

NDA 022399 – FDA Approved Labeling Text dated December 2012

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Patients with renal impairment: Doses of HORIZANT must be adjusted in accordance with renal function. (2.3)

HORIZANT (gabapentin enacarbil) Extended-Release Tablets for oral use

Initial U.S. Approval: 2011

-----**DOSAGE FORMS AND STRENGTHS**-----
Extended-Release Tablets: 300 mg and 600 mg. (3)

-----**CONTRAINDICATIONS**-----
None. (4)

-----**RECENT MAJOR CHANGES**-----
Indications and Usage, Management of Postherpetic Neuralgia (1.2) 06/2012
Dosage and Administration, Postherpetic Neuralgia (2.2) 06/2012
Dosage and Administration, Renal Impairment (2.3) 06/2012
Warnings and Precautions, Somnolence/Sedation and Dizziness (5.2) 06/2012
Warnings and Precautions, Discontinuation of HORIZANT (5.6) 06/2012

-----**WARNINGS AND PRECAUTIONS**-----
• Driving impairment: Warn patients not to drive until they have gained sufficient experience with HORIZANT to assess whether it will impair their ability to drive. (5.1)
• Somnolence/sedation and dizziness: May impair the patient's ability to operate complex machinery. (5.2)
• HORIZANT is not interchangeable with other gabapentin products. (5.3)
• Suicidal thoughts or behaviors: HORIZANT is a prodrug of gabapentin, an antiepileptic drug (AED). AEDs increase the risk of suicidal thoughts or behaviors. Monitor for suicidal thoughts or behaviors. (5.4)

-----**INDICATIONS AND USAGE**-----
HORIZANT is indicated for:
• treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults. (1.1)
• management of postherpetic neuralgia (PHN) in adults. (1.2)

-----**ADVERSE REACTIONS**-----
• RLS: Most common adverse reactions ($\geq 10\%$ and at least 2 times the rate of placebo) were somnolence/sedation and dizziness. (6.1)
• PHN: Most common adverse reactions ($\geq 10\%$ and greater than placebo) were dizziness, somnolence, and headache. (6.1)

-----**DOSAGE AND ADMINISTRATION**-----
Instruct patients to swallow tablets whole and not to cut, crush, or chew tablets. Take with food. (2)
RLS: 600 mg once daily taken at about 5 PM. (2.1)
• A dose of 1,200 mg once daily provided no additional benefit compared with the 600-mg dose, but caused an increase in adverse reactions. (2.1)
• If the dose is not taken at the recommended time, the next dose should be taken the following day as prescribed. (2.1)
PHN: The starting dose is 600 mg in the morning for 3 days, then increase to 600 mg twice daily beginning on day 4. (2.2)
• A daily dose greater than 1,200 mg provided no additional benefit. (2.2)
• If the dose is not taken at the recommended time, skip this dose, and the next dose should be taken at the time of next scheduled dose. (2.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**USE IN SPECIFIC POPULATIONS**-----
Pregnancy: Based on animal data, may cause fetal harm. (8.1)
See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
 - 1.1 Treatment of Restless Legs Syndrome
 - 1.2 Management of Postherpetic Neuralgia
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Restless Legs Syndrome
 - 2.2 Postherpetic Neuralgia
 - 2.3 Renal Impairment
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Effects on Driving
 - 5.2 Somnolence/Sedation and Dizziness
 - 5.3 Lack of Interchangeability With Gabapentin
 - 5.4 Suicidal Behavior and Ideation
 - 5.5 Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity
 - 5.6 Discontinuation of HORIZANT
 - 5.7 Tumorigenic Potential
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience
 - 6.2 Adverse Events Associated With Gabapentin
- 7 DRUG INTERACTIONS
- 8 USE IN SPECIFIC POPULATIONS
 - 8.1 Pregnancy
 - 8.2 Labor and Delivery
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Renal Impairment

- 9 DRUG ABUSE AND DEPENDENCE
 - 9.1 Controlled Substance
 - 9.2 Abuse
 - 9.3 Dependence
- 10 OVERDOSAGE
 - 10.1 Human Overdose Experience
 - 10.2 Overdosage Management
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
 - 12.1 Mechanism of Action
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES
 - 14.1 Restless Legs Syndrome (RLS) 12-Week Pivotal Studies
 - 14.2 Postherpetic Neuralgia (PHN) 12-Week Study
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION
 - 17.1 Effects on Driving
 - 17.2 Somnolence/Sedation and Dizziness
 - 17.3 Suicidal Behavior and Ideation
 - 17.4 Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity
 - 17.5 Lack of Interchangeability With Gabapentin
 - 17.6 Dosing Instructions
 - 17.7 Alcohol

*Sections or subsections omitted from the full prescribing information are not listed.

1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 **1.1 Treatment of Restless Legs Syndrome**

4 HORIZANT[®] (gabapentin enacarbil) Extended-Release Tablets are indicated for the
5 treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults.

6 HORIZANT is not recommended for patients who are required to sleep during the
7 daytime and remain awake at night.

8 **1.2 Management of Postherpetic Neuralgia**

9 HORIZANT (gabapentin enacarbil) Extended-Release Tablets are indicated for the
10 management of postherpetic neuralgia (PHN) in adults.

11 **2 DOSAGE AND ADMINISTRATION**

12 Tablets should be swallowed whole and should not be cut, crushed, or chewed.

13 Tablets should be taken with food.

14 HORIZANT is not interchangeable with other gabapentin products because of differing
15 pharmacokinetic profiles [*see Warnings and Precautions (5.3)*].

16 **2.1 Restless Legs Syndrome**

17 The recommended dosage for HORIZANT is 600 mg once daily at about 5 PM. A daily
18 dose of 1,200 mg provided no additional benefit compared with the 600-mg dose, but caused an
19 increase in adverse reactions [*see Adverse Reactions (6.1)*].

20 If the dose is not taken at the recommended time, the next dose should be taken the
21 following day as prescribed.

22 **2.2 Postherpetic Neuralgia**

23 The recommended dosage of HORIZANT is 600 mg twice daily. HORIZANT should be
24 initiated at a dose of 600 mg in the morning for 3 days of therapy, then increased to 600 mg
25 twice daily (1,200 mg/day) on day four. In the 12-week principal efficacy study, additional
26 benefit of using doses greater than 1,200 mg a day was not demonstrated, and these higher doses
27 resulted in an increase in adverse reactions [*see Adverse Reactions (6.1)*].

28 If the dose is not taken at the recommended time, skip this dose, and the next dose should
29 be taken at the time of the next scheduled dose.

30 **2.3 Renal Impairment**

31 Dosing of HORIZANT is adjusted in accordance with renal function, as represented by
32 creatinine clearance [*see Clinical Pharmacology (12.3)*]. Target dose regimens are listed in
33 Table 1 and Table 2.

34

35 **Table 1. Dosage of HORIZANT for Patients With Restless Legs Syndrome in Accordance**
 36 **With Creatinine Clearance**

Creatinine Clearance (mL/min)	Target Dose Regimen
≥60	600 mg per day
30 – 59	Start at 300 mg per day and increase to 600 mg as needed
15 – 29	300 mg per day
<15	300 mg every other day
<15 on hemodialysis	Not recommended

37
 38 **Table 2. Dosage of HORIZANT for Patients With Postherpetic Neuralgia in Accordance**
 39 **With Creatinine Clearance**

Creatinine Clearance (mL/min)	Titration	Maintenance	Tapering
≥60	600 mg in AM for 3 days	600 mg twice daily	600 mg in AM for 1 week
30 – 59	300 mg in AM for 3 days	300 mg twice daily. Increase to 600 mg twice daily as needed ^a	Reduce current maintenance dose to once daily in AM for 1 week
15 – 29	300 mg in AM on Day 1 and Day 3	300 mg in AM. Increase to 300 mg twice daily if needed ^a	If taking 300 mg twice daily, reduce to 300 mg once daily in AM for 1 week. If taking 300 mg once daily, no taper needed.
<15	None	300 mg every other day in AM. Increase to 300 mg once daily in AM if needed ^a	None
<15 on hemodialysis	None	300 mg following every dialysis. Increase to 600 mg following every dialysis if needed ^a	None

40 ^a Based on tolerability and efficacy

41
 42 In patients with stable renal function, CrCl can be estimated using the equation of
 43 Cockcroft and Gault:

44 for males: $CrCl = (140 - \text{age})(\text{weight}) / [(72)(SCr)]$

45 for females: $CrCl = (0.85)(140 - \text{age})(\text{weight}) / [(72)(SCr)]$

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

47 **3 DOSAGE FORMS AND STRENGTHS**

48 HORIZANT Extended-Release Tablets, 300 mg, are red, oval-shaped tablets debossed
49 with “GS TF7” and 600 mg, are white to off-white, oval-shaped tablets debossed with
50 “GS LFG”. Both the 300 mg and 600 mg tablets may contain occasional black/grey spots.

