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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 Abbott Laboratories at 1-800-241-1643 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. (8.2)
- Elderly: Reductions in GRALISE dose should be made in patients with age-related compromised renal function. (8.4)
- Renal impairment: Dosage adjustment is necessary for patients with impaired renal function. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2011

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1 **FULL PRESCRIBING INFORMATION**

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3 GRALISE™ (gabapentin) Tablets R_x 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.

31

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.

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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).

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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 Laboratory Tests**

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

105 **6 ADVERSE REACTIONS**

106 **6.1 Clinical Trials Experience**

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

110 A total of 359 patients with neuropathic pain associated with postherpetic neuralgia have
111 received GRALISE at doses up to 1800 mg daily during placebo-controlled clinical studies. In
112 clinical trials in patients with postherpetic neuralgia, 9.7% of the 359 patients treated with
113 GRALISE and 6.9% of 364 patients treated with placebo discontinued prematurely due to
114 adverse reactions. In the GRALISE treatment group, the most common reason for
115 discontinuation due to adverse reactions was dizziness. Of GRALISE-treated patients who
116 experienced adverse reactions in clinical studies, the majority of those adverse reactions were
117 either "mild" or "moderate".

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

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121 **Table 4: Treatment-Emergent Adverse Reaction Incidence in Controlled Trials in**
122 **Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at Least 1% of all**
123 **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

124
125 In addition to the adverse reactions reported in Table 4 above, the following adverse
126 reactions with an uncertain relationship to GRALISE were reported during the clinical
127 development for the treatment of postherpetic neuralgia. Events in more than 1% of patients but
128 equally or more frequently in the GRALISE-treated patients than in the placebo group included
129 blood pressure increase, confusional state, gastroenteritis viral, herpes zoster, hypertension, joint
130 swelling, memory impairment, nausea, pneumonia, pyrexia, rash, seasonal allergy, and upper
131 respiratory infection.

132 **6.2 Postmarketing and Other Experience with other Formulations of Gabapentin**

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

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135 marketed gabapentin. These adverse experiences have not been listed above and data are
136 insufficient to support an estimate of their incidence or to establish causation. The listing is
137 alphabetized: angioedema, blood glucose fluctuation, breast hypertrophy, erythema multiforme,
138 elevated liver function tests, fever, hyponatremia, jaundice, movement disorder, Stevens-Johnson
139 syndrome.

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

143 **7 DRUG INTERACTIONS**

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

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

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

155 **7.1 Phenytoin**

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

160 **7.2 Carbamazepine**

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

165 **7.3 Valproic Acid**

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

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170 **7.4 Phenobarbital**

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

174 **7.5 Naproxen**

175 Coadministration of single doses of naproxen (250 mg) and gabapentin immediate release
176 (125 mg) to 18 volunteers increased gabapentin absorption by 12% to 15%. Gabapentin
177 immediate release had no effect on naproxen pharmacokinetics. The doses are lower than the
178 therapeutic doses for both drugs. The effect of coadministration of these drugs at therapeutic
179 doses is not known.

180 **7.6 Hydrocodone**

181 Coadministration of gabapentin immediate release (125 mg and 500 mg) and hydrocodone
182 (10 mg) reduced hydrocodone C_{max} by 3% and 21%, respectively, and AUC by 4% and 22%,
183 respectively. The mechanism of this interaction is unknown. Gabapentin AUC values were
184 increased by 14%; the magnitude of the interaction at other doses is not known.

