

Gralipentin 300 mg, 600 mg

Extended release film coated tablet



FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Gralipentin is indicated for the management of postherpetic neuralgia.

Gralipentin is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

2 DOSAGE AND ADMINISTRATION

2.1 Postherpetic Neuralgia

Do not use Gralipentin interchangeably with other gabapentin products.

Titrate Gralipentin to an 1800 mg dose taken orally once daily with the evening meal.

Gralipentin tablets should be swallowed whole. Do not split, crush, or chew the tablets.

If Gralipentin dose is reduced, discontinued, or substituted with an alternative medication, this should be done gradually over a minimum of one week or longer (at the discretion of the prescriber).

In adults with postherpetic neuralgia, Gralipentin therapy should be initiated and titrated as follows:

Table 1: Gralipentin Recommended Titration Schedule

Day 1	Day 2	Day 3-6	Day 7-10	Day 11-14	Day 15
Daily Dose 300 mg	600 mg	900 mg	1200 mg	1500 mg	1800 mg

2.2 Patients with Renal Impairment

In patients with stable renal function, creatinine clearance (CCr) can be reasonably well estimated using the equation of Cockcroft and Gault:

For females $CCr = (0.85)(140 - \text{age})(\text{weight}) / [(72)(SCr)]$

For males $CCr = (140 - \text{age})(\text{weight}) / [(72)(SCr)]$

where age is in years, weight is in kilograms and SCr is serum creatinine in mg/dL.

The dose of Gralipentin should be adjusted in patients with reduced renal function, according to Table 2. Patients with reduced renal function must initiate Gralipentin at a daily dose of 300 mg. Gralipentin should be titrated following the schedule outlined in Table 1. Daily dosing in patients with reduced renal function must be individualized based on tolerability and desired clinical benefit.

Table 2: Gralipentin Dosage Based on Renal Function

Once-daily dosing	
Creatinine Clearance (mL/min)	GRALIPENTIN Dose (once daily with evening meal)
≥ 60	1800 mg
30 - 60	600 mg to 1800 mg
< 30	GRALIPENTIN should not be administered
patients receiving hemodialysis	GRALIPENTIN should not be administered

3 DOSAGE FORMS AND STRENGTHS

Extended Release Film coated tablets: 300 mg and 600 mg

4 CONTRAINDICATIONS

Gralipentin is contraindicated in patients with demonstrated hypersensitivity to the drug or its ingredients.

5 WARNINGS AND PRECAUTIONS

Gralipentin is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

The safety and effectiveness of Gralipentin in patients with epilepsy has not been studied.

5.1 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including gabapentin, the active ingredient in Gralipentin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Table 3: Risk by Indication for Antiepileptic Drugs (including gabapentin, the active ingredient in Gralipentin) in the Pooled Analysis

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Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Gralipentin must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which products containing active components that are AEDs (such as gabapentin, the active component in Gralipentin) are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that Gralipentin contains gabapentin which is also used to treat epilepsy and that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm.

Behaviors of concern should be reported immediately to healthcare providers.

5.2 Respiratory Depression

There is evidence from case reports, human studies, and animal studies associating gabapentin with serious, life-threatening, or fatal respiratory depression when co-administrated with central nervous system (CNS) depressants, including opioids, or in the setting of underlying respiratory impairment. When the decision is made to co-prescribe Gralipentin with another CNS depressant, particularly an opioid, or to prescribe Gralipentin to patients with underlying respiratory impairment, monitor patients for symptoms of respiratory depression and sedation, and consider initiating Gralipentin at a low dose.

The management of respiratory depression may include close observation, supportive measures, and reduction or withdrawal of CNS depressants (including Gralipentin).

5.3 Withdrawal of Gabapentin

Gabapentin should be withdrawn gradually. If Gralipentin is discontinued, this should be done gradually over a minimum of 1 week or longer (at the discretion of the prescriber).

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms

(DRESS)/Multiorgan Hypersensitivity

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. Gralipentin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.5 Laboratory Tests

Clinical trial data do not indicate that routine monitoring of clinical laboratory procedures is necessary for the safe use of Gralipentin. The value of monitoring gabapentin blood concentrations has not been established.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

**Table 4: Treatment-Emergent Adverse Reaction Incidence in Controlled Trials in Neuropathic Pain Associated with P
ostherpetic Neuralgia (Events in at Least 1% of all Gralipentin-Treated Patients and More Frequent Than in the Placebo Group)**

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Body System – Preferred Term
Ear and Labyrinth Disorders Vertigo
Gastrointestinal Disorders Diarrhea Dry mouth Constipation Dyspepsia
General Disorders Peripheral edema Pain
Infections and Infestations Nasopharyngitis Urinary tract infection
Investigations Weight increased
Musculoskeletal and Connective Tissue Disorders Pain in extremity Back pain Somnolence Headache Lethargy

In addition to the adverse reactions reported in Table 4 above, the following adverse reactions with an uncertain relationship to Gralipentin were reported during the clinical development for the treatment of postherpetic neuralgia.

