

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.

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

Initial U.S. Approval: 2011

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, Effects on Driving (5.1)	03/2013

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)

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)

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

DOSAGE FORMS AND STRENGTHS

Extended-Release Tablets: 300 mg and 600 mg. (3)

CONTRAINDICATIONS

None. (4)

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)

ADVERSE REACTIONS

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

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: 03/2013

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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 may cause significant driving impairment [*see Clinical Studies (14.3)*]. The
56 duration of driving impairment after starting therapy with HORIZANT is unknown. Patients
57 taking HORIZANT should not drive until they have gained sufficient experience to assess
58 whether HORIZANT impairs their ability to drive. However, prescribers and patients should be
59 aware that patients’ ability to assess their own driving competence, as well as their ability to
60 assess the degree of somnolence caused by HORIZANT, can be imperfect. Whether the
61 impairment is related to somnolence [*see Warnings and Precautions (5.2)*] or other effects of
62 HORIZANT is unknown.

63 **5.2 Somnolence/Sedation and Dizziness**

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

68 During the controlled trials in patients with RLS, somnolence/sedation was reported in
69 20% of patients treated with 600 mg of HORIZANT per day compared with 6% of patients
70 receiving placebo. In those patients treated with HORIZANT who reported somnolence, the
71 somnolence persisted during treatment in about 30%. In the remaining patients, symptoms
72 resolved within 3 to 4 weeks. Dizziness was reported in 13% of patients receiving 600 mg of
73 HORIZANT per day compared with 4% of patients receiving placebo. In those patients treated
74 with HORIZANT who reported dizziness, symptoms persisted during treatment in about 20%.
75 Somnolence/sedation led to withdrawal in 2% of patients receiving 600 mg of HORIZANT per
76 day. Dizziness led to withdrawal in 1% of patients receiving 600 mg of HORIZANT per day.
77 The incidence of these adverse reactions was greater in the patients receiving 1,200 mg per day.

78 During the 12-week, controlled study in patients with PHN, somnolence was reported in
79 10% of patients treated with 1,200 mg of HORIZANT per day compared with 8% of patients
80 receiving placebo. Fatigue/asthenia was reported in 6% of patients treated with 1,200 mg of
81 HORIZANT per day compared with 1% of patients receiving placebo. In those patients treated
82 with 1,200 mg of HORIZANT per day who reported somnolence (10%), the somnolence
83 persisted during treatment in about 27%. In the remaining patients, symptoms resolved within 4

84 to 5 weeks. Dizziness was reported in 17% of patients receiving 1,200 mg of HORIZANT per
85 day compared with 15% of patients receiving placebo. In those patients treated with 1,200 mg of
86 HORIZANT per day who reported dizziness, symptoms persisted during treatment in about 6%.
87 Somnolence led to withdrawal in <1% of patients receiving 1,200 mg of HORIZANT per day
88 compared with 2% of patients receiving placebo. Dizziness led to withdrawal in 2% of patients
89 receiving 1,200 mg of HORIZANT per day compared with 3% of patients receiving placebo.

90 **5.3 Lack of Interchangeability With Gabapentin**

91 HORIZANT is not interchangeable with other gabapentin products because of differing
92 pharmacokinetic profiles. The same dose of HORIZANT results in different plasma
93 concentrations of gabapentin relative to other gabapentin products. [*See Clinical Pharmacology*
94 *(12.3).*]

95 The safety and effectiveness of HORIZANT in patients with epilepsy have not been
96 studied.

97 **5.4 Suicidal Behavior and Ideation**

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

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

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

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

123

124 **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

125
126 The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy
127 than in clinical trials for psychiatric or other conditions, but the absolute risk differences were
128 similar for the epilepsy and psychiatric indications.

