

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GRALISE safely and effectively. See full prescribing information for GRALISE.

GRALISE™ (gabapentin) tablets
Initial U.S. Approval: 1993

INDICATIONS AND USAGE

GRALISE is indicated for the management of Postherpetic Neuralgia (PHN).

Important Limitation: GRALISE is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration (See Warnings and Precautions)

DOSAGE AND ADMINISTRATION

- GRALISE should be titrated to an 1800 mg dose taken orally, once-daily, with the evening meal. GRALISE tablets should be swallowed whole. Do not crush, split, or chew the tablets. (2.1)
- If GRALISE dose is reduced, discontinued, or substituted with an alternative medication, this should be done gradually over a minimum of 1 week or longer (at the discretion of the prescriber). (2.1)
- Renal impairment: Dose should be adjusted in patients with reduced renal function. GRALISE should not be used in patients with CrCl less than 30 or in patients on hemodialysis. (2.2)

DOSAGE FORMS AND STRENGTHS

- 300 and 600 mg tablets (3)

CONTRAINDICATIONS

GRALISE is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients. (4)

WARNINGS AND PRECAUTIONS

- GRALISE is not interchangeable with other gabapentin products
- Antiepileptic drugs, including gabapentin, the active ingredient in GRALISE, increase the risk of suicidal thoughts or behavior (5.1)
- Increased seizure frequency may occur in patients with seizure disorders if GRALISE is rapidly discontinued. Withdraw GRALISE gradually over a minimum of 1 week. (5.2)

ADVERSE REACTIONS

The most common adverse reaction (greater than or equal to 5% and twice placebo) is dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Depomed, Inc. at 1-866-458-6389 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- An increase in gabapentin AUC values have been reported when administered with hydrocodone. (7.6)
- An increase in gabapentin AUC values have been reported when administered with morphine. (7.7)
- 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 was taken 2 hours after antacids. It is recommended that GRALISE be taken at least 2 hours following antacid administration. (7.10)

USE IN SPECIFIC POPULATIONS

- Pregnancy: GRALISE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Nursing Mothers: GRALISE should be used in women who are nursing only if the benefits clearly outweigh the risks. (8.3)
- Elderly: Reductions in GRALISE dose should be made in patients with age-related compromised renal function. (8.5)
- Renal impairment: Dosage adjustment is necessary for patients with impaired renal function. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 04/2012

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1 **FULL PRESCRIBING INFORMATION**

2 GRA-004-C.3 APR 2012

3 GRALISE™ (gabapentin) Tablets Rx only

4 **1 INDICATIONS AND USAGE**

5 GRALISE is indicated for the management of postherpetic neuralgia.

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

8 **2 DOSAGE AND ADMINISTRATION**

9 **2.1 Postherpetic Neuralgia**

10 Do not use GRALISE interchangeably with other gabapentin products.

11 Titrate GRALISE to an 1800 mg dose taken orally once daily with the evening meal.
12 GRALISE tablets should be swallowed whole. Do not split, crush, or chew the tablets.

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

16 In adults with postherpetic neuralgia, GRALISE therapy should be initiated and titrated
17 as follows:

18 **Table 1: GRALISE Recommended Titration Schedule**

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

19
20 **2.2 Patients with Renal Impairment**

21 In patients with stable renal function, creatinine clearance (C_{Cr}) can be reasonably well
22 estimated using the equation of Cockcroft and Gault:

23 For females $C_{Cr} = (0.85)(140 - \text{age})(\text{weight}) / [(72)(S_{Cr})]$

24 For males $C_{Cr} = (140 - \text{age})(\text{weight}) / [(72)(S_{Cr})]$

25 where age is in years, weight is in kilograms and S_{Cr} is serum creatinine in mg/dL.

