

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

Dosage and Administration, Renal Impairment (2.2) 12/2011
Warnings and Precautions, DRESS (5.5) 12/2011

INDICATIONS AND USAGE

HORIZANT is indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of HORIZANT is 600 mg once daily taken with food 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)
- Instruct patients to swallow tablets whole and not to cut, crush, or chew tablets. (2.1)
- Patients with renal impairment: Doses of HORIZANT must be adjusted in accordance with renal function. (2.2)

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: Monitor for suicidal thoughts or behaviors. (5.4)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 10\%$ and at least 2 times the rate of placebo) were somnolence/sedation and dizziness. (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: 04/2012

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

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

5
6 HORIZANT is not recommended for patients who are required to sleep during the daytime and
7 remain awake at night.

8 2 DOSAGE AND ADMINISTRATION

9 2.1 Restless Legs Syndrome

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

13
14 If the dose is not taken at the recommended time, the next dose should be taken the following
15 day as prescribed.

16
17 Tablets should be swallowed whole and should not be cut, crushed, or chewed.

18 2.2 Renal Impairment

19 Dosing of HORIZANT is adjusted in accordance with renal function, as represented by
20 creatinine clearance [see *Clinical Pharmacology (12.3)*]. Target dose regimens are listed in
21 Table 1.
22
23

24 **Table 1. Dosage of HORIZANT in Accordance With Creatinine Clearance**

25 Creatinine Clearance (mL/min)	26 Target Dose Regimen
27 ≥ 60	28 600 mg per day
29 30-59	30 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

25 In patients with stable renal function, CrCl can be estimated using the equation of Cockcroft and
26 Gault:

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

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

29 where age is in years, weight is in kilograms, and SCr is serum creatinine in mg/dL.
30

31 **3 DOSAGE FORMS AND STRENGTHS**

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

35 **4 CONTRAINDICATIONS**

36 None.

37 **5 WARNINGS AND PRECAUTIONS**

38

39 **5.1 Effects on Driving**

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

45

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

55

56 **5.2 Somnolence/Sedation and Dizziness**

57 HORIZANT causes somnolence/sedation and dizziness (see Table 3). Patients should be advised
58 not to drive a car or operate other complex machinery until they have gained sufficient
59 experience on HORIZANT to assess whether HORIZANT impairs their ability to perform these
60 tasks.

61 During the controlled trials in patients with RLS, somnolence/sedation was reported in 20% of
62 patients treated with 600 mg of HORIZANT per day compared with 6% of patients receiving
63 placebo. In those patients treated with HORIZANT who reported somnolence, the somnolence
64 persisted during treatment in about 30%. In the remaining patients, symptoms resolved within 3
65 to 4 weeks. Dizziness was reported in 13% of patients receiving 600 mg of HORIZANT per day
66 compared with 4% of patients receiving placebo. In those patients treated with HORIZANT who
67 reported dizziness, symptoms persisted during treatment in about 20%. Somnolence/sedation led
68 to withdrawal in 2% of patients receiving 600 mg of HORIZANT per day. Dizziness led to

69 withdrawal in 1% of patients receiving 600 mg of HORIZANT per day. The incidence of these
70 adverse reactions was greater in the patients receiving 1,200 mg per day.

71

72 **5.3 Lack of Interchangeability With Gabapentin**

73 HORIZANT is not interchangeable with other gabapentin products because of differing
74 pharmacokinetic profiles. The same dose of HORIZANT results in different plasma
75 concentrations of gabapentin relative to other gabapentin products. [See *Clinical Pharmacology*
76 (12.3).]

77

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

79

80 **5.4 Suicidal Behavior and Ideation**

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

87

88 Pooled analyses of 199 placebo-controlled clinical trials (monotherapy and adjunctive therapy)
89 of 11 different AEDs showed that patients randomized to 1 of the AEDs had approximately
90 twice the risk [adjusted relative risk 1.8, 95% confidence interval (CI): 1.2, 2.7] of suicidal
91 thinking or behavior compared with patients randomized to placebo. In these trials, which had a
92 median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or
93 ideation among 27,863 AED-treated patients was 0.43%, compared with 0.24% among
94 16,029 placebo-treated patients, representing an increase of approximately 1 case of suicidal
95 thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated patients
96 in the trials and none in placebo-treated patients, but the number is too small to allow any
97 conclusion about drug effect on suicide.

98

99 The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week
100 after starting drug treatment with AEDs and persisted for the duration of treatment assessed.

101 Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal
102 thoughts or behavior beyond 24 weeks could not be assessed.

103

104 The risk of suicidal thoughts or behavior was generally consistent among drugs in the data
105 analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a
106 range of indications suggests that the risk applies to all AEDs used for any indication. The risk
107 did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. Table 2 shows
108 absolute and relative risk by indication for all evaluated AEDs.