51 **4 CONTRAINDICATIONS**

52 None.

53 **5 WARNINGS AND PRECAUTIONS**

54 **5.1 Effects on Driving**

55 HORIZANT causes significant driving impairment. Patients being treated with
56 HORIZANT should not drive until they have gained sufficient experience to assess whether
57 HORIZANT impairs their ability to drive. However, prescribers and patients should be aware
58 that patients’ ability to assess their own driving competence, as well as their ability to assess the
59 degree of somnolence caused by HORIZANT, can be imperfect.

60 In a 2-week simulated driving study in patients with RLS, a daily single 1,200-mg dose
61 of HORIZANT caused significant impairment within 2 hours and for up to 14 hours after dosing.
62 The impairment was similar to that caused by the active control, a single oral dose of
63 diphenhydramine 50 mg. The effect on driving at times other than 2 weeks is unknown. Whether
64 the impairment is related to somnolence [*see Warnings and Precautions (5.2)*] or other effects of
65 HORIZANT is unknown. The 600-mg dose was not studied. Because a 600-mg/day dose of
66 HORIZANT can cause significant somnolence, similar to that of the 1,200-mg/day dose [*see*
67 *Warnings and Precautions (5.2)*], the 600- and 1,200-mg/day doses may have similar effects on
68 driving behavior.

69 **5.2 Somnolence/Sedation and Dizziness**

70 HORIZANT causes somnolence/sedation and dizziness (see Tables 4 and 5). Patients
71 should be advised not to drive a car or operate other complex machinery until they have gained
72 sufficient experience on HORIZANT to assess whether HORIZANT impairs their ability to
73 perform these tasks.

74 During the controlled trials in patients with RLS, somnolence/sedation was reported in
75 20% of patients treated with 600 mg of HORIZANT per day compared with 6% of patients
76 receiving placebo. In those patients treated with HORIZANT who reported somnolence, the
77 somnolence persisted during treatment in about 30%. In the remaining patients, symptoms
78 resolved within 3 to 4 weeks. Dizziness was reported in 13% of patients receiving 600 mg of
79 HORIZANT per day compared with 4% of patients receiving placebo. In those patients treated
80 with HORIZANT who reported dizziness, symptoms persisted during treatment in about 20%.
81 Somnolence/sedation led to withdrawal in 2% of patients receiving 600 mg of HORIZANT per
82 day. Dizziness led to withdrawal in 1% of patients receiving 600 mg of HORIZANT per day.
83 The incidence of these adverse reactions was greater in the patients receiving 1,200 mg per day.

84 During the 12-week, controlled study in patients with PHN, somnolence was reported in
85 10% of patients treated with 1,200 mg of HORIZANT per day compared with 8% of patients
86 receiving placebo. Fatigue/asthenia was reported in 6% of patients treated with 1,200 mg of
87 HORIZANT per day compared with 1% of patients receiving placebo. In those patients treated
88 with 1,200 mg of HORIZANT per day who reported somnolence (10%), the somnolence
89 persisted during treatment in about 27%. In the remaining patients, symptoms resolved within 4
90 to 5 weeks. Dizziness was reported in 17% of patients receiving 1,200 mg of HORIZANT per
91 day compared with 15% of patients receiving placebo. In those patients treated with 1,200 mg of
92 HORIZANT per day who reported dizziness, symptoms persisted during treatment in about 6%.
93 Somnolence led to withdrawal in <1% of patients receiving 1,200 mg of HORIZANT per day
94 compared with 2% of patients receiving placebo. Dizziness led to withdrawal in 2% of patients
95 receiving 1,200 mg of HORIZANT per day compared with 3% of patients receiving placebo.

96 **5.3 Lack of Interchangeability With Gabapentin**

97 HORIZANT is not interchangeable with other gabapentin products because of differing
98 pharmacokinetic profiles. The same dose of HORIZANT results in different plasma
99 concentrations of gabapentin relative to other gabapentin products. [*See Clinical Pharmacology*
100 (*12.3*).]

101 The safety and effectiveness of HORIZANT in patients with epilepsy have not been
102 studied.

103 **5.4 Suicidal Behavior and Ideation**

104 HORIZANT (gabapentin enacarbil) is a prodrug of gabapentin, an antiepileptic drug
105 (AED). AEDs increase the risk of suicidal thoughts or behavior in patients taking these drugs for
106 any indication. Because HORIZANT is a prodrug of gabapentin, HORIZANT also increases this
107 risk. Patients treated with any AED for any indication should be monitored for the emergence or
108 worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or
109 behavior.

110 Pooled analyses of 199 placebo-controlled clinical trials (monotherapy and adjunctive
111 therapy) of 11 different AEDs showed that patients randomized to 1 of the AEDs had
112 approximately twice the risk [adjusted relative risk 1.8, 95% confidence interval (CI): 1.2, 2.7] of
113 suicidal thinking or behavior compared with patients randomized to placebo. In these trials,
114 which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal
115 behavior or ideation among 27,863 AED-treated patients was 0.43%, compared with 0.24%
116 among 16,029 placebo-treated patients, representing an increase of approximately 1 case of
117 suicidal thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated
118 patients in the trials and none in placebo-treated patients, but the number is too small to allow
119 any conclusion about drug effect on suicide.

120 The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1
121 week after starting drug treatment with AEDs and persisted for the duration of treatment
122 assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk
123 of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

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

129

130 **Table 3. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis**

Indication	Placebo Patients With Events Per 1,000 Patients	Drug Patients With Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients With Events Per 1,000 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

131

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

135 Anyone considering prescribing HORIZANT must balance the risk of suicidal thoughts
 136 or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs
 137 are prescribed are themselves associated with morbidity and mortality and an increased risk of
 138 suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment,
 139 the prescriber needs to consider whether the emergence of these symptoms in any given patient
 140 may be related to the illness being treated.

141 Patients, their caregivers, and families should be informed that HORIZANT increases the
 142 risk of suicidal thoughts and behavior and should be advised of the need to be alert for the
 143 emergence or worsening of the signs and symptoms of depression, any unusual changes in mood
 144 or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm.
 145 Behaviors of concern should be reported immediately to healthcare providers.

146 **5.5 Drug Reaction With Eosinophilia and Systemic Symptoms**
 147 **(DRESS)/Multiorgan Hypersensitivity**

148 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as
 149 multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including
 150 gabapentin. HORIZANT is a prodrug of gabapentin. Some of these events have been fatal or
 151 life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or
 152 lymphadenopathy, in association with other organ system involvement, such as hepatitis,
 153 nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute

154 viral infection. Eosinophilia is often present. Because this disorder is variable in its expression,
155 other organ systems not noted here may be involved.

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

160 **5.6 Discontinuation of HORIZANT**

161 When discontinuing HORIZANT, patients with RLS receiving 600 mg or less once daily
162 can discontinue the drug without tapering. If the recommended dose is exceeded, the dose should
163 be reduced to 600 mg daily for 1 week prior to discontinuation to minimize the potential of
164 withdrawal seizure.

165 In patients with PHN receiving HORIZANT twice daily, the dose should be reduced to
166 once daily for 1 week prior to discontinuation to minimize the potential of withdrawal seizure,
167 see Table 2 [see *Dosage and Administration (2.3)*].

168 **5.7 Tumorigenic Potential**

169 In an oral carcinogenicity study, gabapentin enacarbil increased the incidence of
170 pancreatic acinar cell adenoma and carcinoma in male and female rats [see *Nonclinical*
171 *Toxicology (13.1)*]. The clinical significance of this finding is unknown.

172 In clinical studies of gabapentin as adjunctive therapy in epilepsy comprising 2,085
173 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients
174 (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in*
175 *situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up
176 to 2 years following discontinuation of gabapentin. Without knowledge of the background
177 incidence and recurrence in a similar population not treated with gabapentin, it is impossible to
178 know whether the incidence reported in this cohort is or is not affected by treatment.