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

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

140 **5.5 Drug Reaction With Eosinophilia and Systemic Symptoms** 141 **(DRESS)/Multiorgan Hypersensitivity**

142 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as
143 multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including
144 gabapentin. HORIZANT is a prodrug of gabapentin. Some of these events have been fatal or
145 life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or
146 lymphadenopathy, in association with other organ system involvement, such as hepatitis,
147 nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute
148 viral infection. Eosinophilia is often present. Because this disorder is variable in its expression,
149 other organ systems not noted here may be involved.

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

154 **5.6 Discontinuation of HORIZANT**

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

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

162 **5.7 Tumorigenic Potential**

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

166 In clinical studies of gabapentin as adjunctive therapy in epilepsy comprising 2,085
167 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients
168 (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in*
169 *situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up
170 to 2 years following discontinuation of gabapentin. Without knowledge of the background
171 incidence and recurrence in a similar population not treated with gabapentin, it is impossible to
172 know whether the incidence reported in this cohort is or is not affected by treatment.

173 **6 ADVERSE REACTIONS**

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

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

177 **6.1 Clinical Trials Experience**

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

181 In all controlled and uncontrolled trials across various patient populations, more than
182 2,300 patients have received HORIZANT orally in daily doses ranging from 600 to 3,600 mg.

183 **Restless Legs Syndrome:** The exposure to HORIZANT in 1,201 patients with RLS
184 included 613 exposed for at least 6 months and 371 exposed for at least 1 year. HORIZANT in
185 the treatment of RLS was studied primarily in placebo-controlled trials (n = 642), and in long-
186 term follow-up studies. The population with RLS ranged from 18 to 82 years of age, with 60%
187 being female and 95% being Caucasian.

188 The safety of HORIZANT in doses ranging from 600 to 2,400 mg has been evaluated in
189 515 patients with RLS in 3 double-blind, placebo-controlled, 12-week clinical trials. The 600-mg
190 dose was studied in 2 of the 3 studies. Eleven out of 163 (7%) patients treated with 600 mg of
191 HORIZANT discontinued treatment due to adverse reactions compared with 10 of the 245 (4%)
192 patients who received placebo.

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

197

198 **Table 4. Incidence of Adverse Reactions in 12-Week RLS Studies Reported in $\geq 2\%$ of**
 199 **Patients Treated With 600 or 1,200 mg of HORIZANT and Numerically Greater Than**
 200 **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

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

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

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

207

208 Adverse reactions reported in these three 12-week studies in <2% of patients treated with
209 600 mg of HORIZANT and numerically greater than placebo were balance disorder, blurred
210 vision, disorientation, feeling drunk, lethargy, and vertigo.

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

213 Postherpetic Neuralgia: The exposure to HORIZANT in 417 patients with PHN
214 included 207 patients exposed for at least 3 months. Overall, the mean age of patients in the PHN
215 studies ranged from 61 to 64 years of age across dose groups; the majority of patients were male
216 (45% to 61%) and Caucasian (80% to 98%).

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

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

227

228 **Table 5. Incidence of Adverse Reactions (in At Least 2% of Patients Treated With**
 229 **1,200 mg/day of HORIZANT and Numerically Greater Than the Placebo Rate)**
 230 **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

231
 232 The following adverse reactions were also reported as $\geq 2\%$ at 2,400 mg/day and/or
 233 3,600 mg/day and appeared to be dose-related but were $< 2\%$ at 1,200 mg/day: balance disorder,
 234 confusional state, depression, dry mouth, flatulence, increased appetite, irritability, and vertigo.
 235 Dizziness, somnolence, fatigue, and insomnia appeared to show a dose relationship.

236 6.2 Adverse Events Associated With Gabapentin

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

240 7 DRUG INTERACTIONS

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

244 Morphine: HORIZANT taken in conjunction with morphine causes increased
 245 somnolence/sedation, dizziness, and nausea when compared with either drug alone [*see Clinical*
 246 *Pharmacology (12.3)*].