Events in more than 1% of patients but equally or more frequently in the Gralipentin -treated patients than in the placebo group included blood pressure increase, confusional state, gastroenteritis viral, herpes zoster, hypertension, joint swelling, memory impairment, nausea, pneumonia, pyrexia, rash, seasonal allergy, and upper respiratory infection.

Reporting of suspected adverse reactions

talk to your doctor or you can report directly via The Egyptian Pharmacovigilance Center:

Telephone: +202 23648046/ 23640368/ 23684381

E-mail: Pv.center@eda.mohealth.gov.eg

By reporting side effects, you can help provide more information on the safety of this

6.2 Postmarketing and Other Experience with other Formulations of Gabapentin

In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving other formulations of marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, breast enlargement, bullous pemphigoid, elevated creatine kinase, elevated liver function tests, erythema multiforme, fever, hyponatremia, jaundice, movement disorder, Stevens-Johnson syndrome.

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

There are postmarketing reports of life-threatening or fatal respiratory depression in patients taking gabapentin with opioids or other central nervous system (CNS) depressants, or in the setting of underlying respiratory impairment.

7 DRUG INTERACTIONS

In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 mcg/mL; 1mM) was a slight degree of inhibition (14% to 30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 mcg/mL (approximately 15 times the C_{max} at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs.

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The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

7.1 Phenytoin

In a single (400 mg) and multiple dose (400 mg three times daily) study of gabapentin immediate release in epileptic patients (N=8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

7.2 Carbamazepine

Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin immediate release (400 mg three times daily; N=12) administration.

Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

7.3 Valproic Acid

The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin immediate release administration (400 mg three times daily; N=17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

7.4 Phenobarbital

Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin immediate release (300 mg three times daily; N=12) are identical whether the drugs are administered alone or together.

7.5 Naproxen

Coadministration of single doses of naproxen (250 mg) and gabapentin immediate release (125 mg) to 18 volunteers increased gabapentin absorption by 12% to 15%. Gabapentin immediate release had no effect on naproxen pharmacokinetics. The doses are lower than the therapeutic doses for both drugs. The effect of coadministration of these drugs at therapeutic doses is not known.

7.6 Hydrocodone

Coadministration of gabapentin immediate release (125 mg and 500 mg) and hydrocodone (10 mg) reduced hydrocodone C_{max} by 3% and 21%, respectively, and AUC by 4% and 22%, respectively. The mechanism of this interaction is unknown. Gabapentin AUC values were increased by 14%; the magnitude of the interaction at other doses is not known.

7.7 Morphine

When a single dose (60 mg) of controlled-release morphine capsule was administered 2 hours prior to a single dose (600 mg) of gabapentin immediate release in 12 volunteers, mean gabapentin AUC values increased by 44% compared to gabapentin immediate release administered without morphine. The pharmacokinetics of morphine were not affected by administration of gabapentin immediate release 2 hours after morphine.

The magnitude of this interaction at other doses is not known.

7.8 Cimetidine

Cimetidine 300 mg decreased the apparent oral clearance of gabapentin by 14% and creatinine clearance by 10%. The effect of gabapentin immediate release on cimetidine was not evaluated. This decrease is not expected to be clinically significant.

7.9 Oral Contraceptives

Gabapentin immediate release (400 mg three times daily) had no effect on the pharmacokinetics of norethindrone (2.5 mg) or ethinyl estradiol (50 mcg) administered as a single tablet, except that the C_{max} of norethindrone was increased by 13%. This interaction is not considered to be clinically significant.

7.10 Antacid (containing aluminum hydroxide and magnesium hydroxide)

An antacid containing aluminum hydroxide and magnesium hydroxide reduced the bioavailability of gabapentin immediate release by about approximately 20%, but by only 5% when gabapentin immediate release was taken 2 hours after the antacid. It is recommended that Gralipentin be taken at least 2 hours following the antacid (containing aluminum hydroxide and magnesium hydroxide) administration.