179 **6 ADVERSE REACTIONS**

180 The following adverse reactions are described in more detail in the *Warnings and*
181 *Precautions* section of the label:

- 182 • Somnolence/sedation and dizziness [see *Warnings and Precautions (5.2)*]

183 **6.1 Clinical Trials Experience**

184 Because clinical trials are conducted under widely varying conditions, adverse reaction
185 rates observed in the clinical trials of a drug cannot be directly compared with rates in the
186 clinical trials of another drug and may not reflect the rates observed in practice.

187 In all controlled and uncontrolled trials across various patient populations, more than
188 2,300 patients have received HORIZANT orally in daily doses ranging from 600 to 3,600 mg.

189 **Restless Legs Syndrome:** The exposure to HORIZANT in 1,201 patients with RLS
190 included 613 exposed for at least 6 months and 371 exposed for at least 1 year. HORIZANT in
191 the treatment of RLS was studied primarily in placebo-controlled trials (n = 642), and in long-

192 term follow-up studies. The population with RLS ranged from 18 to 82 years of age, with 60%
193 being female and 95% being Caucasian.

194 The safety of HORIZANT in doses ranging from 600 to 2,400 mg has been evaluated in
195 515 patients with RLS in 3 double-blind, placebo-controlled, 12-week clinical trials. The 600-mg
196 dose was studied in 2 of the 3 studies. Eleven out of 163 (7%) patients treated with 600 mg of
197 HORIZANT discontinued treatment due to adverse reactions compared with 10 of the 245 (4%)
198 patients who received placebo.

199 The most commonly observed adverse reactions ($\geq 5\%$ and at least 2 times the rate of
200 placebo) in these trials for the 600-mg dose of HORIZANT were somnolence/sedation and
201 dizziness (see Table 4). Table 4 lists treatment-emergent adverse reactions that occurred in $\geq 2\%$
202 of patients with RLS treated with HORIZANT and numerically greater than placebo.
203

204 **Table 4. Incidence of Adverse Reactions in 12-Week RLS Studies Reported in ≥2% of**
 205 **Patients Treated With 600 or 1,200 mg of HORIZANT and Numerically Greater Than**
 206 **Placebo**

Body System/Adverse Reaction	Placebo ^a (N = 245) %	HORIZANT 600 mg/day ^b (N = 163) %	HORIZANT 1,200 mg/day ^c (N = 269) %
Nervous system disorders			
Somnolence/sedation	6	20	27
Dizziness	4	13	22
Headache	11	12	15
Gastrointestinal disorders			
Nausea	5	6	7
Dry mouth	2	3	4
Flatulence	<1	3	2
General disorders and administration site conditions			
Fatigue	4	6	7
Irritability	1	4	4
Feeling drunk	0	1	3
Feeling abnormal	<1	<1	3
Peripheral edema	1	<1	3
Metabolism and nutritional disorders			
Weight increased	2	2	3
Increased appetite	<1	2	2
Ear and labyrinth disorders			
Vertigo	0	1	3
Psychiatric disorders			
Depression	<1	<1	3
Libido decreased	<1	<1	2

207 ^a Placebo was a treatment arm in each of the 3 double-blind, placebo-controlled, 12-week
 208 clinical trials.

209 ^b The 600-mg dose of HORIZANT was a treatment arm in 2 of the 3 double-blind, placebo-
 210 controlled, 12-week clinical trials.

211 ^c The 1,200-mg dose of HORIZANT was a treatment arm in each of the 3 double-blind,
 212 placebo-controlled, 12-week clinical trials.

213
 214 Adverse reactions reported in these three 12-week studies in <2% of patients treated with
 215 600 mg of HORIZANT and numerically greater than placebo were balance disorder, blurred
 216 vision, disorientation, feeling drunk, lethargy, and vertigo.

217 The following adverse reactions were dose-related: somnolence/sedation, dizziness,
 218 feeling drunk, libido decreased, depression, headache, peripheral edema, and vertigo.

219 **Postherpetic Neuralgia:** The exposure to HORIZANT in 417 patients with PHN
 220 included 207 patients exposed for at least 3 months. Overall, the mean age of patients in the PHN
 221 studies ranged from 61 to 64 years of age across dose groups; the majority of patients were male
 222 (45% to 61%) and Caucasian (80% to 98%).

223 The safety of HORIZANT in doses ranging from 1,200 to 3,600 mg has been evaluated
 224 in 417 patients with PHN in 3 clinical studies. The principal efficacy study evaluating the
 225 efficacy and safety of HORIZANT in the management of PHN was a 12-week, double-blind,
 226 multicenter study comparing 1,200 mg/day, 2,400 mg/day and 3,600 mg/day to placebo. Six out
 227 of 107 (6%) patients treated with 1,200 mg of HORIZANT discontinued treatment due to
 228 adverse events compared with 12 of the 95 (13%) patients who received placebo.

229 The most commonly observed adverse reactions ($\geq 10\%$ and greater than placebo) in this
 230 trial for the 1,200 mg dose of HORIZANT were dizziness, somnolence, and headache (see
 231 Table 5). Table 5 lists treatment-emergent adverse reactions that occurred in $\geq 2\%$ of patients
 232 with PHN treated with HORIZANT 1,200 mg/day and numerically greater than placebo.

233
 234 **Table 5. Incidence of Adverse Reactions (in At Least 2% of Patients Treated With**
 235 **1,200 mg/day of HORIZANT and Numerically Greater Than the Placebo Rate)**
 236 **Reported in All Patients in the 12-Week PHN Study**

Body System/Adverse Reaction	Placebo	HORIZANT	HORIZANT	HORIZANT
	(N = 95) %	1,200 mg/day (N = 107) %	2,400 mg/day (N = 82) %	3,600 mg/day (N = 87) %
Nervous System				
Dizziness	15	17	26	30
Somnolence	8	10	11	14
Headache	9	10	10	7
Gastrointestinal disorders				
Nausea	5	8	4	9
General disorders and administration site conditions				
Fatigue/Asthenia	1	6	4	10
Peripheral edema	0	6	7	6
Psychiatric disorders				
Insomnia	2	3	5	7
Metabolism and nutritional disorders				
Weight increased	1	3	5	5
Eye disorders				
Blurred vision	0	2	5	2

237
 238 The following adverse reactions were also reported as $\geq 2\%$ at 2,400 mg/day and/or
 239 3,600 mg/day and appeared to be dose-related but were $< 2\%$ at 1,200 mg/day: balance disorder,

240 confusional state, depression, dry mouth, flatulence, increased appetite, irritability, and vertigo.
241 Dizziness, somnolence, fatigue, and insomnia appeared to show a dose relationship.

242 **6.2 Adverse Events Associated With Gabapentin**

243 The following adverse events have been reported in patients receiving gabapentin, either
244 in clinical trials or postmarketing: breast enlargement, gynecomastia, and elevated creatine
245 kinase.

246 **7 DRUG INTERACTIONS**

247 Gabapentin enacarbil is released faster from HORIZANT Extended-Release tablets in the
248 presence of alcohol. Consumption of alcohol is not recommended when taking HORIZANT [*see*
249 *Clinical Pharmacology (12.3)*].

250 **8 USE IN SPECIFIC POPULATIONS**

251 **8.1 Pregnancy**

252 Pregnancy Category C. There are no adequate and well-controlled studies with
253 HORIZANT in pregnant women. In nonclinical studies in rat and rabbits, administration of
254 gabapentin enacarbil was developmentally toxic when administered to pregnant animals at doses
255 and gabapentin exposures greater than those used clinically. HORIZANT should be used during
256 pregnancy only if the potential benefit justifies the potential risk to the fetus.

257 When pregnant rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or
258 5,000 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased
259 at the 2 highest doses and fetal body weights were decreased at the high dose. The no-effect dose
260 for embryo-fetal developmental toxicity in rats (200 mg/kg/day) represents approximately
261 2 times the gabapentin exposure associated with the maximum recommended human dose
262 (MRHD) of 1,200 mg/day gabapentin enacarbil on an area under the curve (AUC) basis.