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

32

Table 2: GRALISE Dosage Based on Renal Function

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

33

34 **3 DOSAGE FORMS AND STRENGTHS**

35 Tablets: 300 mg and 600 mg [*see Description (11) and How Supplied/Storage and*
36 *Handling (16)*]

37 **4 CONTRAINDICATIONS**

38 GRALISE is contraindicated in patients with demonstrated hypersensitivity to the drug or
39 its ingredients.

40 **5 WARNINGS AND PRECAUTIONS**

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

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

44 **5.1 Suicidal Behavior and Ideation**

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

50 Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of
51 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice
52 the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared
53 to patients randomized to placebo. In these trials, which had a median treatment duration of 12
54 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated
55 patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an
56 increase of approximately one case of suicidal thinking or behavior for every 530 patients treated.
57 There were four suicides in drug-treated patients in the trials and none in placebo-treated patients,
58 but the number is too small to allow any conclusion about drug effect on suicide.

59 The increased risk of suicidal thoughts or behavior with AEDs was observed as early as
60 one week after starting drug treatment with AEDs and persisted for the duration of treatment
61 assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk
62 of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

63 The risk of suicidal thoughts or behavior was generally consistent among drugs in the data
 64 analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a
 65 range of indications suggests that the risk applies to all AEDs used for any indication. The risk
 66 did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 3 shows
 67 absolute and relative risk by indication for all evaluated AEDs.

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

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

70
 71 The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy
 72 than in clinical trials for psychiatric or other conditions, but the absolute risk differences were
 73 similar for the epilepsy and psychiatric indications.

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

81 Patients, their caregivers, and families should be informed that GRALISE contains
 82 gabapentin which is also used to treat epilepsy and that AEDs increase the risk of suicidal
 83 thoughts and behavior and should be advised of the need to be alert for the emergence or
 84 worsening of the signs and symptoms of depression, any unusual changes in mood or behavior,
 85 or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of
 86 concern should be reported immediately to healthcare providers.

87 **5.2 Withdrawal of Gabapentin**

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

90 **5.3 Tumorigenic Potential**

91 In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high
92 incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats.
93 The clinical significance of this finding is unknown.

94 In clinical trials of gabapentin therapy in epilepsy comprising 2,085 patient-years of
95 exposure in patients over 12 years of age, new tumors were reported in 10 patients, and pre-
96 existing tumors worsened in 11 patients, during or within 2 years after discontinuing the drug.
97 However, no similar patient population untreated with gabapentin was available to provide
98 background tumor incidence and recurrence information for comparison. Therefore, the effect
99 of gabapentin therapy on the incidence of new tumors in humans or on the worsening or
100 recurrence of previously diagnosed tumors is unknown.

101 **5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan**
102 **Hypersensitivity**

103 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as
104 Multiorgan Hypersensitivity, has been reported in patients taking antiepileptic drugs, including
105 GRALISE. Some of these events have been fatal or life-threatening. DRESS typically, although
106 not exclusively, presents with fever, rash, and/or lymphadenopathy in association with other
107 organ system involvement, such as hepatitis, nephritis, hematological abnormalities,
108 myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often
109 present. Because this disorder is variable in its expression, other organ systems not noted here
110 may be involved.

111 It is important to note that early manifestations of hypersensitivity, such as fever or
112 lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms
113 are present, the patient should be evaluated immediately. GRALISE should be discontinued if
114 an alternative etiology for the signs or symptoms cannot be established.

115 **5.5 Laboratory Tests**

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

119 **6 ADVERSE REACTIONS**

120 **6.1 Clinical Trials Experience**

121 Because clinical trials are conducted under widely varying conditions, adverse reaction
122 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical
123 trials of another drug and may not reflect the rates observed in practice.

124 A total of 359 patients with neuropathic pain associated with postherpetic neuralgia have
125 received GRALISE at doses up to 1800 mg daily during placebo-controlled clinical studies. In
126 clinical trials in patients with postherpetic neuralgia, 9.7% of the 359 patients treated with

127 GRALISE and 6.9% of 364 patients treated with placebo discontinued prematurely due to
128 adverse reactions. In the GRALISE treatment group, the most common reason for
129 discontinuation due to adverse reactions was dizziness. Of GRALISE-treated patients who
130 experienced adverse reactions in clinical studies, the majority of those adverse reactions were
131 either "mild" or "moderate".