7.11 Probenecid

Gabapentin immediate release pharmacokinetic parameters were comparable with and without probenecid, indicating that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

7.12 Drug/Laboratory Test Interactions

False positive readings were reported with the Ames-N-Multistix SG® dipstick test for urine protein when gabapentin was added to other antiepileptic drugs; therefore, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy category C

There are no adequate and well-controlled studies in pregnant women.

This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Nursing Mothers

Gabapentin is secreted into human milk following oral administration.

A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, Gralipentin should be used in women who are nursing only if the benefits clearly outweigh the risks.

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8.3 Pediatric Use

The safety and effectiveness of Gralipentin in the management of postherpetic neuralgia in patients less than 18 years of age has not been studied.

8.4 Geriatric Use

The total number of patients treated with Gralipentin in controlled clinical trials in patients with postherpetic neuralgia was 359, of which 63% were 65 years of age or older. The types and incidence of adverse events were similar across age groups except for peripheral edema, which tended to increase in incidence with age.

Gralipentin is known to be substantially excreted by the kidney. Reductions in Gralipentin dose should be made in patients with age-related compromised renal function.

8.6 Hepatic Impairment

Because gabapentin is not metabolized, studies have not been conducted in patients with hepatic impairment.

8.7 Renal Impairment

Gralipentin is known to be substantially excreted by the kidney. Dosage adjustment is necessary in patients with impaired renal function. Gralipentin should not be administered in patients with CrCL between 15 and 30 or in patients undergoing hemodialysis.

9 DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of Gralipentin has not been evaluated in human studies.

10 OVERDOSAGE

Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.

Acute oral overdoses of gabapentin have been reported. Symptoms include double-vision, tremor, slurred speech, drowsiness, altered mental status, dizziness, lethargy, and diarrhea. Fatal respiratory depression has been reported with gabapentin overdose, alone and in combination with other central nervous system (CNS) depressants.

Gabapentin can be removed by hemodialysis. Hemodialysis has been performed in overdose cases reported, and it may be indicated by the patient's clinical state or in patients with significant renal impairment.

11 DESCRIPTION

Gralipentin is supplied as Extended Release Film Coated Tablets containing 300 mg or 600 mg of gabapentin. Gralipentin Extended Release Film Coated Tablets swell in gastric fluid and gradually release gabapentin.

Each 300 mg Extended Release Film Coated Tablets contains the inactive ingredients: Hydroxypropyl Methyl Cellulose K15 (Methocel K15M), Hydroxypropyl Cellulose Extra Fine (Klucel EF), Colloidal Silicone Dioxide (Aerosil 200) and Magnesium Stearate.

Coat:

Hydroxy Propyl Methyl Cellulose E5 (Hyperomellose E5), Polyethylene Glycol 6000 (Macrogol 6000), Titanium Dioxide and Talc Purified.

Each 600 mg Extended Release Film Coated Tablets contains the inactive ingredients: Hydroxy Propyl Methyl Cellulose K15 (Methocel K15M), Hydroxypropyl Cellulose Extra Fine (Klucel EF), Colloidal Silicone Dioxide (Aerosil 200) and Magnesium Stearate.

Coat:

Hydroxypropyl Methyl Cellulose E5 (Hyperomellose E5), Polyethylene Glycol 6000 (Macrogol 6000), Titanium Dioxide, Talc and Iron Oxide Yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action by which gabapentin exerts its analgesic action is unknown but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli).

Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formulin test), but does not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid), but it does not modify GABAA or GABAB radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. In radioligand binding assays at concentrations up to 100 μ M, gabapentin did not exhibit affinity for a number of other receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine; alpha 1, alpha 2, or beta adrenergic; adenosine A1 or A2; cholinergic, muscarinic, or nicotinic; dopamine D1 or D2; histamine H1; serotonin S1 or S2; opiate mu, delta, or kappa; cannabinoid 1; voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem; or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A20-alpha-benzoate. Gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus.

A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated. It is hypothesized that gabapentin antagonizes thrombospondin binding to α 2 δ -1 as a receptor involved in excitatory synapse formation and suggested that gabapentin may function therapeutically by blocking new synapse formation.

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12.2 Pharmacodynamics

No pharmacodynamic studies have been conducted with Gralipentin.

12.3 Pharmacokinetics

Absorption and Bioavailability

Gabapentin is absorbed from the proximal small bowel by a saturable L-amino transport system. Gabapentin bioavailability is not dose proportional; as the dose is increased, bioavailability decreases.