247

248 8 USE IN SPECIFIC POPULATIONS**249 8.1 Pregnancy**

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

255 When pregnant rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or
256 5,000 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased
257 at the 2 highest doses and fetal body weights were decreased at the high dose. The no-effect dose
258 for embryo-fetal developmental toxicity in rats (200 mg/kg/day) represents approximately
259 2 times the gabapentin exposure associated with the maximum recommended human dose
260 (MRHD) of 1,200 mg/day gabapentin enacarbil on an area under the curve (AUC) basis.

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

267 When female rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or
268 5,000 mg/kg/day) throughout the pregnancy and lactation periods, offspring growth and survival
269 were decreased at the two highest doses. The no-effect dose for pre- and post-natal
270 developmental toxicity in rats is approximately 2 times the MRHD on an AUC basis.

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

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

287 **8.2 Labor and Delivery**

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

289 **8.3 Nursing Mothers**

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

295 **8.4 Pediatric Use**

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

297 **8.5 Geriatric Use**

298 Of the 515 patients treated with HORIZANT in the 3 double-blind, placebo-controlled,
299 12-week clinical trials for RLS, 11% were 65 to 74 years of age and 1% were 75 years of age
300 and older. Clinical trials of HORIZANT for the treatment of RLS did not include a sufficient
301 number of patients 65 years and older to determine whether they respond differently from
302 younger individuals.

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

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

316 **8.6 Renal Impairment**

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

319 **9 DRUG ABUSE AND DEPENDENCE**

320 **9.1 Controlled Substance**

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

322 **9.2 Abuse**

323 Gabapentin does not exhibit affinity for benzodiazepine, opiate (μ , δ , or κ), or
324 cannabinoid 1 receptor sites. A small number of postmarketing cases report gabapentin misuse
325 and abuse. These individuals were taking higher than recommended doses of gabapentin for

326 unapproved uses. Most of the individuals described in these reports had a history of poly-
327 substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances.

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

331 **9.3 Dependence**

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

339 **10 OVERDOSAGE**

340 **10.1 Human Overdose Experience**

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

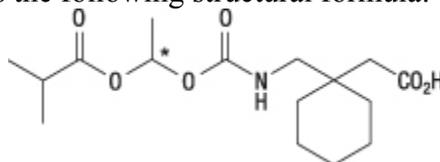
346 **10.2 Overdosage Management**

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

352 Further management should be as clinically indicated or as recommended by a poison
353 control center.

354 **11 DESCRIPTION**

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



359

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

363 HORIZANT is administered orally. Each HORIZANT Extended-Release Tablet contains
364 300 mg or 600 mg of gabapentin enacarbil and the following inactive ingredients: colloidal
365 silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium stearate,
366 sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric oxide.

367 **12 CLINICAL PHARMACOLOGY**

368 **12.1 Mechanism of Action**

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

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

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

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

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

388 **12.3 Pharmacokinetics**

389 HORIZANT is an extended-release formulation of gabapentin enacarbil, a prodrug of
390 gabapentin. HORIZANT provides approximately dose-proportional and extended exposure to
391 gabapentin over the range 300 to 6,000 mg. HORIZANT and gabapentin are not interchangeable
392 because the same daily dose of each results in different plasma concentrations of gabapentin.

393 For subjects with PHN taking HORIZANT 600 mg twice daily, the estimated steady state
394 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
395 3.63 $\mu\text{g/mL}$, and mean peak trough ratio was 1.5.

396 **Absorption:** The pathway for absorption of gabapentin enacarbil is believed to include
397 active transport via a proton-linked monocarboxylate transporter, MCT-1. This transporter is
398 expressed at high levels in the intestinal tract and is not saturated by administration of high doses

399 of HORIZANT. Mean bioavailability of gabapentin (based on urinary recovery of gabapentin)
400 for HORIZANT in the fed state is about 75%. Bioavailability under fasting conditions has been
401 estimated by gabapentin urinary recovery to be 42% to 65%. In a food effect study, the exposure
402 of gabapentin increased by 24%, 34%, and 44% with low, moderate, and high fat meals,
403 respectively. The T_{max} of gabapentin after administration of 600 mg of HORIZANT was
404 5.0 hours in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with
405 daily administration.