263 When pregnant rabbits were administered gabapentin enacarbil (oral doses of 200, 500,
264 or 2,500 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was
265 increased and fetal body weights were decreased at the high dose. The no-effect dose for
266 embryo-fetal developmental toxicity in rabbits (500 mg/kg/day) represents approximately
267 9 times the gabapentin exposure associated with the MRHD of 1,200 mg/day gabapentin
268 enacarbil on an AUC basis.

269 When female rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or
270 5,000 mg/kg/day) throughout the pregnancy and lactation periods, offspring growth and survival
271 were decreased at the two highest doses. The no-effect dose for pre- and post-natal
272 developmental toxicity in rats is approximately 2 times the MRHD on an AUC basis.

273 In reproductive and developmental studies of gabapentin, developmental toxicity was
274 observed at all doses tested. Increased incidences of hydronephrosis and/or hydroureter were
275 observed in rat offspring following treatment of pregnant animals in studies of fertility and
276 general reproductive performance, embryo-fetal development, and peri- and post-natal
277 development. Overall, a no-effect dose was not established. In mice, treatment of pregnant
278 animals with gabapentin during the period of organogenesis resulted in delayed fetal skeletal

279 ossification at all but the lowest dose tested. When pregnant rabbits were treated with gabapentin
280 during the period of organogenesis, an increase in embryo-fetal mortality was observed at all
281 doses of gabapentin tested.

282 In a published study, gabapentin (400 mg/kg/day) was administered by intraperitoneal
283 injection to neonatal mice during the first postnatal week, a period of synaptogenesis in rodents
284 (corresponding to the last trimester of pregnancy in humans). Gabapentin caused a marked
285 decrease in neuronal synapse formation in brains of intact mice and abnormal neuronal synapse
286 formation in a mouse model of synaptic repair. Gabapentin has been shown *in vitro* to interfere
287 with activity of the $\alpha 2\delta$ subunit of voltage-activated calcium channels, a receptor involved in
288 neuronal synaptogenesis. The clinical significance of these findings is unknown.

289 **8.2 Labor and Delivery**

290 The effect of HORIZANT on labor and delivery is unknown.

291 **8.3 Nursing Mothers**

292 It is not known whether gabapentin derived from HORIZANT is secreted in human milk;
293 however, gabapentin is secreted into human milk following oral administration of gabapentin
294 products. Because of the potential for adverse reactions in nursing infants from HORIZANT, a
295 decision should be made whether to discontinue nursing or to discontinue the drug, taking into
296 account the importance of the drug to the mother.

297 **8.4 Pediatric Use**

298 Safety and effectiveness of HORIZANT in pediatric patients have not been studied.

299 **8.5 Geriatric Use**

300 Of the 515 patients treated with HORIZANT in the 3 double-blind, placebo-controlled,
301 12-week clinical trials for RLS, 11% were 65 to 74 years of age and 1% were 75 years of age
302 and older. Clinical trials of HORIZANT for the treatment of RLS did not include a sufficient
303 number of patients 65 years and older to determine whether they respond differently from
304 younger individuals.

305 In the 12-week, double-blind, placebo-controlled study of HORIZANT for the
306 management of PHN (n = 276 patients treated with HORIZANT), 37% were 65 to 74 years of
307 age and 13% were 75 years of age and older. The overall incidence of adverse events was
308 comparable between the patients aged ≥ 18 to < 65 years and ≥ 65 to < 74 years. No overall
309 differences in the safety and effectiveness were observed between these subjects and younger
310 subjects, and other reported clinical experience has not identified differences in responses
311 between the elderly and younger patients, but greater sensitivity of some older individuals cannot
312 be ruled out.

313 Gabapentin is known to be almost exclusively excreted by the kidney, and the risk of
314 adverse reactions to this drug may be greater in patients with impaired renal function. Because
315 elderly patients are more likely to have decreased renal function, the frequency of dosing may
316 need to be adjusted based on calculated creatinine clearance in these patients [*see Dosage and*
317 *Administration (2.3)*].

318 **8.6 Renal Impairment**

319 The dose of HORIZANT should be adjusted in patients with renal impairment [*see*
320 *Dosage and Administration (2.3), Clinical Pharmacology (12.3)*].

321 **9 DRUG ABUSE AND DEPENDENCE**

322 **9.1 Controlled Substance**

323 HORIZANT, a prodrug of gabapentin, is not a scheduled drug.

324 **9.2 Abuse**

325 Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta, or kappa), or
326 cannabinoid 1 receptor sites. A small number of postmarketing cases report gabapentin misuse
327 and abuse. These individuals were taking higher than recommended doses of gabapentin for
328 unapproved uses. Most of the individuals described in these reports had a history of poly-
329 substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances.

330 When prescribing products that deliver gabapentin, carefully evaluate patients for a
331 history of drug abuse and observe them for signs and symptoms of gabapentin misuse or abuse
332 (e.g., development of tolerance, self dose escalation, and drug-seeking behavior).

333 **9.3 Dependence**

334 There are rare postmarketing reports of individuals experiencing withdrawal symptoms
335 shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses
336 for which the drug is not approved. Such symptoms included agitation, disorientation, and
337 confusion after suddenly discontinuing gabapentin that resolved after restarting gabapentin. Most
338 of these individuals had a history of poly-substance abuse or used gabapentin to relieve
339 symptoms of withdrawal from other substances. The dependence and abuse potential of
340 gabapentin has not been evaluated in human studies.

341 **10 OVERDOSAGE**

342 **10.1 Human Overdose Experience**

343 There have been no reports describing individuals who have taken an overdose of
344 HORIZANT. The highest single dose of gabapentin enacarbil administered to date is 6,000 mg in
345 healthy subjects. At this supratherapeutic dose there were no serious adverse events. The
346 incidence of central nervous system adverse reactions, particularly dizziness and
347 somnolence/sedation, is increased with doses greater than 600 mg daily.

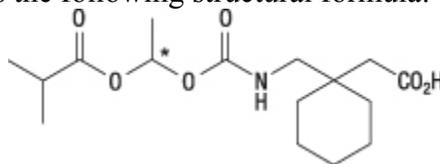
348 **10.2 Overdosage Management**

349 In the event of an overdose, the patient should be treated supportively with appropriate
350 monitoring as necessary. Gabapentin derived from gabapentin enacarbil can be removed from
351 plasma by hemodialysis. The mean percentage of gabapentin recovered following hemodialysis
352 in patients with end-stage renal disease was 29% (expressed as a proportion of the gabapentin
353 released from HORIZANT).

354 Further management should be as clinically indicated or as recommended by a poison
355 control center.

356 **11 DESCRIPTION**

357 HORIZANT (gabapentin enacarbil) is a prodrug of gabapentin. Gabapentin enacarbil is
 358 described as (1-{{(1*RS*)-1-[(2-Methylpropanoyl)oxy]ethoxy}carbonyl)amino]methyl}
 359 cyclohexyl) acetic acid. It has a molecular formula of C₁₆H₂₇NO₆ and a molecular weight of
 360 329.39. It is a racemate and has the following structural formula:



361
 362 Gabapentin enacarbil is a white to off-white crystalline solid with a melting onset of
 363 approximately 64°C and a solubility of 0.5 mg/mL in water and 10.2 mg/mL in phosphate buffer
 364 (pH 6.3).

365 HORIZANT is administered orally. Each HORIZANT Extended-Release Tablet contains
 366 300 mg or 600 mg of gabapentin enacarbil and the following inactive ingredients: colloidal
 367 silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium stearate,
 368 sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric oxide.

369 **12 CLINICAL PHARMACOLOGY**

370 **12.1 Mechanism of Action**

371 Gabapentin enacarbil is a prodrug of gabapentin and, accordingly, its therapeutic effects
 372 in RLS and PHN are attributable to gabapentin.

373 The precise mechanism by which gabapentin is efficacious in RLS and PHN is unknown.

374 The mechanism of action by which gabapentin is efficacious in PHN is unknown but in
 375 animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to
 376 a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli).
 377 Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and
 378 mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection
 379 model). Gabapentin also decreases pain-related responses after peripheral inflammation
 380 (carrageenan footpad test, late phase of formalin test), but does not alter immediate pain-related
 381 behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to
 382 human pain is not known.

383 Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid
 384 (GABA) but has no effect on GABA binding, uptake, or degradation. Gabapentin enacarbil and
 385 gabapentin have been tested in radioligand binding assays, and neither exhibited affinity for a
 386 number of other common receptor, ion channel, or transporter proteins.