109

110 **Table 2. 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

111

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

115

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

122

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

128

129 **5.5 Drug Reaction With Eosinophilia and Systemic Symptoms**
130 **(DRESS)/Multiorgan Hypersensitivity**

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

139

140 It is important to note that early manifestations of hypersensitivity, such as fever or
141 lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are
142 present, the patient should be evaluated immediately. HORIZANT should be discontinued if an
143 alternative etiology for the signs or symptoms cannot be established.
144

145 **5.6 Discontinuation of HORIZANT**

146 When discontinuing HORIZANT, patients receiving the recommended dose of 600 mg daily can
147 discontinue the drug without tapering. If the recommended dose is exceeded, the dose should be
148 reduced to 600 mg daily for 1 week prior to discontinuation to minimize the potential of
149 withdrawal seizure.
150

151 **5.7 Tumorigenic Potential**

152 In an oral carcinogenicity study, gabapentin enacarbil increased the incidence of pancreatic
153 acinar cell adenoma and carcinoma in male and female rats [see *Nonclinical Toxicology (13.1)*].
154 The clinical significance of this finding is unknown.
155

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

163 **6 ADVERSE REACTIONS**

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

- 166 • Somnolence/sedation and dizziness [see *Warnings and Precautions (5.2)*]
- 167

168 **6.1 Clinical Trials Experience**

169 In all controlled and uncontrolled trials across various patient populations prior to approval of
170 HORIZANT, more than 2,300 patients have received HORIZANT orally in daily doses ranging
171 from 600 to 3,600 mg.
172

173 The exposure to HORIZANT in 1,201 patients with RLS included 613 exposed for at least 6
174 months and 371 exposed for at least 1 year. HORIZANT in the treatment of RLS was studied
175 primarily in placebo-controlled trials (n = 642), and in long-term follow-up studies. The
176 population with RLS ranged from 18 to 82 years of age, with 60% being female and 95% being
177 Caucasian.
178

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

182
183 The safety of HORIZANT in doses ranging from 600 to 2,400 mg has been evaluated in
184 515 patients with RLS in 3 double-blind, placebo-controlled, 12-week clinical trials. The 600-mg
185 dose was studied in 2 of the 3 studies. Eleven out of 163 (7%) patients treated with 600 mg of
186 HORIZANT discontinued treatment due to adverse reactions compared with 10 of the 245 (4%)
187 patients who received placebo.

188
189 The most commonly observed adverse reactions ($\geq 5\%$ and at least 2 times the rate of placebo) in
190 these trials for the 600-mg dose of HORIZANT were somnolence/sedation and dizziness (see
191 Table 3). Table 3 lists treatment-emergent adverse reactions that occurred in $\geq 2\%$ of patients
192 with RLS treated with HORIZANT and numerically greater than placebo.

193

194 **Table 3. Incidence of Adverse Reactions in 12-Week RLS Studies Reported in $\geq 2\%$ of**
 195 **Patients Treated With 600 or 1,200 mg of HORIZANT and Numerically Greater Than**
 196 **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

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

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

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

203
 204 Adverse reactions reported in these three 12-week studies in <2% of patients treated with 600 mg
 205 of HORIZANT and numerically greater than placebo were balance disorder, blurred vision,
 206 disorientation, feeling drunk, lethargy, and vertigo.

207
 208 The following adverse reactions were dose-related: somnolence/sedation, dizziness, feeling
 209 drunk, libido decreased, depression, headache, peripheral edema, and vertigo.

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6.2 Adverse Events Associated With Gabapentin

The following adverse events have been reported in patients receiving gabapentin, either in clinical trials or postmarketing: breast enlargement and gynecomastia.

7 DRUG INTERACTIONS

Neither gabapentin enacarbil nor gabapentin are substrates, inhibitors, or inducers of the major cytochrome P450 enzymes. Gabapentin enacarbil is neither a substrate nor an inhibitor of P-glycoprotein *in vitro*. [See *Clinical Pharmacology (12.3)*.]

Pharmacokinetic drug-drug interaction studies were conducted to examine the potential for an interaction of gabapentin enacarbil with cimetidine and naproxen. No significant pharmacokinetic interactions were observed. No clinically relevant pharmacokinetic interactions are expected between HORIZANT and other substrates of organic cation transporter type 2 (OCT2) and monocarboxylate transporter type 1 (MCT-1) [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

When pregnant rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or 5,000 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased at the 2 highest doses and fetal body weights were decreased at the high dose. The no-effect dose for embryo-fetal developmental toxicity in rats is approximately 3 times the recommended human dose (RHD) of 600 mg/day on a body surface area (mg/m²) basis.