132 Table 4 lists all adverse reactions, regardless of causality, occurring in at least 1% of
133 patients with neuropathic pain associated with postherpetic neuralgia in the GRALISE group for
134 which the incidence was greater than in the placebo group.

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

Body System – Preferred Term	GRALISE N = 359 %	Placebo N = 364 %
Ear and Labyrinth Disorders		
Vertigo	1.4	0.5
Gastrointestinal Disorders		
Diarrhea	3.3	2.7
Dry mouth	2.8	1.4
Constipation	1.4	0.3
Dyspepsia	1.4	0.8
General Disorders		
Peripheral edema	3.9	0.3
Pain	1.1	0.5
Infections and Infestations		
Nasopharyngitis	2.5	2.2
Urinary tract infection	1.7	0.5
Investigations		
Weight increased	1.9	0.5
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	1.9	0.5
Back pain	1.7	1.1
Nervous System Disorders		
Dizziness	10.9	2.2
Somnolence	4.5	2.7
Headache	4.2	4.1
Lethargy	1.1	0.3

138
 139 In addition to the adverse reactions reported in Table 4 above, the following adverse
 140 reactions with an uncertain relationship to GRALISE were reported during the clinical
 141 development for the treatment of postherpetic neuralgia. Events in more than 1% of patients but
 142 equally or more frequently in the GRALISE-treated patients than in the placebo group included
 143 blood pressure increase, confusional state, gastroenteritis viral, herpes zoster, hypertension, joint
 144 swelling, memory impairment, nausea, pneumonia, pyrexia, rash, seasonal allergy, and upper
 145 respiratory infection.

146 **6.2 Postmarketing and Other Experience with other Formulations of Gabapentin**

147 In addition to the adverse experiences reported during clinical testing of gabapentin, the
 148 following adverse experiences have been reported in patients receiving other formulations of

149 marketed gabapentin. These adverse experiences have not been listed above and data are
150 insufficient to support an estimate of their incidence or to establish causation. The listing is
151 alphabetized: angioedema, blood glucose fluctuation, breast enlargement, elevated creatine
152 kinase, elevated liver function tests, erythema multiforme, fever, hyponatremia, jaundice,
153 movement disorder, Stevens-Johnson syndrome.

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

157 **7 DRUG INTERACTIONS**

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

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

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

169 **7.1 Phenytoin**

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

174 **7.2 Carbamazepine**

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

179 **7.3 Valproic Acid**

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

184 **7.4 Phenobarbital**

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

188 **7.5 Naproxen**

189 Coadministration of single doses of naproxen (250 mg) and gabapentin immediate release
190 (125 mg) to 18 volunteers increased gabapentin absorption by 12% to 15%. Gabapentin
191 immediate release had no effect on naproxen pharmacokinetics. The doses are lower than the
192 therapeutic doses for both drugs. The effect of coadministration of these drugs at therapeutic
193 doses is not known.

194 **7.6 Hydrocodone**

195 Coadministration of gabapentin immediate release (125 mg and 500 mg) and hydrocodone
196 (10 mg) reduced hydrocodone C_{max} by 3% and 21%, respectively, and AUC by 4% and 22%,
197 respectively. The mechanism of this interaction is unknown. Gabapentin AUC values were
198 increased by 14%; the magnitude of the interaction at other doses is not known.

199 **7.7 Morphine**

200 When a single dose (60 mg) of controlled-release morphine capsule was administered 2
201 hours prior to a single dose (600 mg) of gabapentin immediate release in 12 volunteers, mean
202 gabapentin AUC values increased by 44% compared to gabapentin immediate release
203 administered without morphine. The pharmacokinetics of morphine were not affected by
204 administration of gabapentin immediate release 2 hours after morphine. The magnitude of this
205 interaction at other doses is not known.

206 **7.8 Cimetidine**

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

210 **7.9 Oral Contraceptives**

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

215 **7.10 Antacid (containing aluminum hydroxide and magnesium hydroxide)**

216 An antacid containing aluminum hydroxide and magnesium hydroxide reduced the
217 bioavailability of gabapentin immediate release by about approximately 20%, but by only 5%
218 when gabapentin immediate release was taken 2 hours after the antacid. It is recommended that

219 GRALISE be taken at least 2 hours following the antacid (containing aluminum hydroxide and
220 magnesium hydroxide) administration.