387 *In vitro* studies have shown that gabapentin binds with high affinity to the $\alpha 2\delta$ subunit of
 388 voltage-activated calcium channels; however, the relationship of this binding to the therapeutic
 389 effects of gabapentin enacarbil in RLS and PHN is unknown.

390 **12.3 Pharmacokinetics**

391 HORIZANT is an extended-release formulation of gabapentin enacarbil, a prodrug of
 392 gabapentin. HORIZANT provides approximately dose-proportional and extended exposure to

393 gabapentin over the range 300 to 6,000 mg. HORIZANT and gabapentin are not interchangeable
394 because the same daily dose of each results in different plasma concentrations of gabapentin.

395 For subjects with PHN taking HORIZANT 600 mg twice daily, the estimated steady state
396 mean C_{\max} was 5.35 $\mu\text{g/mL}$, mean AUC_{24} was approximately 109 $\mu\text{g}\cdot\text{hr/mL}$, mean C_{\min} was
397 3.63 $\mu\text{g/mL}$, and mean peak trough ratio was 1.5.

398 **Absorption:** The pathway for absorption of gabapentin enacarbil is believed to include
399 active transport via a proton-linked monocarboxylate transporter, MCT-1. This transporter is
400 expressed at high levels in the intestinal tract and is not saturated by administration of high doses
401 of HORIZANT. Mean bioavailability of gabapentin (based on urinary recovery of gabapentin)
402 for HORIZANT in the fed state is about 75%. Bioavailability under fasting conditions has been
403 estimated by gabapentin urinary recovery to be 42% to 65%. In a food effect study, the exposure
404 of gabapentin increased by 24%, 34%, and 44% with low, moderate, and high fat meals,
405 respectively. The T_{\max} of gabapentin after administration of 600 mg of HORIZANT was
406 5.0 hours in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with
407 daily administration.

408 **Distribution:** Plasma protein binding of gabapentin has been reported to be <3%. The
409 apparent volume of distribution of gabapentin in subjects receiving HORIZANT is 76 L.

410 **Metabolism:** After oral administration, gabapentin enacarbil undergoes extensive
411 first-pass hydrolysis by non-specific carboxylesterases primarily in enterocytes and to a lesser
412 extent in the liver, to form gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid. Levels
413 of gabapentin enacarbil in blood are low and transient ($\leq 2\%$ of corresponding gabapentin plasma
414 levels). Released gabapentin is not appreciably metabolized in humans. Neither gabapentin
415 enacarbil nor gabapentin are substrates, inhibitors, or inducers of the major cytochrome P450
416 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1,
417 and CYP3A4). Gabapentin enacarbil is neither a substrate nor an inhibitor of P-glycoprotein *in*
418 *vitro*.

419 **Elimination:** Following hydrolysis of gabapentin enacarbil, the released gabapentin is
420 excreted unchanged by the kidney. Gabapentin renal excretion is believed to involve a
421 component of active secretion via an organic cation transporter (OCT2) present in the kidney. In
422 a human pharmacokinetic study with immediate release ^{14}C gabapentin enacarbil, mean recovery
423 of total radioactivity in urine was 94%, with 5% of the radioactive dose recovered in feces.

424 Apparent oral clearance (CL/F) of gabapentin from plasma after dosing of HORIZANT
425 with food ranged from 6.0 to 9.3 L/hr. Following oral dosing of HORIZANT, plasma clearance
426 of gabapentin is approximately proportional to creatinine clearance. Renal clearance (CL_r) of
427 gabapentin ranged from 5 to 7 L/hr, regardless of food intake or food type. The elimination
428 half-life ($t_{1/2}$) of gabapentin ranges from 5.1 to 6.0 hours and is unaltered by dose or following
429 multiple doses of HORIZANT.

430 **Special Populations: Race:** In the population pharmacokinetic study, the majority
431 (94%) of subjects in the clinical studies was Caucasian, and no single other race was greater than
432 4%; therefore, the effect of race could not be studied.

433 **Gender:** There are no clinically meaningful differences in pharmacokinetics of
434 HORIZANT between male and female patients.

435 **Geriatric Patients:** There are no clinically significant differences in pharmacokinetics
436 of HORIZANT between geriatric patients (≥ 65 years of age) and younger patients (18 to
437 < 65 years of age). However, the pharmacokinetics in geriatric patients may be affected by an
438 age-related decline in renal function [*see Use in Specific Populations (8.5)*].

439 **Renal Impairment:** Gabapentin clearance after dosing with HORIZANT is
440 approximately proportional to CrCl. Apparent oral clearance (CL/F) decreased in moderate
441 (4.2 L/hr) and severe renal impairment patients (1.7 L/hr) compared with 6.0 to 9.3 L/hr in
442 patients without renal impairment. Similarly, CL_r was decreased to 3 and 1 L/hr in moderate and
443 severe renal impairment patients, respectively, compared with 5 to 7 L/hr in non-renal
444 impairment patients. Dosage reduction in patients with renal dysfunction not on dialysis is
445 necessary.

446 Gabapentin is effectively removed from plasma by hemodialysis. The mean percentage of
447 gabapentin recovered following hemodialysis in patients with end-stage renal disease was 29%
448 (expressed as a proportion of the gabapentin released from HORIZANT). For patients with PHN
449 on hemodialysis, dosage reduction is required [*see Dosage and Administration (2.3)*]. For
450 patients with RLS on hemodialysis, treatment with HORIZANT is not recommended [*see*
451 *Dosage and Administration (2.3)*].

452 **Drug Interactions:** Neither gabapentin enacarbil nor gabapentin are substrates,
453 inhibitors, or inducers of the major cytochrome P450 enzymes. Gabapentin enacarbil is neither a
454 substrate or an inhibitor of P-glycoprotein *in vitro*.

455 Pharmacokinetic drug-drug interaction studies were conducted to examine the potential
456 for an interaction of gabapentin enacarbil with cimetidine and naproxen. No significant
457 pharmacokinetic interactions were observed. No clinically relevant pharmacokinetic interactions
458 are expected between HORIZANT and other substrates of organic cation transporter type 2
459 (OCT2) and monocarboxylate transporter type 1 (MCT-1).

460 **Ethanol:** An *in vitro* dissolution study was conducted to evaluate the impact of ethanol
461 (5, 10, 20, and 40%), on the extended-release characteristics of HORIZANT. The *in vitro* study
462 showed that about 63% of the total gabapentin enacarbil dose was released at 1 hour at the
463 highest alcohol level (40%), and about 43% of total drug was released at 1 hour with 5% alcohol.
464 Ethanol causes a more rapid release of gabapentin enacarbil from the extended-release tablets
465 that may increase the risk for adverse events associated with HORIZANT. Consumption of
466 alcohol is not recommended when taking HORIZANT.

467 **Cimetidine:** Gabapentin released from HORIZANT is eliminated by renal clearance
468 via OCT2. Cimetidine is a known substrate for this same elimination pathway. Coadministration
469 of 1,200 mg of HORIZANT once daily with cimetidine 400 mg 4 times daily showed no effect
470 on cimetidine exposure. There was an increase in AUC of gabapentin (24%) and a decrease in
471 renal clearance of gabapentin (20%); these effects are not expected to be clinically relevant. No

472 clinically relevant pharmacokinetic interactions are expected between HORIZANT and other
473 substrates of OCT2.

474 *Naproxen*: The pathway for absorption of gabapentin enacarbil includes active
475 transport via a proton-linked MCT-1. Coadministration of 1,200 mg of HORIZANT once daily
476 with naproxen 500 mg twice daily, a known substrate of MCT-1, showed no effect on naproxen
477 exposure or steady-state gabapentin C_{max} and AUC. No clinically relevant pharmacokinetic
478 interactions are expected between HORIZANT and other substrates of MCT-1.

479 **13 NONCLINICAL TOXICOLOGY**

480 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

481 Carcinogenesis: Oral (gavage) carcinogenicity studies were conducted in mice and rats.
482 In mice, gabapentin enacarbil was tested at doses of 500, 2,000, or 5,000 mg/kg/day for up to
483 104 weeks. There was no evidence of drug-related carcinogenicity. The highest dose tested is
484 16 times the MRHD of 1,200 mg/day, on a plasma AUC basis.