185 **7.7 Morphine**

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

192 **7.8 Cimetidine**

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

196 **7.9 Oral Contraceptives**

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

201 **7.10 Antacid (containing aluminum hydroxide and magnesium hydroxide)**

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

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

207 **7.11 Probenecid**

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

211 **7.12 Drug/Laboratory Test Interactions**

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

216 **8 USE IN SPECIFIC POPULATIONS**

217 **8.1 Pregnancy**

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

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

249 **8.2 Nursing Mothers**

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

254 **8.3 Pediatric Use**

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

257 **8.4 Geriatric Use**

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

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

265 **8.5 Hepatic Impairment**

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

268 **8.6 Renal Impairment**

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

273 **9 DRUG ABUSE AND DEPENDENCE**

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

275 **10 OVERDOSAGE**

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

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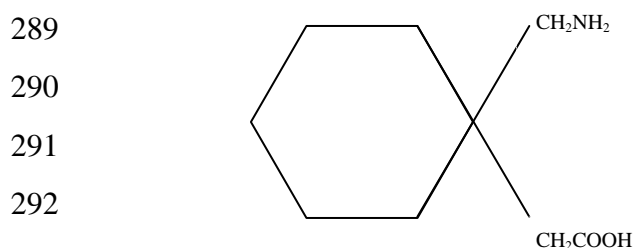
279 Acute oral overdoses of gabapentin immediate release in humans up to 49 grams have
280 been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea
281 were observed. All patients recovered with supportive care.

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

285 11 DESCRIPTION

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

288 The structural formula is:



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

298 GRALISE is supplied as tablets containing 300 mg or 600 mg of gabapentin. GRALISE
299 tablets swell in gastric fluid and gradually release gabapentin. Each 300 mg tablet contains the
300 inactive ingredients copovidone, hypromellose, magnesium stearate, microcrystalline cellulose,
301 polyethylene oxide, and Opadry® II white. Opadry® II white contains polyvinyl alcohol,
302 titanium dioxide, talc, polyethylene glycol 3350, and lecithin (soya). Each 600 mg tablet
303 contains the inactive ingredients copovidone, hypromellose, magnesium stearate, polyethylene
304 oxide, and Opadry® II beige. Opadry® II beige contains polyvinyl alcohol, titanium dioxide,
305 talc, polyethylene glycol 3350, iron oxide yellow, and iron oxide red.

306 12 CLINICAL PHARMACOLOGY

307 12.1 Mechanism of Action

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

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

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

329 *In vitro* studies with radiolabeled gabapentin have revealed a gabapentin binding site in
330 areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in
331 animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium
332 channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.
333 It is hypothesized that gabapentin antagonizes thrombospondin binding to α2δ-1 as a receptor
334 involved in excitatory synapse formation and suggested that gabapentin may function
335 therapeutically by blocking new synapse formation.

336 **12.2 Pharmacodynamics**

337 No pharmacodynamic studies have been conducted with GRALISE.

338 **12.3 Pharmacokinetics**

339 ***Absorption and Bioavailability***

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

343 When GRALISE (1800 mg once daily) and gabapentin immediate release (600 mg three
344 times a day) were administered with high fat meals (50% of calories from fat), GRALISE has a
345 higher C_{max} and lower AUC at steady state compared to gabapentin immediate release (Table 5).
346 Time to reach maximum plasma concentration (T_{max}) for GRALISE is 8 hours, which is about
347 4-6 hours longer compared to gabapentin immediate release.

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348 **Table 5: Mean (SD) Steady-State Pharmacokinetics for GRALISE and Gabapentin**
349 **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

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

352

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

355

356 Administration of GRALISE with food increases the rate and extent of absorption of
357 gabapentin compared to the fasted state. C_{max} of gabapentin increases 33-84% and AUC of
358 gabapentin increases 33-118% with food depending on the fat content of the meal. GRALISE
359 should be taken with food.

360

Distribution

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

363

Metabolism and Excretion

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

368 Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly
369 proportional to creatinine clearance. In elderly patients and patients with impaired renal
370 function, plasma clearance is reduced. Gabapentin can be removed from plasma by
371 hemodialysis.

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

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375 12.4 Special Populations

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

378 In patients (N=60) with creatinine clearance of at least 60, 30 to 59, or less than
379 30 mL/min, the median renal clearance rates for a 400 mg single dose of gabapentin immediate
380 release were 79, 36, and 11 mL/min, respectively, and the median $t_{1/2}$ values were 9.2, 14, and
381 40 hours, respectively.