221 **7.11 Probenecid**

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

225 **7.12 Drug/Laboratory Test Interactions**

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

230 **8 USE IN SPECIFIC POPULATIONS**

231 **8.1 Pregnancy**

232 Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing
233 delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These
234 effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the
235 period of organogenesis, or approximately 3 to 8 times the maximum dose of 1800 mg/day given
236 to PHN patients on a mg/m² basis. The no effect level was 500 mg/kg/day representing
237 approximately the maximum recommended human dose [MRHD] on a mg/m² body surface area
238 (BSA) basis. When rats were dosed prior to and during mating, and throughout gestation, pups
239 from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent
240 to approximately 3 to 11 times the MRHD on a mg/m² BSA basis. There was an increased
241 incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general
242 reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology
243 study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study
244 at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are
245 approximately 3 to 11 times the maximum human dose of 1800 mg/day on a mg/m² basis; the no-
246 effect doses were approximately 5 times (Fertility and General Reproductive Performance study)
247 and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m² BSA
248 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the
249 incidence of malformations was not increased compared to controls in offspring of mice, rats, or
250 rabbits given doses up to 100 times (mice), 60 times (rats), and 50 times (rabbits) the human
251 daily dose on a mg/kg basis, or 8 times (mice), 10 times (rats), or 16 times (rabbits) the human
252 daily dose on a mg/m² BSA basis. In a teratology study in rabbits, an increased incidence of
253 postimplantation fetal loss occurred in dams exposed to 60, 300, and 1500 mg/kg/day, or 0.6 to
254 16 times the maximum human dose on a mg/m² BSA basis. There are no adequate and well-
255 controlled studies in pregnant women. This drug should be used during pregnancy only if the
256 potential benefit justifies the potential risk to the fetus.

257 To provide information regarding the effects of *in utero* exposure to GRALISE,
258 physicians are advised to recommend that pregnant patients taking GRALISE enroll in the
259 North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by
260 calling the toll free number 1-888-233-2334, and must be done by patients themselves.
261 Information on the registry can also be found at the website
262 <http://www.aedpregnancyregistry.org/>.

263 **8.3 Nursing Mothers**

264 Gabapentin is secreted into human milk following oral administration. A nursed infant
265 could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the
266 effect on the nursing infant is unknown, GRALISE should be used in women who are nursing
267 only if the benefits clearly outweigh the risks.

268 **8.4 Pediatric Use**

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

271 **8.5 Geriatric Use**

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

276 GRALISE is known to be substantially excreted by the kidney. Reductions in GRALISE
277 dose should be made in patients with age-related compromised renal function. [*see Dosage and*
278 *Administration (2.2)*].

279 **8.6 Hepatic Impairment**

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

282 **8.7 Renal Impairment**

283 GRALISE is known to be substantially excreted by the kidney. Dosage adjustment is
284 necessary in patients with impaired renal function. GRALISE should not be administered in
285 patients with CrCL between 15 and 30 or in patients undergoing hemodialysis. [*see Dosage and*
286 *Administration (2.2)*].

287 **9 DRUG ABUSE AND DEPENDENCE**

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

289 **10 OVERDOSAGE**

290 A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses
291 as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing,
292 ptosis, sedation, hypoactivity, or excitation.

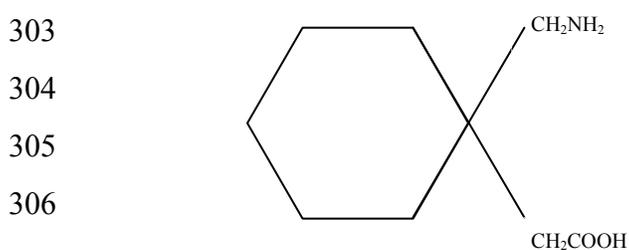
293 Acute oral overdoses of gabapentin immediate release in humans up to 49 grams have
294 been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea
295 were observed. All patients recovered with supportive care.