485 In rats, gabapentin enacarbil was tested at doses of 500, 2,000, or 5,000 mg/kg/day for up
486 to 97 weeks in mid-dose males, 90 weeks in high-dose males, and 104 weeks in females. The
487 plasma exposures (AUC) for gabapentin at these doses are approximately 4, 17, and 37 times,
488 respectively, that in humans at the MRHD. Increases in the incidence of pancreatic acinar
489 adenoma and carcinoma were found in mid-dose males and high-dose males and females.

490 In 2-year dietary carcinogenicity studies of gabapentin, no evidence of drug-related
491 carcinogenicity was observed in mice treated at doses up to 2,000 mg/kg/day. In rats, increases in
492 the incidence of pancreatic acinar cell adenoma and carcinoma were found in male rats receiving
493 the highest dose (2,000 mg/kg), but not at doses of 250 or 1,000 mg/kg/day. At 1,000 mg/kg/day,
494 the plasma AUC for gabapentin is estimated to be approximately 13 times that in humans at the
495 MRHD.

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

501 Mutagenesis: Gabapentin enacarbil was negative in *in vitro* bacterial reverse mutation
502 (Ames) and *in vivo* rat micronucleus assays. In an *in vitro* human lymphocyte assay, there was an
503 increase in the number of chromosomal aberrations with gabapentin enacarbil. This *in vitro*
504 response was attributed to acetaldehyde released by hydrolysis of gabapentin enacarbil during
505 the incubation period. Acetaldehyde is known to cause chromosome aberrations *in vitro*, but is
506 readily metabolized *in vivo*. The small quantity of acetaldehyde formed from gabapentin
507 enacarbil *in vivo* is rapidly cleared by normal metabolic activity.

508 Impairment of Fertility: Oral administration of gabapentin enacarbil (doses of 0, 200,
509 1,000, or 5,000 mg/kg/day) to male and female rats prior to and throughout mating and

510 continuing in females up to day 7 of gestation resulted in no adverse effects on fertility. The
511 highest dose tested is approximately 39 times the MRHD on an AUC basis.

512 **14 CLINICAL STUDIES**

513 **14.1 Restless Legs Syndrome (RLS) 12-Week Pivotal Studies**

514 The effectiveness of HORIZANT in the treatment of moderate-to-severe primary RLS
515 was demonstrated in two 12-week clinical studies in adults diagnosed with RLS using the
516 International Restless Legs Syndrome Study Group diagnostic criteria. Key diagnostic criteria
517 for RLS are: an urge to move the legs usually accompanied or caused by uncomfortable and
518 unpleasant leg sensations, symptoms begin or worsen during periods of rest or inactivity such as
519 lying or sitting, symptoms are partially or totally relieved by movement such as walking or
520 stretching at least as long as the activity continues, and symptoms are worse or occur only in the
521 evening or night. Patients were required to have a total score of ≥ 15 on the International Restless
522 Legs Syndrome (IRLS) Rating Scale at baseline. Patients with RLS secondary to other
523 conditions (e.g., pregnancy, renal failure, iron deficiency anemia) were excluded. In study 1,
524 patients were randomized to receive 1,200 mg of HORIZANT (N = 112) or placebo (N = 108)
525 taken once daily at about 5 PM with food. In study 2, patients were randomized to receive
526 600 mg of HORIZANT (N = 114), 1,200 mg of HORIZANT (N = 111), or placebo (N = 96)
527 taken once daily at about 5 PM with food.

528 Efficacy was evaluated using the IRLS Rating Scale and Clinical Global Impression of
529 Improvement (CGI-I) scores. The IRLS Rating Scale contains 10 items designed to assess the
530 severity of sensory and motor symptoms, sleep disturbance, daytime somnolence/sedation, and
531 impact on activities of daily living and mood associated with RLS. The range of scores is 0 to 40,
532 with 0 being absence of RLS symptoms and 40 the most severe symptoms. The CGI-I Scale
533 allows the investigator to rate the patient's overall change in RLS symptoms since baseline,
534 whether or not in the opinion of the investigator the change is related to study drug treatment.
535 The change from baseline in the IRLS Rating Scale at Week 12 and the proportion of responders
536 on the CGI-I Scale defined as a rating of "much improved" or "very much improved" at
537 Week 12 were co-primary outcomes in these studies.

538 In these 2 studies, the mean age of patients studied was 50 years (range: 18 to 81 years);
539 59% of the patients were female. The racial distribution for these studies was as follows:
540 Caucasian, 95%; black, 2%; and other, 3%.

541 Statistically significant differences ($P < 0.05$) between the treatment groups receiving 600
542 and 1,200 mg of HORIZANT and the group receiving placebo were observed at Week 12 for
543 both the mean change from baseline in the IRLS Scale total score and the proportion of
544 responders ("much improved" or "very much improved") on the CGI-I Scale as described in
545 Table 6.

546

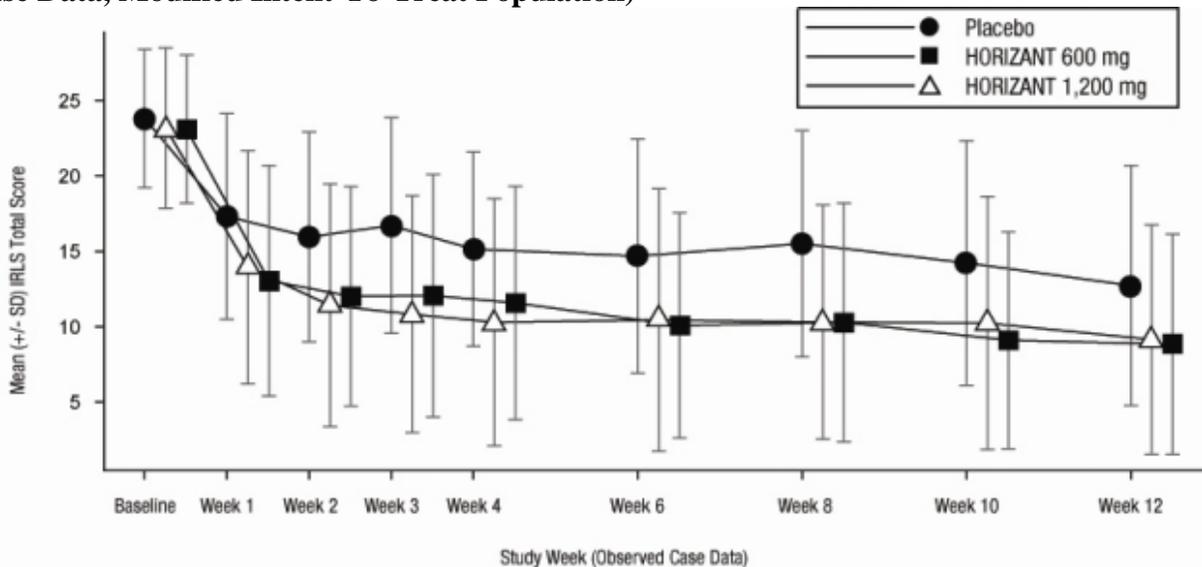
547 **Table 6. Mean Change in IRLS Scale Total Score and Proportion of Responders on CGI-I**
 548 **Scale at Week 12**

Week 12	Study 1		Study 2		
	HORIZANT 1,200 mg (N = 112)	Placebo (N = 108)	HORIZANT 600 mg (N = 114)	HORIZANT 1,200 mg (N = 111)	Placebo (N = 96)
Mean Change in IRLS Score	-13.2	-8.8	-13.8	-13.0	-9.8
Proportion of Responders ^a on CGI-I	76%	39%	73%	77%	45%

549 ^a CGI-I Responders = “much improved” and “very much improved.”

550
 551 Figure 1 presents the improvement in mean IRLS Rating Scale total score in patients
 552 treated with placebo or 600 or 1,200 mg of HORIZANT over the 12 weeks of treatment in
 553 study 2.