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

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

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

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

396 **Pediatrics:** The pharmacokinetics of GRALISE have not been studied in patients less than
397 18 years of age.

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

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

404 13 NONCLINICAL TOXICOLOGY

405 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

406 Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at
407 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence
408 of pancreatic acinar cell adenoma and carcinomas was found in male rats receiving the high
409 dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma
410 concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg/day were more than
411 10 times higher than plasma concentrations in humans receiving 1800 mg per day and in rats

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

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

421 Gabapentin did not demonstrate mutagenic or genotoxic potential in 3 *in vitro* and 4 *in*
422 *vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in
423 Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations
424 in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal
425 aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was
426 negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA
427 synthesis in hepatocytes from rats given gabapentin.

428 No adverse effects on fertility or reproduction were observed in rats at doses up to
429 2000 mg/kg (approximately 11 times the maximum recommended human dose on an mg/m²
430 basis).

431 **14 CLINICAL STUDIES**

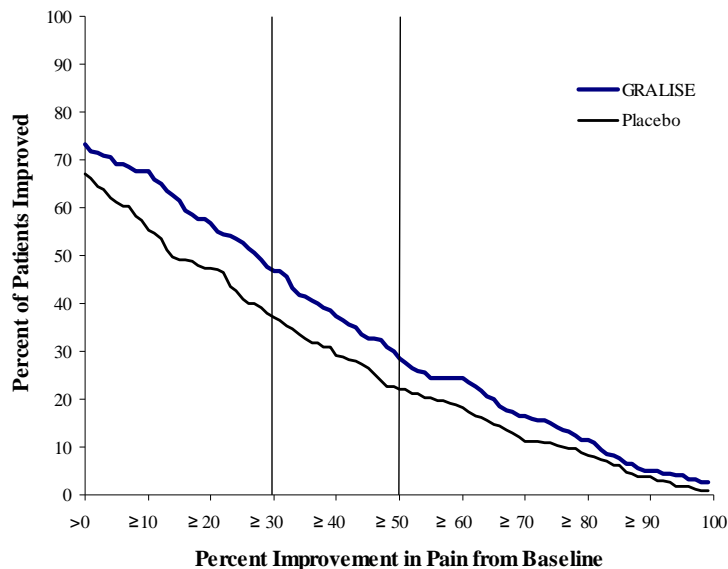
432 The efficacy of GRALISE for the management of postherpetic neuralgia was established
433 in a double-blind, placebo-controlled, multicenter study. This study enrolled patients between
434 the age of 21 to 89 with postherpetic neuralgia persisting for at least 6 months following healing
435 of herpes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

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

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

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



453

454

Figure 1: Percent of Patients Achieving Various Levels of Pain Relief

455 **16 HOW SUPPLIED/STORAGE AND HANDLING**

456 GRALISE (gabapentin) Tablets are supplied as follows:

457 **300 mg tablets:**

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

460 NDC 0032-5830-39 (Bottle of 30)

461 NDC 0032-5830-09 (Bottle of 90)

462 NDC 0032-5830-32 (Bottle of 300)

463 NDC 0032-5830-47 (Unit-Dose Blister of 10)

464 **600 mg tablets:**

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

467 NDC 0032-5860-09 (Bottle of 90)

468 NDC 0032-5860-32 (Bottle of 300)

469 NDC 0032-5860-47 (Unit-Dose Blister of 10)

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470 **30-Day Starter Pack:**

471 NDC 0032-5890-29 (Blister package containing 78 tablets: 9 x 300 mg tablets and 69 x
472 600 mg tablets)

473 **Storage**

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

476 Keep out of reach of children.

477

478 **17 PATIENT COUNSELING INFORMATION**

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

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494 **17.1 Medication Guide**

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

497 **17.2 Suicidal Thoughts and Behavior**

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

504 **17.3 Dosing and Administration**

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

508

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510 Abbott Laboratories
511 North Chicago, IL 60064 U.S.A.