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

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

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

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

428 **Special Populations:** **Race:** In the population pharmacokinetic study, the majority
429 (94%) of subjects in the clinical studies was Caucasian, and no single other race was greater than
430 4%; therefore, the effect of race could not be studied.

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

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

437 **Renal Impairment:** Gabapentin clearance after dosing with HORIZANT is
438 approximately proportional to CrCl. Apparent oral clearance (CL/F) decreased in moderate

439 (4.2 L/hr) and severe renal impairment patients (1.7 L/hr) compared with 6.0 to 9.3 L/hr in
440 patients without renal impairment. Similarly, CL_r was decreased to 3 and 1 L/hr in moderate and
441 severe renal impairment patients, respectively, compared with 5 to 7 L/hr in non-renal
442 impairment patients. Dosage reduction in patients with renal dysfunction not on dialysis is
443 necessary.

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

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

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

458 ***Ethanol:*** An *in vitro* dissolution study was conducted to evaluate the impact of ethanol
459 (5, 10, 20, and 40%), on the extended-release characteristics of HORIZANT. The *in vitro* study
460 showed that about 63% of the total gabapentin enacarbil dose was released at 1 hour at the
461 highest alcohol level (40%), and about 43% of total drug was released at 1 hour with 5% alcohol.
462 Ethanol causes a more rapid release of gabapentin enacarbil from the extended-release tablets
463 that may increase the risk for adverse events associated with HORIZANT. Consumption of
464 alcohol is not recommended when taking HORIZANT.

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

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

477 ***Morphine:*** Administration of a single 600-mg dose of HORIZANT 2 hours after a
478 single 60-mg dose of extended-release morphine sulfate in 18 subjects was associated with

479 increased somnolence/sedation, dizziness, and nausea for the combination compared to Horizant
480 or morphine alone as measured by the visual analog scale. No changes in C_{max} and AUC of
481 gabapentin, morphine or its active metabolite morphine-6-glucuronide were observed.

482 **13 NONCLINICAL TOXICOLOGY**

483 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

484 Carcinogenesis: Oral (gavage) carcinogenicity studies were conducted in mice and rats.
485 In mice, gabapentin enacarbil was tested at doses of 500, 2,000, or 5,000 mg/kg/day for up to
486 104 weeks. There was no evidence of drug-related carcinogenicity. The highest dose tested is
487 16 times the MRHD of 1,200 mg/day, on a plasma AUC basis.

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

493 In 2-year dietary carcinogenicity studies of gabapentin, no evidence of drug-related
494 carcinogenicity was observed in mice treated at doses up to 2,000 mg/kg/day. In rats, increases in
495 the incidence of pancreatic acinar cell adenoma and carcinoma were found in male rats receiving
496 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,
497 the plasma AUC for gabapentin is estimated to be approximately 13 times that in humans at the
498 MRHD.

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

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

511 Impairment of Fertility: Oral administration of gabapentin enacarbil (doses of 0, 200,
512 1,000, or 5,000 mg/kg/day) to male and female rats prior to and throughout mating and
513 continuing in females up to day 7 of gestation resulted in no adverse effects on fertility. The
514 highest dose tested is approximately 39 times the MRHD on an AUC basis.

515 14 CLINICAL STUDIES**516 14.1 Restless Legs Syndrome (RLS) 12-Week Pivotal Studies**