554
 555 **Figure 1. Study 2, Mean (±SD) IRLS Rating Scale Total Score Over 12 Weeks (Observed**
 556 **Case Data, Modified Intent-To-Treat Population)**



Treatment Group	n	n	n	n	n	n	n	n	n
Placebo	96	88	91	87	84	83	81	74	74
HORIZANT 600 mg	114	110	110	105	104	102	102	103	101
HORIZANT 1,200 mg	111	104	102	103	101	97	95	97	93

557
 558
 559 **14.2 Postherpetic Neuralgia (PHN) 12-Week Study**

560 The efficacy of HORIZANT for the management of postherpetic neuralgia was
 561 established in a multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-
 562 week study evaluating the efficacy, safety, and dose response of 3 maintenance doses of
 563 HORIZANT (1,200, 2,400, and 3,600 mg/day, with 107, 82, and 87 patients in each dosing
 564 group, respectively). Patients greater than 18 years of age with a documented medical diagnosis

565 of PHN of at least three months duration were enrolled. To ensure that patients had significant
 566 pain, randomized patients were required to have a minimum baseline 24-hour average Pain
 567 Intensity Numerical Rating Scale (PI-NRS) intensity score of at least 4.0 on the 11-point
 568 numerical PI-NRS, ranging from 0 (“no pain”) to 10 (“pain as bad as you can imagine”).

569 In this study, a total of 276 patients received HORIZANT while 95 patients received
 570 placebo. Following a 1-week baseline period during which patients were screened for eligibility,
 571 patients began a 1-week up-titration period followed by a 12-week maintenance treatment
 572 period, and then a 1-week down-titration period.

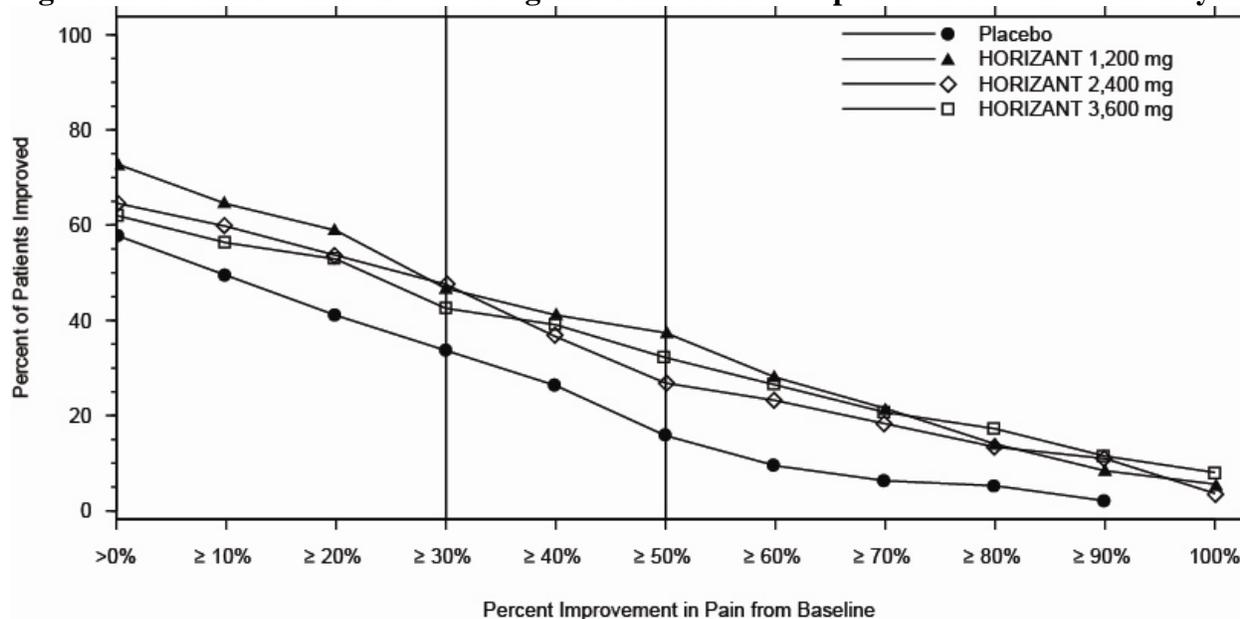
573 Treatment with HORIZANT statistically significantly improved the mean pain score and
 574 increased the proportion of patients with at least a 50% reduction in pain score from baseline at
 575 all doses tested. A benefit over placebo was observed for all 3 doses of HORIZANT as early as
 576 Week 1 and maintained to the end of treatment. Additional benefit of using doses of greater than
 577 1,200 mg a day was not demonstrated.

578 For various degrees of improvement in pain from baseline to end of maintenance
 579 treatment, Figure 2 shows the fraction of patients achieving that degree of improvement. The
 580 figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also
 581 included at every level of improvement below 50%. Patients who did not complete the study
 582 were assigned 0% improvement.

583

584

Figure 2. Percent of Patients Achieving Various Levels of Improvement in Pain Intensity



585

586

587 **16 HOW SUPPLIED/STORAGE AND HANDLING**

588 HORIZANT Extended-Release Tablets containing 300 mg of gabapentin enacarbil are
 589 red, with occasional black/grey spots, oval-shaped tablets debossed with “GS TF7”.

590 HORIZANT Extended-Release Tablets containing 600 mg of gabapentin enacarbil are
591 white to off-white, with occasional black/grey spots, oval-shaped tablets debossed with
592 “GS LFG”. They are supplied as follows:
593 300 mg: NDC 0173-0832-13: Bottles of 30
594 600 mg: NDC 0173-0806-01: Bottles of 30
595 Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F) [see USP
596 Controlled Room Temperature]. Protect from moisture. Do not remove desiccants.

597 **17 PATIENT COUNSELING INFORMATION**

598 *See FDA-approved patient labeling (Medication Guide).*

599 Physicians should instruct their patients to read the Medication Guide before starting
600 therapy with HORIZANT and to reread it upon prescription renewal for new information
601 regarding the use of HORIZANT.

602 **17.1 Effects on Driving**

603 Patients should be told that HORIZANT can cause significant driving impairment.
604 Accordingly, they should be advised not to drive a car until they have gained sufficient
605 experience on HORIZANT to assess whether HORIZANT impairs their ability to drive. Patients
606 should be told that it is not known how long this effect lasts.

607 **17.2 Somnolence/Sedation and Dizziness**

608 Patients should be told that HORIZANT can cause significant somnolence and dizziness.
609 This typically resolves within several weeks of initiating treatment. Accordingly, they should be
610 told not to operate dangerous machinery until they have gained sufficient experience on
611 HORIZANT to assess whether HORIZANT impairs their ability to operate dangerous machinery
612 safely.

613 **17.3 Suicidal Behavior and Ideation**

614 Patients, their caregivers, and families should be counseled that HORIZANT may
615 increase the risk of suicidal thoughts and behavior, and should be advised of the need to be alert
616 for the emergence or worsening of symptoms of depression, any unusual changes in mood or
617 behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm.
618 Behaviors of concern should be reported immediately to healthcare providers.

619 **17.4 Drug Reaction With Eosinophilia and Systemic Symptoms** 620 **(DRESS)/Multiorgan Hypersensitivity**

621 Patients should be instructed that multiorgan hypersensitivity reactions may occur with
622 HORIZANT. Patients should contact their physician immediately if they experience any signs or
623 symptoms of these conditions [see Warnings and Precautions (5.5)].

624 **17.5 Lack of Interchangeability With Gabapentin**

625 Patients should be advised that doses of HORIZANT and other gabapentin products are
626 not interchangeable.

627 **17.6 Dosing Instructions**

- 628 • Instruct patients to take HORIZANT only as prescribed.

- 629 • Instruct patients to swallow tablets whole and do not cut, crush, or chew tablets.
630 • Instruct patients to take HORIZANT with food.
631 • For Restless Legs Syndrome, 600 mg HORIZANT should be taken once daily at about 5 PM.
632 If the dose is not taken at the recommended time, the patient should take the next dose at
633 about 5 PM the following day.
634 • For Postherpetic Neuralgia, the starting dose is 600 mg HORIZANT in the morning for
635 3 days. Starting on day 4, 600 mg HORIZANT should be taken twice daily. If the dose is not
636 taken at the recommended time, the next dose should be taken at the time of next scheduled
637 dose.
638 • Instruct patients about how to discontinue HORIZANT.

