GABATREX®

Gabapentin

ACTION

Gabapentin is a lipophillic analogue structurally related to GABA. Its precise mechanism of action is not yet known. Gabapentin is not active at $GABA^A$ and $GABA^B$ receptors nor at GABA uptake carriers in the brain. Gabapentin binds with high affinity to binding sites in the brain which are associated with alpha2delta-subunits of voltage sensitive calcium channels. In vitro, gabapentin modulates the activity of the GABA sensitizing enzyme GAD as well as the activity of the glutamate synthesizing enzyme. NMR investigations revealed that gabapentin increases GABA synthesis in rat and human brain. The release of various monoamine neurotransmitters is being reduced. In various animal models, gabapentin showed anticonvulsive, analgesic, anxiolytic and neuroprotective properties.

Mean C_{max} plasma gabapentin concentrations occurred approximately 3 hours (t_{max}) following single oral doses of gabapentin regardless of dose size or formulation. Mean t_{max} values following multiple dose administration were approximately 1 hour shorter than the values following single-dose administration.

Mean C_{max} and AUC values increased with increasing dose; pharmacokinetic investigations were performed in 24 healthy children between the ages of 4 and 12 years. In general, plasma gabapentin concentrations found in children are similar to those in adults. Following repeated, three times daily gabapentin administration, steady-state was achieved within 1 to 2 days and was maintained throughtout the dosing regime. Absolute bioavailability of a 300 mg capsule was approximately 60%. At doses of 300 mg and 400 mg, gabapentin was unchanged following multiple-dose administration. The presence of food did not influence the bioavailability of gabapentin. Gabapentin is not metabolized in humans and does not lead an enzyme induction of the enzymes responsible for metabolization of drugs (hepatic mixed function oxidase enzymes). Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 liters. Elimination half-life ($t_{1/2}$) of gabapentin ranged from 5 to 7 hours. Gabapentin elimination parameters such as elimination half-life ($t_{1/2}$) and renal clearance (Cl_R), were independent of dose and remained unchanged following repeated administration. Renal clearance was the sole elimination pathway for gabapentin. In elderly patients, age-related alterations in renal function (determined as decreased createnine clearance) decrease gabapentin plasma clearance and increase gabapentin elimination half-life. Gabapentin is removed from plasma by hemodialysis. Dosage adjustment in patients with impaired renal function or undergoing hemodialysis is recommended.

INDICATIONS

Neuropathic pain:

For the treatment of neuropathic pain in adults.

Monotherapy and add-on therapy in epilepsy.

DOSAGE AND ADMINISTRATION

It must be noted that Gabatrex is available in capsule form in the strengths of 100 mg, 300 mg and 400 mg gabapentin.

The dose is determined by the treating physician depending on the individual tolerance and effect.

Dosage increases to an initial maintenance dose and further increases of the required dose may be attained quickly.

• Neuropathic pain:

Initial and maintenance dose

On the first 3 days of treatment, step-wise dose increase may be made to 900 mg gabapentin/day according to the following dosing scheme:

	Morning	Noon	Evening
Day 1 (300 mg gabapentin/day)	---	---	1 Gabatrex 300 mg Capsule
Day 2 (600 mg gabapentin/day)	1 Gabatrex 300 mg capsule	---	1 Gabatrex 300 mg capsule
Day 3 (900 mg gabapentin/day)	1 Gabatrex 300 mg capsule	1 Gabatrex 300 mg capsule	1 Gabatrex 300 mg capsule

As an alternative, if the pain intensity requires, 3 x daily 1 Gabatrex 300 mg capsule (corresponding to 900 mg gabapentin/day) may be taken starting on Day 1.

Then the daily dose may be increased within a week to 1800 mg gabapentin, thereafter to maximally 3600 mg gabapentin, if necessary. The total daily dose may not exceed 3600 mg gabapentin.

The total daily dose should be divided into three equal single doses.

• Note for all indications

Dosage increases should be made in increments using Gabapentin 100 mg capsules for patients in poor general condition, with low body weight, or following transplantation, etc.

For patients with impaired renal function (creatinine clearance less than 80 ml/min), and patients undergoing hemodialysis, the dosage should be adjusted according to the following table. In these patients, Gabatrex should be administered in capsule form (100 mg, 300 mg or 400 mg).

Dosage in reduced renal function

Renal function Creatinine clearance (mL/min)	Gabapentin total daily dose* (range in mg/day)
≥ 80	900-3600 mg
50-79	600-1800 mg
30-49	300-900 mg
15-29	150**-600 mg
<15	150**-300 mg

* Divided into three single doses daily ** 300 mg gabapentin every other day

For patients undergoing hemodialysis who have never received Gabatrex, a loading dose of 300 mg to 400 mg gabapentin is recommended, then 200 mg to 300 mg gabapentin following each 4 hours of hemodialysis. On dialysis-free days there should be no treatment with Gabatrex.

Method and duration of administration

Gabatrex capsules should be swallowed whole with sufficient fluid intake. Administration may be made during or between meals. In three-times daily administration, care should be taken that the interval between two single doses does not exceed 12 hours.

Whether a missed dose of Gabatrex (this means more than 12 hours passed since the last administration) should be made up for by taking an additional dose of Gabatrex later or not is at the physician's discretion.