517 The effectiveness of HORIZANT in the treatment of moderate-to-severe primary RLS
518 was demonstrated in two 12-week clinical studies in adults diagnosed with RLS using the
519 International Restless Legs Syndrome Study Group diagnostic criteria. Key diagnostic criteria
520 for RLS are: an urge to move the legs usually accompanied or caused by uncomfortable and
521 unpleasant leg sensations, symptoms begin or worsen during periods of rest or inactivity such as
522 lying or sitting, symptoms are partially or totally relieved by movement such as walking or
523 stretching at least as long as the activity continues, and symptoms are worse or occur only in the
524 evening or night. Patients were required to have a total score of ≥ 15 on the International Restless
525 Legs Syndrome (IRLS) Rating Scale at baseline. Patients with RLS secondary to other
526 conditions (e.g., pregnancy, renal failure, iron deficiency anemia) were excluded. In study 1,
527 patients were randomized to receive 1,200 mg of HORIZANT (N = 112) or placebo (N = 108)
528 taken once daily at about 5 PM with food. In study 2, patients were randomized to receive
529 600 mg of HORIZANT (N = 114), 1,200 mg of HORIZANT (N = 111), or placebo (N = 96)
530 taken once daily at about 5 PM with food.

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

541 In these 2 studies, the mean age of patients studied was 50 years (range: 18 to 81 years);
542 59% of the patients were female. The racial distribution for these studies was as follows:
543 Caucasian, 95%; black, 2%; and other, 3%.

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

549

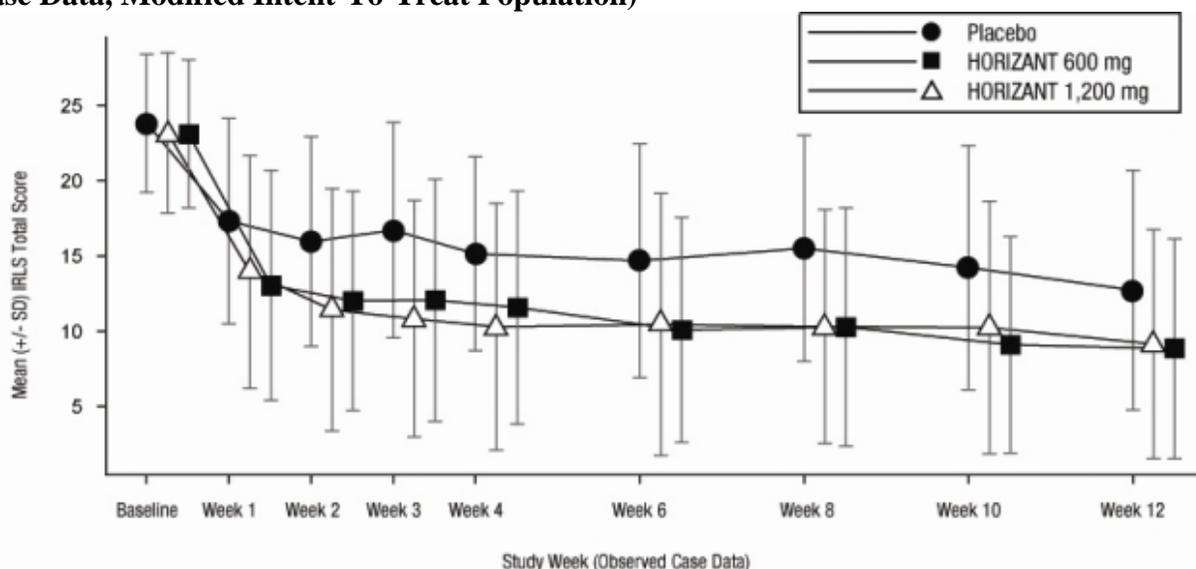
550 **Table 6. Mean Change in IRLS Scale Total Score and Proportion of Responders on CGI-I**
 551 **Scale at Week 12**

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%

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

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

557
 558 **Figure 1. Study 2, Mean (±SD) IRLS Rating Scale Total Score Over 12 Weeks (Observed**
 559 **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