639 **17.7 Alcohol**

- 640 • Advise patients to avoid alcohol when taking HORIZANT [*see Drug Interactions (7);*
641 *Clinical Pharmacology (12.3)*].
642

643 HORIZANT is a registered trademark of GlaxoSmithKline.
644

645 Manufactured by:

646 Patheon Inc.

647 Research Triangle Park, NC 27709
648

for:



GlaxoSmithKline
Research Triangle Park, NC 27709

Licensed from:



XenoPort, Inc.
Santa Clara, CA 95051

649
650 ©2012, GlaxoSmithKline. All rights reserved.
651
652 HZT:XPI

653 **PHARMACIST—DETACH HERE AND GIVE TO PATIENT**

654

655

MEDICATION GUIDE

656

HORIZANT® (*ho-ri' zant*)

657

(gabapentin enacarbil)

658

Extended-Release Tablets

659

660 Read this Medication Guide before you start taking HORIZANT and each time you
661 get a refill. There may be new information. This information does not take the place
662 of talking to your healthcare provider about your medical condition or treatment.

663

664 **What is the most important information I should know about HORIZANT?**

665

HORIZANT can cause serious side effects:

666

1. Do not drive after taking your dose of HORIZANT until you know how HORIZANT affects you, including the morning after you take your dose.

667

668 **Do not** operate heavy machinery or do other dangerous activities until you
669 know how HORIZANT affects you. HORIZANT can cause sleepiness, dizziness,
670 slow thinking, and can affect your coordination. Ask your healthcare provider
671 when it would be okay to do these activities.

672

2. HORIZANT may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

673

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

675

676

- thoughts about suicide or dying

677

- attempt to commit suicide

678

- new or worse depression

679

- new or worse anxiety

680

- feeling agitated

681

- new or worse restlessness

682

- panic attacks

683

- new or worse trouble sleeping (insomnia)

684

- new or worse irritability

685

- acting aggressive, being angry, or violent

686

- acting on dangerous impulses

687

- an extreme increase in activity and talking (mania)

688

- other unusual changes in behavior or mood

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

- 690 • Pay attention to any changes, especially sudden changes, in mood,
691 behaviors, thoughts, or feelings.
692 • Keep all follow-up visits with your healthcare provider as scheduled.
693 • Call your healthcare provider between visits as needed, especially if you are
694 worried about symptoms.

695 **Do not stop HORIZANT without first talking to a healthcare provider.**

696 Suicidal thoughts or actions can be caused by things other than medicines. If
697 you have suicidal thoughts or actions, your healthcare provider may check for
698 other causes.

699 **3. HORIZANT may cause a serious or life-threatening allergic reaction** that
700 may affect your skin or other parts of your body such as your liver or blood
701 cells. You may or may not have rash with these types of reactions. Call a
702 healthcare provider right away if you have any of the following symptoms:

- 703 • skin rash
704 • hives
705 • fever
706 • swollen glands that do not go away
707 • swelling of your lips or tongue
708 • yellowing of your skin or eyes
709 • unusual bruising or bleeding
710 • severe fatigue or weakness
711 • unexpected, severe muscle pain
712 • frequent infections

713
714 These symptoms may be the first signs of a serious reaction. A healthcare provider
715 should examine you to decide if you should continue taking HORIZANT.

716
717 **What is HORIZANT?**

718 HORIZANT is a prescription medicine used to treat adults with:

- 719 • moderate-to-severe primary Restless Legs Syndrome (RLS).
720 • pain from damaged nerves (postherpetic pain) that follows healing of shingles (a
721 painful rash that comes after a herpes zoster infection).

722 HORIZANT is not for people with RLS who need to sleep during the daytime and
723 need to stay awake at night.

724 HORIZANT is not the same medicine as gabapentin (for example, NEURONTIN® or
725 GRALISE®) and should not be used in its place.

726 It is not known if HORIZANT is safe and effective in children.

727

728 **What should I tell my healthcare provider before taking HORIZANT?**

729 Before taking HORIZANT, tell your healthcare provider if you:

- 730 • have or have had kidney problems or are on hemodialysis.
- 731 • have or have had depression, mood problems, or suicidal thoughts or behavior.
- 732 • have or have had seizures.
- 733 • have a history of drug abuse.
- 734 • have any other medical conditions.
- 735 • are pregnant or plan to become pregnant. It is not known if HORIZANT will harm
- 736 your unborn baby. Talk to your healthcare provider if you are pregnant or plan
- 737 to become pregnant while taking HORIZANT. You and your healthcare provider
- 738 will decide if you should take HORIZANT while you are pregnant.
- 739 • are breastfeeding or plan to breastfeed. Your body turns HORIZANT into another
- 740 drug (gabapentin) that passes into your milk. It is not known if this can harm
- 741 your baby. You and your healthcare provider should decide if you will take
- 742 HORIZANT or breastfeed.
- 743 • drink alcohol.

744

745 **Tell your healthcare provider about all the medicines you take**, including
746 prescription and non-prescription medicines, vitamins, and herbal supplements.

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

749

750 **How should I take HORIZANT?**

- 751 • Take HORIZANT exactly as your healthcare provider tells you to take it. Your
- 752 healthcare provider will tell you how much HORIZANT to take and when to take
- 753 it.
- 754 • Take HORIZANT tablets whole. **Do not** cut, crush, or chew your tablet.
- 755 • Take HORIZANT tablets with food.
- 756 • **Do not stop taking HORIZANT without talking to your healthcare**
- 757 **provider first.** If you stop taking HORIZANT suddenly, you may develop side
- 758 effects.
- 759 • If you forget to take your medicine at the time recommended by your healthcare
- 760 provider, just skip the missed dose. Take the next dose at your regular time. **Do**
- 761 **not** take 2 doses at one time.
- 762 • If you take too much HORIZANT, call your healthcare provider or go to the
- 763 nearest hospital emergency room right away.

764

765 **What should I avoid while taking HORIZANT?**

- 766 • Do not take other medicines that make you sleepy or dizzy while taking
767 HORIZANT without first talking with your healthcare provider. Taking HORIZANT
768 with medicines that cause sleepiness or dizziness may make your sleepiness or
769 dizziness worse.
- 770 • Do not take other gabapentin drugs (for example, NEURONTIN or GRALISE)
771 while you take HORIZANT.
- 772 • Do not consume alcohol when taking HORIZANT.

773

774 **What are the possible side effects of HORIZANT?**

- 775 • See **“What is the most important information I should know about**
776 **HORIZANT?”**

777 The most common side effects of HORIZANT include:

- 778 • sleepiness
779 • dizziness
780 • headache

781 Tell your healthcare provider if you have any side effect that bothers you or that
782 does not go away.

783 These are not all the possible side effects of HORIZANT. For more information, ask
784 your healthcare provider or pharmacist.

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

787

788 **How should I store HORIZANT?**

- 789 • Store HORIZANT between 59° and 86°F (15° and 30°C).
790 • Keep HORIZANT dry and away from moisture.
791 • Keep HORIZANT tightly closed in the bottle provided to you. Do not remove any
792 moisture control packs that may come in the bottle.

793 **Keep HORIZANT and all medicines out of the reach of children.**

794

795 **General Information about the safe and effective use of HORIZANT**

796 Medicines are sometimes prescribed for purposes other than those listed in a
797 Medication Guide. Do not use HORIZANT for a condition for which it was not
798 prescribed. Do not give HORIZANT to other people, even if they have the same
799 symptoms that you have. It may harm them.

800 This Medication Guide summarizes the most important information about
801 HORIZANT. If you would like more information, talk with your healthcare provider.

802 You can ask your healthcare provider or pharmacist for information about
803 HORIZANT that was written for healthcare professionals.

804 For more information about HORIZANT, go to www.gsk.com or call 1-888-825-
805 5249.

806

807 **What are the ingredients in HORIZANT?**

808 **Active ingredients:** gabapentin enacarbil

809 **Inactive ingredients:** Both the 300 mg and 600 mg tablets contain colloidal
810 silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium
811 stearate, sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric
812 oxide.

813

814 **This Medication Guide has been approved by the U.S. Food and Drug
815 Administration.**

816

817 Manufactured by:

818 Patheon Inc.

819 Research Triangle Park, NC 27709

820

for:



GlaxoSmithKline

Research Triangle Park, NC 27709

Licensed from:



XenoPort, Inc.

Santa Clara, CA 95051

821

822 Revised: 12/2012

823

824 HORIZANT is a registered trademark of GlaxoSmithKline. The other brands listed
825 are trademarks of their respective owners and are not trademarks of
826 GlaxoSmithKline. The makers of these brands are not affiliated with and do not
827 endorse GlaxoSmithKline or its products.

828

829 ©2012, GlaxoSmithKline. All rights reserved.

830

831 HZT: XMG