When Gralipentin (1800 mg once daily) and gabapentin immediate release (600 mg three times a day) were administered with high fat meals (50% of calories from fat), Gralipentin has a higher C_{max} and lower AUC at steady state compared to gabapentin immediate release (Table 5). Time to reach maximum plasma concentration (T_{max}) for Gralipentin is 8 hours, which is about 4-6 hours longer compared to gabapentin immediate release.

Table 5: Mean (SD) Steady- State Pharmacokinetics for Gralipentin and Gabapentin Immediate Release in Plasma of Healthy Subjects (Day 5, n = 21)

Pharmacokinetic Parameters (Mean ± SD)	Gralipentin 1800 mg QD	Gabapentin Immediate Release 600 mg TID
AUC ₀₋₂₄ (ng·hr/mL)	132,808 ± 34,701	141,301 ± 29,759
C _{max} (ng/mL)	9,585 ± 2,326	8,536 ± 1,715
C _{min} (ng/mL)	1,842 ± 654	2,588 ± 783
T _{max} (hr) median (range)	8 (3-12)	2 (1-5)*
* = relative to most recent dose		

Do not use Gralipentin interchangeably with other gabapentin products because of differing pharmacokinetic profiles that affect frequency of administration.

Gralipentin should be taken with evening meals. If it is taken on an empty stomach, the bioavailability will be substantially lower. Administration of Gralipentin with food increases the rate and extent of absorption of gabapentin compared to the fasted state. C_{max} of gabapentin increases 33-84% and AUC of gabapentin increases 33-118% with food depending on the fat content of the meal. Gralipentin should be taken with food.

Distribution

Gabapentin is less than 3% bound to plasma proteins. After 150 mg intravenous administration, the mean ± SD volume of distribution is 58 ± 6 L.

Metabolism and Excretion

Gabapentin is eliminated by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans. In patients with normal renal function given gabapentin immediate release 1200 to 3000 mg/day, the drug elimination half-life (t_{1/2}) was 5 to 7 hours. Elimination kinetics do not change with dose level or multiple doses.

Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. In elderly patients and patients with impaired renal function, plasma clearance is reduced.

Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function is necessary. In patients undergoing hemodialysis, Gralipentin should not be administered.

12.4 Special Populations

Renal Insufficiency: As renal function decreases, renal and plasma clearances and the apparent elimination rate constant decrease, while C_{max} and t_{1/2} increase.

In patients (N=60) with creatinine clearance of at least 60, 30 to 59, or less than 30 mL/min, the median renal clearance rates for a 400 mg single dose of gabapentin immediate release were 79, 36, and 11 mL/min, respectively, and the median t_{1/2} values were 9.2, 14, and 40 hours, respectively.

Dosage adjustment is necessary in patients with impaired renal function

Hemodialysis: In a study in anuric adult subjects (N=11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects. Gralipentin should not be administered in patients undergoing hemodialysis. Alternative formulations of gabapentin products should be considered in patients undergoing hemodialysis.

Elderly: Apparent oral and renal clearances of gabapentin decrease with increasing age, although this may be related to the decline in renal function with age. Reductions in gabapentin dose should be made in patients with age-related compromised renal function.

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Hepatic Impairment: Because gabapentin is not metabolized, studies have not been conducted in patients with hepatic impairment.

Pediatrics: The pharmacokinetics of Gralipentin have not been studied in patients less than 18 years of age.

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

13 HOW SUPPLIED/STORAGE AND HANDLING

Gralipentin (gabapentin) Extended Release Film Coated Tablets are supplied as follows:

300 mg Extended Release Film Coated Tablets:

Gralipentin 300 mg Extended Release Film Coated Tablets are white, oblong biconvex Extended Release Film Coated Tablets.

600 mg Extended Release Film Coated Tablets:

Gralipentin 600 mg Extended Release Film Coated Tablets are yellow, oblong biconvex Extended Release Film Coated Tablets

Storage

Store at temperature not exceeding 30°C, in a dry place.

Keep out of reach of children

14 NATURE AND CONTENTS OF CONTAINERS

Carton box containing 1,2,3 (AL/PVC) blisters, each of 10 extended release film coated tablets with insert leaflet

15 MANUFACTURER:

ATCO Pharma for pharmaceutical industries

Head office & Factory: Industrial Quisna Zone-Quisna-El Menofia-Egypt

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