296 Gabapentin can be removed by hemodialysis. Although hemodialysis has not been
297 performed in the few overdose cases reported, it may be indicated by the patient's clinical state
298 or in patients with significant renal impairment.

299 11 DESCRIPTION

300 Gabapentin is 1-(aminomethyl)cyclohexaneacetic acid; γ -amino-2-cyclohexyl-butyric acid
301 with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24.

302 The structural formula is:



309 Gabapentin is a white to off-white crystalline solid with a pKa1 of 3.7 and a pKa2 of 10.7.
310 It is freely soluble in water and acidic and basic solutions. The log of the partition coefficient
311 (n-octanol/ 0.05M phosphate buffer) at pH 7.4 is -1.25.

312 GRALISE is supplied as tablets containing 300 mg or 600 mg of gabapentin. GRALISE
313 tablets swell in gastric fluid and gradually release gabapentin. Each 300 mg tablet contains the
314 inactive ingredients copovidone, hypromellose, magnesium stearate, microcrystalline cellulose,
315 polyethylene oxide, and Opadry® II white. Opadry® II white contains polyvinyl alcohol,
316 titanium dioxide, talc, polyethylene glycol 3350, and lecithin (soya). Each 600 mg tablet
317 contains the inactive ingredients copovidone, hypromellose, magnesium stearate, polyethylene
318 oxide, and Opadry® II beige. Opadry® II beige contains polyvinyl alcohol, titanium dioxide,
319 talc, polyethylene glycol 3350, iron oxide yellow, and iron oxide red.

320 12 CLINICAL PHARMACOLOGY

321 12.1 Mechanism of Action

322 The mechanism of action by which gabapentin exerts its analgesic action is unknown but in
323 animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to
324 a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli).
325 Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and
326 mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection
327 model). Gabapentin also decreases pain-related responses after peripheral inflammation
328 (carrageenan footpad test, late phase of formulin test), but does not alter immediate pain-related

329 behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to
330 human pain is not known.

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

343 *In vitro* studies with radiolabeled gabapentin have revealed a gabapentin binding site in
344 areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in
345 animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium
346 channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.
347 It is hypothesized that gabapentin antagonizes thrombospondin binding to $\alpha 2\delta$ -1 as a receptor
348 involved in excitatory synapse formation and suggested that gabapentin may function
349 therapeutically by blocking new synapse formation.

350 **12.2 Pharmacodynamics**

351 No pharmacodynamic studies have been conducted with GRALISE.

352 **12.3 Pharmacokinetics**

353 ***Absorption and Bioavailability***

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

357 When GRALISE (1800 mg once daily) and gabapentin immediate release (600 mg three
358 times a day) were administered with high fat meals (50% of calories from fat), GRALISE has a
359 higher C_{max} and lower AUC at steady state compared to gabapentin immediate release (Table 5).
360 Time to reach maximum plasma concentration (T_{max}) for GRALISE is 8 hours, which is about
361 4-6 hours longer compared to gabapentin immediate release.

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

Pharmacokinetic Parameters (Mean ± SD)	GRALISE 1800 mg QD	Gabapentin Immediate Release 600 mg TID
AUC₀₋₂₄ (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

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

366
 367 GRALISE should be taken with evening meals. If it is taken on an empty stomach, the
 368 bioavailability will be substantially lower.

369
 370 Administration of GRALISE with food increases the rate and extent of absorption of
 371 gabapentin compared to the fasted state. C_{max} of gabapentin increases 33-84% and AUC of
 372 gabapentin increases 33-118% with food depending on the fat content of the meal. GRALISE
 373 should be taken with food.

374 ***Distribution***

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

377 ***Metabolism and Excretion***

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

382 Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly
 383 proportional to creatinine clearance. In elderly patients and patients with impaired renal
 384 function, plasma clearance is reduced. Gabapentin can be removed from plasma by
 385 hemodialysis.