560
 561

562 **14.2 Postherpetic Neuralgia (PHN) 12-Week Study**

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

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

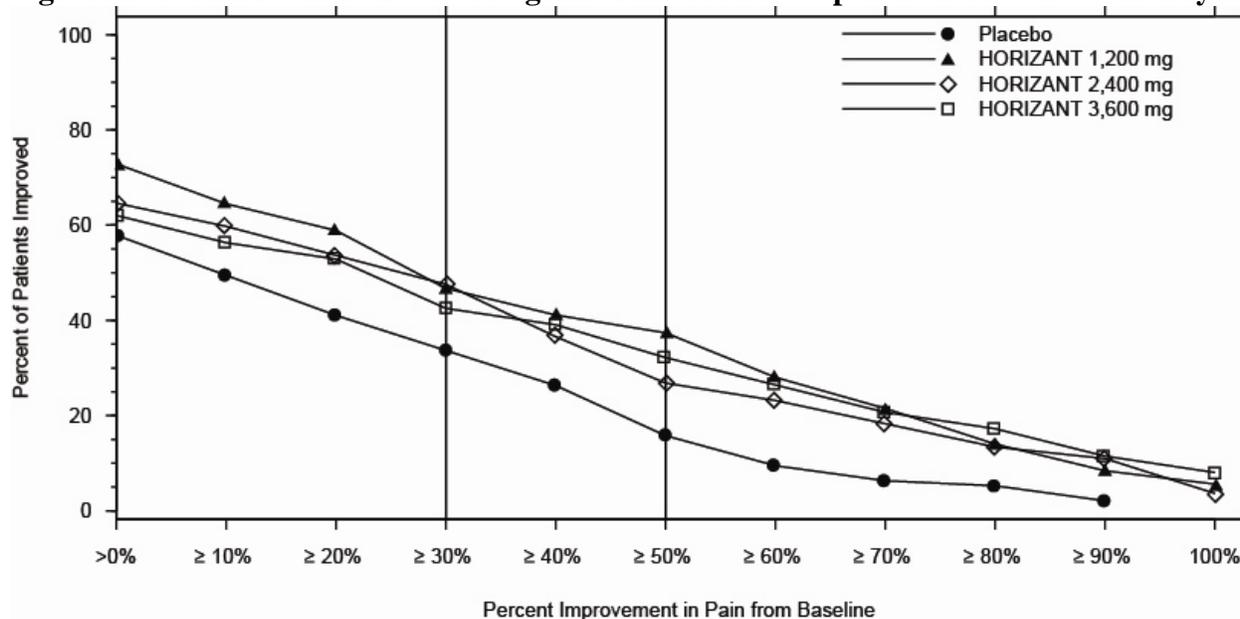
572 In this study, a total of 276 patients received HORIZANT while 95 patients received
 573 placebo. Following a 1-week baseline period during which patients were screened for eligibility,
 574 patients began a 1-week up-titration period followed by a 12-week maintenance treatment
 575 period, and then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

576 Treatment with HORIZANT statistically significantly improved the mean pain score and
 577 increased the proportion of patients with at least a 50% reduction in pain score from baseline at
 578 all doses tested. A benefit over placebo was observed for all 3 doses of HORIZANT as early as
 579 Week 1 and maintained to the end of treatment. Additional benefit of using doses of greater than
 580 1,200 mg a day was not demonstrated.

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

586
 587

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



588
 589

14.3 Effects on Driving

591 Driving performance was assessed in a three way crossover study in healthy volunteers
 592 (mean age 36 years). Subjects were dosed at approximately 5 pm with HORIZANT 600 mg (for
 593 five days), diphenhydramine 50 mg (1 dose), and placebo (for five days). After the last dose,

594 driving was evaluated on a computer-based simulation for 1 hour in the evening approximately 2
 595 to 4 hours after dosing (7 to 9 pm), in the morning after dosing (7 to 9 am), and at midday the
 596 day after dosing (11 am to 1pm). The primary endpoint of the study was lane position variability.
 597 There was no difference in change from baseline in lane position variability for HORIZANT
 598 compared to placebo at any of the simulated driving timepoints. Secondary measures included
 599 speed variability and the occurrence of simulated crashes. Subjects in this study experienced
 600 simulated crashes as described in Table 7. At the times that simulated crashes occurred, there
 601 was an increase in average speed variability in the HORIZANT and diphenhydramine treated
 602 groups that was most notable in patients who experienced simulated crashes, but no increases in
 603 lane position variability. Later time points post-dosing or the effects of driving after more than
 604 five days of dosing with HORIZANT were not evaluated.