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520 **MEDICATION GUIDE**

521 **GRALISE™ (gra leez')**

522 **(gabapentin) Tablets**

523

524 Read this Medication Guide before you start taking GRALISE and each time you get a refill.

525 There may be new information. This information does not take the place of talking to your

526 healthcare provider about your medical condition or treatment. If you have any questions about

527 GRALISE, ask your healthcare provider or pharmacist.

528 **What is the most important information I should know about GRALISE?**

529 **Do not stop taking GRALISE without first talking with your healthcare provider.** Stopping
530 GRALISE suddenly can cause serious problems.

531 Like other antiepileptic drugs, gabapentin, the active ingredient in GRALISE, may cause suicidal
532 thoughts or actions in a very small number of people, about 1 in 500. However, it is not known
533 if GRALISE is safe and effective in people with seizure problems (epilepsy). Therefore,
534 GRALISE should not be used in place of other gabapentin products.

535 **Call a healthcare provider right away if you have any of these symptoms, especially if**
536 **they are new, worse, or worry you:**

- 537
- 538 • thoughts about suicide or dying
 - 539 • attempts to commit suicide
 - 540 • new or worse depression
 - 541 • new or worse anxiety
 - 542 • feeling agitated or restless
 - 543 • panic attacks
 - 544 • trouble sleeping (insomnia)
 - 545 • new or worse irritability
 - 546 • acting aggressive, being angry, or violent
 - 547 • acting on dangerous impulses
 - 548 • an extreme increase in activity and talking (mania)
 - 549 • other unusual changes in behavior or mood

549 **How can I watch for early symptoms of suicidal thoughts and actions?**

- 550
- 551 • Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts,
552 or feelings.
 - Keep all follow-up visits with your healthcare provider as scheduled.

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- 553 • Call your healthcare provider between visits as needed, especially if you are worried
554 about symptoms.

555 **Do not stop taking GRALISE without first talking with your healthcare provider.**

- 556 • Stopping GRALISE suddenly can cause serious problems.

557 **What is GRALISE?**

558 GRALISE is a prescription medicine used in adults, 18 years and older, to treat:

- 559 • pain from damaged nerves (neuropathic pain) that follows healing of shingles (a painful
560 rash that comes after a herpes zoster infection).

561 It is not known if GRALISE is safe and effective in people with seizure problems (epilepsy).

562 It is not known if GRALISE is safe and effective in children under 18 years of age with
563 postherpetic pain.

564 GRALISE is not interchangeable with other gabapentin products.

565 **Who should not take GRALISE?**

566 Do not take GRALISE if you are allergic to gabapentin or any of the ingredients in GRALISE.
567 See the end of this Medication Guide for a complete list of ingredients in GRALISE.

568 **What should I tell my healthcare provider before taking GRALISE?**

569 Before taking GRALISE, tell your healthcare provider if you:

- 570 • have or have had depression, mood problems or suicidal thoughts or behavior
- 571 • have seizures
- 572 • have kidney problems or get kidney dialysis
- 573 • are pregnant or plan to become pregnant. It is not known if GRALISE can harm your
574 unborn baby. Tell your healthcare provider right away if you become pregnant while
575 taking GRALISE. You and your healthcare provider will decide if you should take
576 GRALISE while you are pregnant.
- 577 ○ If you become pregnant while taking GRALISE, talk to your healthcare provider
578 about registering with the North American Antiepileptic Drug (NAAED)
579 Pregnancy Registry. The purpose of this registry is to collect information about
580 the safety of antiepileptic drugs, including gabapentin, the active ingredient in
581 GRALISE, during pregnancy. You can enroll in this registry by calling 1-888-
582 233-2334.
- 583 • are breastfeeding or plan to breastfeed. GRALISE can pass into your breast milk. You
584 and your healthcare provider should decide how you will feed your baby while you take
585 GRALISE.