In concurrent treatment with magnesium or aluminum containing antacids, Gabatrex should be taken at least 2 hours after administration of the antacid. This largely avoids a reduction in gabapentin bioavailability.

The duration of administration depends on the clinical requirements.

If therapy with Gabatrex capsules should be discontinued, the dose reduced, or switched to another drug, this should be done gradually over a minimum of one week, although there is no avidence of a rebound phenomenon.

In the treatment of neuropathic pain, efficacy and safety has not been examined in clinical studies for treatment periods longer than 5 months.

CONTRAINDICATIONS

Gabatrex is not to be used in known hypersensitivity to any of the ingredients.

Gabatrex is contraindicated in patients with acute pancreatitis.

Gabatrex is not effective against primarily generalized seizures, such as absences.

WARNINGS AND PRECAUTIONS

For patients with impaired renal function, the gabapentin dosage must be reduced.

Hemorrhagic pancreatitis has been reported under treatment with gabapentin.

For this reason, treatment with Gabatrex must be stopped at the first sign of clinical symptoms of pancreatitis (persistent upper abdominal complaints, nausea and recurrent vomiting). In addition to thorough clinical examination, appropriate laboratory tests should also be performed for early recognition of pancreatitis. Experience with the use of gabapentin in chronic pancreatitis is not adequate. The treating physician must decide in such cases whether treatment with Gabatrex should be continued or withdrawn.

Pregnancy and lactation

Gabatrex should be taken during pregnancy only after careful benefit-risk assessment, since no experience has been made with the safety of use during pregnancy. Gabapentin is excreted in human milk. Since it cannot be ruled out that Gabatrex may cause side effects in the infant, gabapentin treatment of the mother should only be continued if the benefits clearly outweigh the risks.

Elderly

No systematic studies in patients 65 years or older have been conducted with Gabatrex. However, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

Effects on ability to drive and use machines

Gabatrex acts on the CNS and may cause individually sedation, dizziness or other signs of CNS depression. Therefore, Gabatrex - even if administered as prescribed - may slow down reactions to such a degree that the capability to drive a car, to operate complex machinery or to work in exposed places is impaired. This applies particularly at the start of treatment, if the dose is increased, or if the medication is changed as well as in conjunction with alcohol.

Drug Interactions

Pharmacokinetic interaction studies have been performed on interaction between gabapentin and phenytoin, valproic acid, carbamezapine, or phenobarbital. During the clinical trials, no significant changes in plasma concentration levels of these drugs were observed after additional administration of gabapentin to patients receiving these antiepileptic drugs as standard therapy. Gabatrex does not influence the effect of oral contraceptives containing norethisterone and/or ethinylestradiol. However, in combination with other anti-epileptics known to disrupt the effect of oral contraceptives, failure of the contraceptive effect must be expected.

Concurrent administration of Gabatrex with magnesium or aluminum containing antacids may reduce the bioavailability of gabapentin by up to 24%. Gabatrex should not be administered earlier than at least 2 hours after the antacid intake.

The renal elimination of gabapentin is slightly decreased when co-administrated with cimetidine.

Alcohol or centrally acting drugs of abuse may exaggerate some Gabatrex CNS side effects (e.g. somnolence and ataxia).

Note regarding interactions with clinical-chemical laboratory findings:

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.

SIDE EFFECTS

The most frequent adverse events under treatment with Gabatrex are somnolence, fatigue, dizziness, headache, nausea, vomiting, weight increase, nervousness, insomnia, ataxia, nystagmus, paresthesias, and anorexia, asthenia, visual disturbances (amblyopia, diplopia), tremor, dysarthria, thinking abnormal, amnesia, dry mouth, depression, and emotional liability. The following adverse events also occurred occasionally during clinical studies: Dyspepsia, constipation, abdominal pain, urinary incontinence, increased appetite, rhinitis, pharyngitis, coughing, myalgia, back pain, edema in face, extremities or the whole body, impotence, dental abnormalities, gingivitis, pruritus, leukopenia, fractures, vasodilatation and hypertension. In addition, aggressive behavior and excessive, partly uncontrolled movements (hyperkinesia) were observed in clinical trials in children below 12 years of age.

The occurrence of hemorrhagic pancreatitis has been reported under treatment with gabapentin. Allergic reactions (Stevens-Johnson syndrome and Erythema multiforme) have been reported in single cases under treatment with gabapentin.

Laboratory findings

Elevated liver function tests have been reported in combination with other antiepileptic drugs.

OVERDOSE

Symptoms of overdoses included dizziness, diplopia, dysarthria, sedation and mild diarrhea. Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 g per day. Gabapentin can be removed from the circulating blood by means of hemodialysis. Experience has shown that this is not usually necessary. Hemodialysis may be indicated in patients with impaired renal function.

STORAGE

Store below 25°C.

PRESENTATIONS

Capsules:

Gabatrex 100:	Gabapentin 100 mg/ capsule
Gabatrex 300:	Gabapentin 300 mg/ capsule
Gabatrex 400:	Gabapentin 400 mg/ capsule

Excipients: *Corn starch, Talc.*

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Manufactured by:
HIKMA Pharmaceuticals. Amman-Jordan

Keep medicament out of the reach of children

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