathic Pain/
Anti-Convulsant

DESCRIPTION
Gabapentin (GABIX®) is a new antiepileptic drug that is structurally similar to the neurotransmitter gamma aminobutyric acid (GABA) and the endogenous amino acid L-leucine. Chemically gabapentin is 1-(aminomethyl) cyclohexaneacetic acid. Its molecular formula is $C_9H_{17}NO_2$. The structural formula is:



Gabapentin

FORMULATION
Gabapentin (GABIX®) is available for oral administration as:

1. Gabapentin (GABIX®) Capsules 100mg
   Each capsule contains:
   Gabapentin …100mg

2. Gabapentin (GABIX®) Capsules 300mg
   Each capsule contains:
   Gabapentin …300mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Gabapentin has proven affinity for special site in brain tissues such as neocortex and hippocampus. Though exact mechanism of its CNS depressant and anticonvulsant activity is not fully understood, it is thought to be activated through peptide binding sites (receptor).

Pharmacokinetics
Absorption
Gabapentin is absorbed from the gastrointestinal tract by means of saturable mechanism. Gabapentin bioavailability is not dose proportional i.e., as dose is increased bioavailability is decreased. Absolute bioavailability of 300mg oral dose is approximately 60%. At doses of 300mg and 400mg, gabapentin bioavailability was unchanged following multiple-dose administration. Food has no effect on the rate and extent of absorption.

Distribution
Gabapentin circulates largely unbound (<3%) to plasma proteins. Gabapentin is distributed into breast milk.

Metabolism and Elimination
Gabapentin is not appreciably metabolised and is eliminated from the systemic circulation by renal excretion as unchanged drug. Elimination half-life ($t_{1/2}$) ranges from 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance and renal clearance are directly proportional to creatinine clearance.

Special Populations
Renal Insufficiency
The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance (CL_{cr}) >60mL/min) to 52 hours (CL_{cr} <30mL/min) and gabapentin renal clearance ranged from 90mL/min (CL_{cr} >60mL/min) to about 10mL/min (CL_{cr} <30mL/min). Gabapentin dosage should be adjusted in patients with compromised renal function.

Patients on Hemodialysis
In anuric patients, the elimination half-life of gabapentin on a nondialysis day was about 132 hours; during dialysis the apparent half-life was reduced to 3.8 hours. Thus hemodialysis has a significant effect on gabapentin elimination in anuric patients.
Gabapentin dosage should be adjusted in patients undergoing hemodialysis.

Elderly Patients
The apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225mL/min in those under 30 years of age to about 125mL/min in those over 70 years of age. Reduction of gabapentin dose may be required in patients who have age related compromised renal function.

Drug-Drug Interactions
Naproxen: Co-administration of naproxen sodium (250mg) with gabapentin (125mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose is not known.

Hydrocodone: Co-administration of gabapentin decreases hydrocodone C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone. Hydrocodone increases gabapentin AUC values by 14%.

Morphine: When 60mg of morphine administered 2 hours prior to 600mg of gabapentin, the mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine.

THERAPEUTIC INDICATIONS
Gabapentin (GABIX®) is indicated:
- For various types of neuropathic pain in adults:
  - Postherpetic neuralgia (PHN)
  - Peripheral diabetic neuropathies.
  - Trigeminal neuralgia.
- As adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Gabapentin (GABIX®) is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 6 – 12 years.

DOSAGE & ADMINISTRATION
Gabapentin (GABIX®) is given in titrations that lead to an effective dose. Treatment progresses rapidly and can be accomplished over a few days. The total dose should be divided into three doses given at intervals not exceeding 12 hours. Gabapentin (GABIX®) may be given orally with or without food.

Neuropathic Pain (Adults-over the age of 18)
The initial daily dose of Gabapentin (GABIX®) can be titrated as given in the table below. Thereafter the dose maybe increased in increments of 300mg daily up to a maximum of 3600mg/day in three divided doses. It is not necessary to divide the doses equally when titrating Gabapentin (GABIX®).

Day 1	Day 2	Day 3
300mg Once a day	300mg Two times a day	300mg Three times a day.

Effectiveness as an adjunct therapy of neuropathic pain in pediatric patients has not been established.

Epilepsy
Adults and children over 12 years of age:
Therapy may be initiated by administering 300mg three times a day on day 1 or by titrating the dose as described in the following table.

Day 1	Day 2	Day 3
300mg Once a day	300mg Two times a day	300mg Three times a day.

Thereafter the dose maybe increased in increments of 300mg daily until effective epileptic control is achieved, which is usually within the range of 900-1200mg daily. Higher doses up to a maximum of 2400mg daily may be required in some patients.