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586 Tell your healthcare provider about all the medicines you take including prescription and non-
587 prescription medicines, vitamins or herbal supplements.

588 Taking GRALISE with certain other medicines can cause side effects or affect how well they
589 work. Do not start or stop other medicines without talking to your healthcare provider.

590 Know the medicines you take. Keep a list of them and show it to your healthcare provider and
591 pharmacist when you get a new medicine.

592 **How should I take GRALISE?**

593 • Take GRALISE exactly as prescribed. Your healthcare provider will tell you how much
594 GRALISE to take and when to take it. Take GRALISE at the same time each day.

595 • **Do not change your dose or stop taking GRALISE without talking with your**
596 **healthcare provider.** If you stop taking GRALISE suddenly, you may experience side
597 effects. Talk with your healthcare provider about how to stop GRALISE slowly.

598 • Take GRALISE with food one time each day with your evening meal.

599 • Take GRALISE tablets whole. Do not split, crush, or chew GRALISE tablets before
600 swallowing.

601 • Your healthcare provider may change your dose of GRALISE. Do not change your dose
602 of GRALISE without talking to your healthcare provider.

603 • If you miss a dose, take it as soon as you remember with food. If it is almost time for
604 your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not**
605 **take two doses at the same time.**

606 • If you take too much GRALISE, call your healthcare provider or poison control center,
607 or go to the nearest emergency room right away.

608 • If you are taking an antacid containing aluminum hydroxide and magnesium hydroxide,
609 it is recommended that GRALISE be taken at least 2 hours following administration of
610 the antacid.

611 **What should I avoid while taking GRALISE?**

612 • Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking
613 GRALISE without first talking to your healthcare provider. Taking GRALISE with
614 alcohol or medicines that cause sleepiness or dizziness may make you sleepiness or
615 dizziness worse.

616 • Do not operate heavy machines or do other dangerous activities until you know how
617 GRALISE affects you. GRALISE can slow your thinking and motor skills.

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618 **What are the possible side effects of GRALISE?**

619 The most common side effect of GRALISE is:

- 620
 - dizziness

621 Tell your healthcare provider about any side effect that bothers you or that does not go away.

622 These are not all the possible side effects of GRALISE. For more information, ask your
623 healthcare provider or pharmacist.

624 Call your doctor for medical advice about side effects. You may report side effects to FDA at
625 1-800-FDA-1088.

626

627 **How should I store GRALISE?**

628 Store GRALISE at 59°F to 86°F (15°C to 30°C)

- 629
 - **Keep GRALISE and all medicines out of the reach of children.**

630 **General information about the safe and effective use of GRALISE**

631 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

632 Do not use GRALISE for a condition for which it was not prescribed. Do not give GRALISE to
633 other people, even if they have the same symptoms you have. It may harm them.

634 This Medication Guide summarizes the most important information about GRALISE. If you
635 would like more information, talk with your healthcare provider. You can ask your healthcare
636 provider or pharmacist for information about GRALISE that is written for health professionals.

637 For more information about GRALISE, call 1-800-241-1643.

638 **What are the ingredients in GRALISE?**

639 Active ingredient: gabapentin

640 Inactive ingredients:

641 300 mg tablet: copovidone, hypromellose, magnesium stearate, microcrystalline cellulose,
642 polyethylene oxide, and Opadry® II white. Opadry® II white contains polyvinyl alcohol,
643 titanium dioxide, talc, polyethylene glycol 3350, and lecithin (soya).

644 600 mg tablet: copovidone, hypromellose, magnesium stearate, polyethylene oxide, and
645 Opadry® II beige. Opadry® II beige contains polyvinyl alcohol, titanium dioxide, talc,
646 polyethylene glycol 3350, iron oxide yellow, and iron oxide red.

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649 North Chicago, IL 60064 U.S.A.

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656 This Medication Guide has been approved by the U.S. Food and Drug Administration.

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