When pregnant rabbits were administered gabapentin enacarbil (oral doses of 200, 500, or 2,500 mg/kg/day) throughout the period of organogenesis, embryo-fetal mortality was increased and fetal body weights were decreased at the high dose. The no-effect dose for embryo-fetal developmental toxicity in rabbits (500 mg/kg/day) is approximately 16 times the RHD on a mg/m² basis.

When female rats were administered gabapentin enacarbil (oral doses of 200, 1,000, or 5,000 mg/kg/day) throughout the pregnancy and lactation periods, offspring growth and survival were decreased at the two highest doses. The no-effect dose for pre- and post-natal developmental toxicity in rats is approximately 3 times the RHD on a mg/m² basis.

249 In reproductive and developmental studies of gabapentin, developmental toxicity was observed
250 at all doses tested. Increased incidences of hydronephrosis and/or hydronephrosis were observed in
251 rat offspring following treatment of pregnant animals in studies of fertility and general
252 reproductive performance, embryo-fetal development, and peri- and post-natal development.
253 Overall, a no-effect dose was not established. In mice, treatment of pregnant animals with
254 gabapentin during the period of organogenesis resulted in delayed fetal skeletal ossification at all
255 but the lowest dose tested. When pregnant rabbits were treated with gabapentin during the period
256 of organogenesis, an increase in embryo-fetal mortality was observed at all doses of gabapentin
257 tested.

258
259 In a published study, gabapentin (400 mg/kg/day) was administered by intraperitoneal injection
260 to neonatal mice during the first postnatal week, a period of synaptogenesis in rodents
261 (corresponding to the last trimester of pregnancy in humans). Gabapentin caused a marked
262 decrease in neuronal synapse formation in brains of intact mice and abnormal neuronal synapse
263 formation in a mouse model of synaptic repair. Gabapentin has been shown *in vitro* to interfere
264 with activity of the $\alpha 2\delta$ subunit of voltage-activated calcium channels, a receptor involved in
265 neuronal synaptogenesis. The clinical significance of these findings is unknown.

266

267 **8.2 Labor and Delivery**

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

269

270 **8.3 Nursing Mothers**

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

276

277 **8.4 Pediatric Use**

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

279

280 **8.5 Geriatric Use**

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

285

286 Gabapentin is known to be almost exclusively excreted by the kidney, and the risk of adverse
287 reactions to this drug may be greater in patients with impaired renal function. Because elderly
288 patients are more likely to have decreased renal function, the frequency of dosing may need to be

289 adjusted based on calculated creatinine clearance in these patients [see Dosage and
290 Administration (2.2)].

291

292 **8.6 Renal Impairment**

293 The dose of HORIZANT should be adjusted in patients with renal impairment [see Dosage and
294 Administration (2.2), Clinical Pharmacology (12.3)].

295 **10 OVERDOSAGE**

296

297 **10.1 Human Overdose Experience**

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

303

304 **10.2 Overdosage Management**

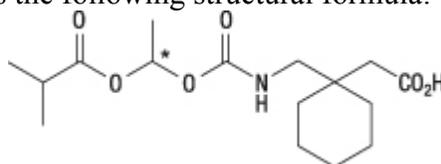
305 In the event of an overdose, the patient should be treated supportively with appropriate
306 monitoring as necessary. Gabapentin derived from gabapentin enacarbil can be removed from
307 plasma by hemodialysis. The mean percentage of gabapentin recovered following hemodialysis
308 in patients with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

310

311 Further management should be as clinically indicated or as recommended by a poison control
312 center.

313 **11 DESCRIPTION**

314 HORIZANT (gabapentin enacarbil) is a prodrug of gabapentin. Gabapentin enacarbil is
315 described as (1-{{(1RS)-1-[(2-Methylpropanoyl)oxy]ethoxy}carbonyl)amino}methyl}
316 cyclohexyl) acetic acid. It has a molecular formula of C₁₆H₂₇NO₆ and a molecular weight of
317 329.39. It is a racemate and has the following structural formula:



318

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

322

323 HORIZANT is administered orally. Each HORIZANT Extended-Release Tablet contains
324 300 mg or 600 mg of gabapentin enacarbil and the following inactive ingredients: colloidal

325 silicon dioxide, dibasic calcium phosphate dihydrate, glyceryl behenate, magnesium stearate,
326 sodium lauryl sulfate, and talc. The 300 mg tablets also contain red ferric oxide.

327 **12 CLINICAL PHARMACOLOGY**

328

329 **12.1 Mechanism of Action**

330 Gabapentin enacarbil is a prodrug of gabapentin and, accordingly, its therapeutic effects in RLS
331 are attributable to gabapentin.

332

333 The precise mechanism by which gabapentin is efficacious in RLS is unknown. Gabapentin is
334 structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect
335 on GABA binding, uptake, or degradation. Gabapentin enacarbil and gabapentin have been
336 tested in radioligand binding assays, and neither exhibited affinity for a number of other common
337 receptor, ion channel, or transporter proteins.