386 Dosage adjustment in patients with compromised renal function is necessary. In patients
 387 undergoing hemodialysis, GRALISE should not be administered [*see Dosage and*
 388 *Administration (2.2)*].

389 12.4 Special Populations

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

392 In patients (N=60) with creatinine clearance of at least 60, 30 to 59, or less than
393 30 mL/min, the median renal clearance rates for a 400 mg single dose of gabapentin immediate
394 release were 79, 36, and 11 mL/min, respectively, and the median $t_{1/2}$ values were 9.2, 14, and
395 40 hours, respectively.

396 Dosage adjustment is necessary in patients with impaired renal function [*see Dosage and*
397 *Administration (2.2)*].

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

404 **Elderly:** Apparent oral and renal clearances of gabapentin decrease with increasing age,
405 although this may be related to the decline in renal function with age. Reductions in gabapentin
406 dose should be made in patients with age-related compromised renal function [*see Dosage and*
407 *Administration (2.2)*].

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

410 **Pediatrics:** The pharmacokinetics of GRALISE have not been studied in patients less than
411 18 years of age.

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

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

418 13 NONCLINICAL TOXICOLOGY

419 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

420 Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at
421 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence
422 of pancreatic acinar cell adenoma and carcinomas was found in male rats receiving the high
423 dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma
424 concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg/day were more than
425 10 times higher than plasma concentrations in humans receiving 1800 mg per day and in rats

426 receiving 1000 mg/kg/day peak plasma concentrations were more than 6.5 times higher than in
427 humans receiving 1800 mg/day. The pancreatic acinar cell carcinomas did not affect survival,
428 did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic
429 risk in humans is unclear.

430 Studies designed to investigate the mechanism of gabapentin-induced pancreatic
431 carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar
432 cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is
433 not known whether gabapentin has the ability to increase cell proliferation in other cell types or
434 in other species, including humans.

435 Gabapentin did not demonstrate mutagenic or genotoxic potential in 3 *in vitro* and 4 *in*
436 *vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in
437 Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations
438 in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal
439 aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was
440 negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA
441 synthesis in hepatocytes from rats given gabapentin.

442 No adverse effects on fertility or reproduction were observed in rats at doses up to
443 2000 mg/kg (approximately 11 times the maximum recommended human dose on an mg/m²
444 basis).

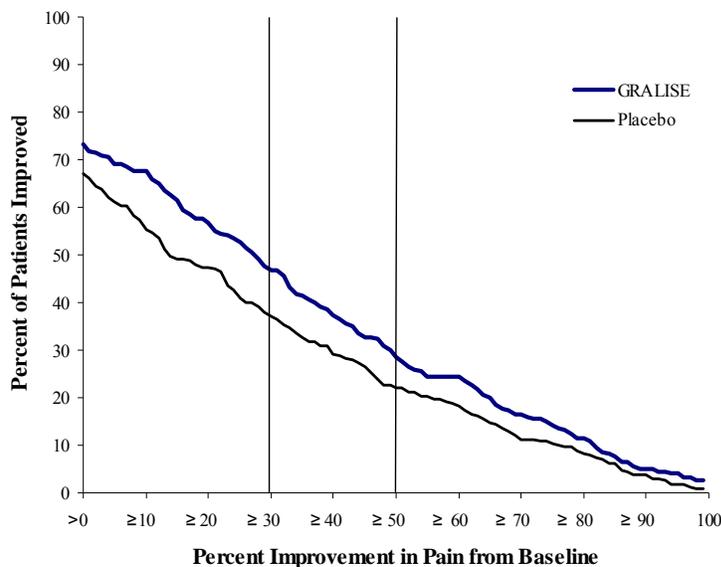
445 **14 CLINICAL STUDIES**

446 The efficacy of GRALISE for the management of postherpetic neuralgia was established
447 in a double-blind, placebo-controlled, multicenter study. This study enrolled patients between
448 the age of 21 to 89 with postherpetic neuralgia persisting for at least 6 months following healing
449 of herpes zoster rash and a minimum baseline pain intensity score of at least 4 on an 11-point
450 numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain).