Children aged 6 to 12 years:
The initial recommended dose of Gabapentin (GABIX®) is 25-35mg/kg/day given in divided doses (3 times a day). Titration to an effective dose can take place over 3 days by giving 10mg/kg/day on day 1, 20mg/kg/day on day 2, and 25-35mg/kg/day on day 3.
The following table shows the recommended maintenance doses according to the respective weight.

Weight Range (Kg)	Daily Dose (mg/day)
26-36	900
37-50	1200

Special Populations
Renal Impaired Patients
A dosage adjustment is recommended in renally impaired patients with neuropathic pain or epilepsy.

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

[a]Total daily dose should be administered as a tid regimen. Doses used to treat patients with normal renal function (creatinine clearance >80mL/min) range from 900 to 3600mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance <79mL/min)
[b]To be administered on every other day.

Patients undergoing Hemodialysis
The recommended loading dose of Gabapentin (GABIX®) is 300-400mg then 200-300mg following each 4 hours of hemodialysis.

ADVERSE REACTIONS
Neuropathic Pain
Common: Dizziness, somnolence.

Less Common: Diarrhea, dry mouth, peripheral oedema, weight gain, abnormal gait, amnesia, ataxia, abnormal thinking, rash and amblyopia.

Rare: Accidental injury, asthenia, back pain, constipation, flatulence, nausea, confusion, hypesthesia, vertigo, dyspnea and pharyngitis.

Epilepsy (Adults)
Common: Dizziness, somnolence.

Less Common: Ataxia, fatigue, nystagmus, tremor, diplopia, amblyopia, abnormal vision, dysarthria, amnesia, asthenia, paraesthesia, arthralgia, purpura, dyspepsia, anxiety, weight increase, urinary tract infection and pharyngitis.

Uncommon: Leucopenia, nervousness, rhinitis and male sexual dysfunction (impotence).

Rare: Urinary incontinence, pancreatitis, elevated liver function tests, erythema multiforme and Stevens Johnson Syndrome, confusion, depression, emotional lability, hostility, abnormal thinking and psychoses/hallucinations, blood glucose fluctuations in patients with diabetes, myalgia, headache, nausea and/or vomiting.

Epilepsy (Children 3-12 years)
Common: Emotional lability, nervousness and thinking abnormally. All reports of these events were rated as mild or moderate and discontinuation or dose reduction was infrequent.

Uncommon: Somnolence, fatigue, weight increase, hostility, emotional lability, dizziness, hyperkinesia, nausea/vomiting, viral infection, fever, bronchitis, respiratory infection.

Adverse events associated with both epilepsy and neuropathic pain include: acute kidney failure, allergic reaction including urticaria, alopecia, angioedema, chest pain, hepatitis, jaundice, movement disorders such as choreoathetosis, dyskinesia and dystonia, palpitation, thrombocytopenia, and tinnitus.

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

CONTRAINDICATIONS
Gabapentin is contraindicated in patients with known hypersensitivity to gabapentin or any of the components of the product.

PRECAUTIONS
- Gabapentin should not be abruptly discontinued because of the possibility of increasing seizure frequency.
- Caution is recommended in patients with a history of psychotic illness.
- Gabapentin should not be considered a treatment of absence seizures and may exacerbate these seizures in some patients. Consequently, gabapentin should be used with caution in patients who have mixed seizure disorders that include absence seizures.
- Patients should be advised neither to drive a car nor to operate complex machinery until they have gained sufficient experience on gabapentin.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Gabapentin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Gabapentin is secreted into breast milk following oral administration. The effect on the nursing infant is unknown. Therefore, gabapentin should be used in nursing women only if the potential benefits clearly out weigh the risks.

Drug Interactions
Phenytoin, Valproic acid, Carbamazepine or Phenobarbitone: There is no interaction during the concomitant administration of gabapentin with these drugs. Gabapentin steady-state pharmacokinetics is similar for healthy subjects and patients with epilepsy receiving anti-epileptic agents.

Morphine: 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.

Antacid: Gabapentin's bioavailability was reduced by up to 24% when co-administered at the same time with an aluminum and magnesium containing antacid. It is recommended that gabapentin be taken about two hours following any such antacid administration.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

Keep out of reach of children.

AVAILABILITY
Gabapentin (GABIX®) 100mg capsules are available in blister pack of 10's.

Gabapentin (GABIX®) 300mg capsules are available in blister pack of 10's.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to FDA: www.fda.gov.ph

REGISTRATION NUMBER:
Gabix Capsule 100mg: DR-XY34011
Gabix Capsule 300mg: DR-XY34012

DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION
Gabix Capsule 100mg:
Initial: 27 November, 2007
Renewal: 05 December, 2012

Gabix Capsule 300mg:
Initial: 27 November, 2007
Renewal: 06 December, 2012

DATE OF REVISION OF PACKAGING INSERT 02 October, 2017.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Getz pharma (PVT) LIMITED
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