605

606 **Table 7. Simulated Crashes at Evaluated Timepoints (Secondary Measure)**

Simulated Driving Timepoint and Hours Post Dose	Baseline N = 36 n (%)	Placebo N = 36 n (%)	HORIZANT 600 mg N = 35 n (%)	Diphenhydramine 50 mg N = 36 n (%)
Day 5 Evening (7 to 9pm) 2 to 4 hours post dose	0 (0)	0 (0)	0 (0)	3 (9)
Day 6 Morning (7 to 9am) 14 to 16 hours post dose	2 (6)	1 (3)	1 (3)	0 (0)
Day 6 Midday (11am to 1pm) 18 to 20 hours post dose	1 (3)	0 (0)	3 (9)	3 (8)

607

608 The results of a separate 2-week driving simulation study in patients (mean age 47 years)
 609 with moderate-to-severe primary RLS showed that once daily doses of 1,200 mg and 1,800 mg
 610 of HORIZANT significantly impaired simulated driving performance based on lane position
 611 variability. An increased number of simulated crashes were reported in patients tested near T_{max}
 612 after receiving 1,200 mg or 1,800 mg of HORIZANT compared to patients treated with
 613 diphenhydramine 50 mg. In addition patients receiving 1,200 mg of HORIZANT experienced an
 614 increased number of simulated crashes at 14 to 16 hours after dosing compared with placebo,
 615 diphenhydramine, and 1,800 mg of HORIZANT.

616 The design limitations of these two studies do not permit inference regarding dose
 617 response relationship or the duration of the effect HORIZANT has on driving in patients with
 618 RLS.

619 The results of a separate driving simulation study comparing untreated RLS patients and
 620 healthy subjects showed no difference in lane position variability but an increase in speed

621 variability associated with a greater number of simulated crashes in RLS patients relative to
622 healthy subjects, which may indicate impaired driving in RLS patients in the absence of
623 medication.

624 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

627 HORIZANT Extended-Release Tablets containing 600 mg of gabapentin enacarbil are
628 white to off-white, with occasional black/grey spots, oval-shaped tablets debossed with
629 “GS LFG”. They are supplied as follows:

630 300 mg: NDC 0173-0832-13: Bottles of 30

631 600 mg: NDC 0173-0806-01: Bottles of 30

632 Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F) [see USP
633 Controlled Room Temperature]. Protect from moisture. Do not remove desiccants.

634 **17 PATIENT COUNSELING INFORMATION**

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

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

639 **17.1 Effects on Driving**

640 Patients should be told that HORIZANT may cause a significant driving impairment.
641 Accordingly, they should be advised not to drive a car until they have gained sufficient
642 experience on HORIZANT to assess whether HORIZANT impairs their ability to drive, although
643 patients’ ability to determine their level of impairment can be unreliable. Patients should be told
644 that it is not known how long this effect lasts.

645 **17.2 Somnolence/Sedation and Dizziness**

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

651 **17.3 Suicidal Behavior and Ideation**

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

657 **17.4 Drug Reaction With Eosinophilia and Systemic Symptoms**
658 **(DRESS)/Multiorgan Hypersensitivity**

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

662 **17.5 Lack of Interchangeability With Gabapentin**

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

665 **17.6 Dosing Instructions**

- 666 • Instruct patients to take HORIZANT only as prescribed.
667 • Instruct patients to swallow tablets whole and do not cut, crush, or chew tablets.
668 • Instruct patients to take HORIZANT with food.
669 • For Restless Legs Syndrome, 600 mg HORIZANT should be taken once daily at about 5 PM.
670 If the dose is not taken at the recommended time, the patient should take the next dose at
671 about 5 PM the following day.
672 • For Postherpetic Neuralgia, the starting dose is 600 mg HORIZANT in the morning for
673 3 days. Starting on day 4, 600 mg HORIZANT should be taken twice daily. If the dose is not
674 taken at the recommended time, the next dose should be taken at the time of next scheduled
675 dose.
676 • Instruct patients about how to discontinue HORIZANT.