451 This 11-week study compared GRALISE 1800 mg once daily with placebo. A total of 221
452 and 231 patients were treated with GRALISE or placebo, respectively. The study treatment
453 including titration for all patients comprised a 10-week treatment period followed by 1-week of
454 dose tapering. Double-blind treatment began with titration starting at 300 mg/day and titrated
455 up to a total daily dose of 1800 mg over 2 weeks, followed by 8 weeks fixed dosing at 1800 mg
456 once daily, and then 1 week of dose tapering. During the 8-week stable dosing period, patients
457 took 3 active or placebo tablets each night with the evening meal. During baseline and
458 treatment, patients recorded their pain in a daily diary using an 11-point numeric pain rating
459 scale. The mean baseline pain score was 6.6 and 6.5 for GRALISE and placebo-treated patients,
460 respectively.

461 Treatment with GRALISE statistically significantly improved the endpoint mean pain
462 score from baseline. For various degrees of improvement in pain from baseline to study
463 endpoint, Figure 1 shows the fraction of patients achieving that degree of improvement. The
464 figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also

465 included at every level of improvement below 50%. Patients who did not complete the study
466 were assigned 0% improvement.



467
468 **Figure 1: Percent of Patients Achieving Various Levels of Pain Relief**

469 **16 HOW SUPPLIED/STORAGE AND HANDLING**

470 GRALISE (gabapentin) Tablets are supplied as follows:

471 **300 mg tablets:**

472 GRALISE 300 mg tablets are white, oval shaped tablets debossed with “SLV” on one side
473 and “300” on the other side.

474 NDC 13913-004-13 (Bottle of 30)

475 **600 mg tablets:**

476 GRALISE 600 mg tablets are beige, oval shaped tablets debossed with “SLV” on one side
477 and “600” on the other side.

478 NDC 13913-005-19 (Bottle of 90)

479 **30-Day Starter Pack:**

480 NDC 13913-006-16 (Blister package containing 78 tablets: 9 x 300 mg tablets and 69 x
481 600 mg tablets)

482 **Storage**

483 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP
484 Controlled Room Temperature].

485 Keep out of reach of children.

486

487 **17 PATIENT COUNSELING INFORMATION**

- 488 • Advise patients that GRALISE is not interchangeable with other formulations of
489 gabapentin.
- 490 • Advise patients to take GRALISE only as prescribed. GRALISE may cause dizziness,
491 somnolence, and other signs and symptoms of CNS depression.
- 492 • Advise patients not to drive or operate other complex machinery until they have gained
493 sufficient experience on GRALISE to gauge whether or not it adversely affects their
494 mental and/or motor performance. Advise patients who require concomitant treatment
495 with morphine to tell their prescriber if they develop signs of CNS depression such as
496 somnolence. If this occurs the dose of GRALISE or morphine should be reduced
497 accordingly.
- 498 • Advise patients that if they miss a dose of GRALISE to take it with food as soon as they
499 remember. If it is almost time for the next dose, just skip the missed dose and take the
500 next dose at the regular time. Do not take two doses at the same time.
- 501 • Advise patients that if they take too much GRALISE, to call their healthcare provider or
502 poison control center, or go to the nearest emergency room right away.

503 **17.1 Medication Guide**

504 Advise patients of the availability of a Medication Guide, and instruct them to read the
505 Medication Guide prior to taking GRALISE.

506 **17.2 Suicidal Thoughts and Behavior**

507 Advise patients, their caregivers, and families that AEDs, including gabapentin, the active
508 ingredient in GRALISE, may increase the risk of suicidal thoughts and behavior and should be
509 advised of the need to be alert for the emergence or worsening of symptoms of depression, any
510 unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or
511 thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare
512 providers [*see Warnings and Precautions (5.1)*].

513 **17.3 Dosing and Administration**

514 Advise patients that GRALISE should be taken orally once-daily with the evening meal.
515 GRALISE tablets should be swallowed whole. Do not split, crush, or chew the tablets [*see*
516 *Dosage and Administration (2.1)*].

517

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520 Menlo Park, CA 94025

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