677 **17.7 Alcohol**

- 678 • Advise patients to avoid alcohol when taking HORIZANT [see *Drug Interactions (7)*;
679 *Clinical Pharmacology (12.3)*].
680

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682
683 Manufactured by:

684 Patheon Inc.

685 Research Triangle Park, NC 27709

686

for:



GlaxoSmithKline
Research Triangle Park, NC 27709

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689

690 HZT:XPI

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

692 -----

693

MEDICATION GUIDE

694

HORIZANT[®] (*ho-ri' zant*)

695

(gabapentin enacarbil)

696

Extended-Release Tablets

697

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

701

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

703

HORIZANT can cause serious side effects:

704

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.

705

706

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

707

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710

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

711

712

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

713

714

• thoughts about suicide or dying

715

• attempt to commit suicide

716

• new or worse depression

717

• new or worse anxiety

718

• feeling agitated

719

• new or worse restlessness

720

• panic attacks

721

• new or worse trouble sleeping (insomnia)

722

• new or worse irritability

723

• acting aggressive, being angry, or violent

724

• acting on dangerous impulses

725

• an extreme increase in activity and talking (mania)

726

• other unusual changes in behavior or mood

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

- 728 • Pay attention to any changes, especially sudden changes, in mood,
729 behaviors, thoughts, or feelings.
730 • Keep all follow-up visits with your healthcare provider as scheduled.
731 • Call your healthcare provider between visits as needed, especially if you are
732 worried about symptoms.

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

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

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

- 741 • skin rash
742 • hives
743 • fever
744 • swollen glands that do not go away
745 • swelling of your lips or tongue
746 • yellowing of your skin or eyes
747 • unusual bruising or bleeding
748 • severe fatigue or weakness
749 • unexpected, severe muscle pain
750 • frequent infections

751
752 These symptoms may be the first signs of a serious reaction. A healthcare provider
753 should examine you to decide if you should continue taking HORIZANT.

754
755 **What is HORIZANT?**

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

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

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

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

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

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What should I tell my healthcare provider before taking HORIZANT?

Before taking HORIZANT, tell your healthcare provider if you:

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

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

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

How should I take HORIZANT?

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

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

- 805 • Do not take other medicines that make you sleepy or dizzy while taking
806 HORIZANT without first talking with your healthcare provider. Taking HORIZANT
807 with medicines that cause sleepiness or dizziness may make your sleepiness or
808 dizziness worse.
- 809 • Do not take other gabapentin drugs (for example, NEURONTIN or GRALISE)
810 while you take HORIZANT.
- 811 • Do not consume alcohol when taking HORIZANT.

812

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

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

816 The most common side effects of HORIZANT include:

- 817 • sleepiness
818 • dizziness
819 • headache

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

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

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

826

827 **How should I store HORIZANT?**

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

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

833

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

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

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

841 You can ask your healthcare provider or pharmacist for information about
842 HORIZANT that was written for healthcare professionals.
843 For more information about HORIZANT, go to www.gsk.com or call 1-888-825-
844 5249.

845
846 **What are the ingredients in HORIZANT?**

847 **Active ingredients:** gabapentin enacarbil
848 **Inactive ingredients:** Both the 300 mg and 600 mg tablets contain colloidal
849 silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium
850 stearate, sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric
851 oxide.

852
853 **This Medication Guide has been approved by the U.S. Food and Drug**
854 **Administration.**

855
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857 Patheon Inc.
858 Research Triangle Park, NC 27709
859

for:



GlaxoSmithKline
Research Triangle Park, NC 27709

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866 endorse GlaxoSmithKline or its products.

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870 HZT: XMG