338

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

342

343 **12.3 Pharmacokinetics**

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

348

349 **Absorption:** The pathway for absorption of gabapentin enacarbil is believed to include active
350 transport via a proton-linked monocarboxylate transporter, MCT-1. This transporter is expressed
351 at high levels in the intestinal tract and is not saturated by administration of high doses of
352 HORIZANT. Mean bioavailability of gabapentin (based on urinary recovery of gabapentin) for
353 HORIZANT in the fed state is about 75%. Bioavailability under fasting conditions has been
354 estimated by gabapentin urinary recovery to be 42% to 65%. In a food effect study, the exposure
355 of gabapentin increased by 24%, 34%, and 44% with low, moderate, and high fat meals,
356 respectively. The T_{max} of gabapentin after administration of 600 mg of HORIZANT was
357 5.0 hours in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with
358 daily administration.

359

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

362

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

372
373 **Elimination:** Following hydrolysis of gabapentin enacarbil, the released gabapentin is excreted
374 unchanged by the kidney. Gabapentin renal excretion is believed to involve a component of
375 active secretion via an organic cation transporter (OCT2) present in the kidney. In a human
376 pharmacokinetic study with immediate release ^{14}C gabapentin enacarbil, mean recovery of total
377 radioactivity in urine was 94%, with 5% of the radioactive dose recovered in feces.

378
379 Apparent oral clearance (CL/F) of gabapentin from plasma after dosing of HORIZANT with
380 food ranged from 6.0 to 9.3 L/hr. Following oral dosing of HORIZANT, plasma clearance of
381 gabapentin is approximately proportional to creatinine clearance. Renal clearance (CL_r) of
382 gabapentin ranged from 5 to 7 L/hr, regardless of food intake or food type. The elimination
383 half-life ($t_{1/2}$) of gabapentin ranges from 5.1 to 6.0 hours and is unaltered by dose or following
384 multiple doses of HORIZANT.

385
386 **Special Populations: Race:** The majority (94%) of subjects in the clinical studies were
387 Caucasian, and no single other race was greater than 4%; therefore, the effect of race could not
388 be studied.

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

391
392 **Geriatric Patients:** There are no clinically significant differences in pharmacokinetics of
393 HORIZANT between geriatric patients (≥ 65 years of age) and younger patients (18 to < 65 years
394 of age). However, the pharmacokinetics in geriatric patients may be affected by an age-related
395 decline in renal function [*see Use in Specific Populations (8.5)*].

396
397 **Renal Impairment:** Gabapentin clearance after dosing with HORIZANT is approximately
398 proportional to CrCl. Apparent oral clearance (CL/F) decreased in moderate (4.2 L/hr) and
399 severe renal impairment patients (1.7 L/hr) compared with 6.0 to 9.3 L/hr in patients without
400 renal impairment. Similarly, CL_r was decreased to 3 and 1 L/hr in moderate and severe renal
401 impairment patients, respectively, compared with 5 to 7 L/hr in non-renal impairment patients.
402 Dosage reduction in patients with renal dysfunction not on dialysis is necessary. For patients on

403 hemodialysis, treatment with HORIZANT is not recommended [see Dosage and Administration
404 (2.2)].

405

406 **Drug Interactions: Cimetidine:** Gabapentin released from HORIZANT is eliminated by renal
407 clearance via OCT2. Cimetidine is a known substrate for this same elimination pathway.

408 Coadministration of 1,200 mg of HORIZANT once daily with cimetidine 400 mg 4 times daily
409 showed no effect on cimetidine exposure. There was an increase in AUC of gabapentin (24%)
410 and a decrease in renal clearance of gabapentin (20%); these effects are not expected to be
411 clinically relevant. No clinically relevant pharmacokinetic interactions are expected between
412 HORIZANT and other substrates of OCT2.

413

414 **Naproxen:** The pathway for absorption of gabapentin enacarbil includes active transport via a
415 proton-linked MCT-1. Coadministration of 1,200 mg of HORIZANT once daily with naproxen
416 500 mg twice daily, a known substrate of MCT-1, showed no effect on naproxen exposure or
417 steady-state gabapentin C_{max} and AUC. No clinically relevant pharmacokinetic interactions are
418 expected between HORIZANT and other substrates of MCT-1.

419 **13 NONCLINICAL TOXICOLOGY**

420

421 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

422 **Carcinogenesis:** Oral (gavage) carcinogenicity studies were conducted in mice and rats. In
423 mice, gabapentin enacarbil was tested at doses of 500, 2,000, or 5,000 mg/kg/day for up to
424 104 weeks. There was no evidence of drug-related carcinogenicity. The highest dose tested is
425 40 times the RHD of 600 mg/day, on a body surface area (mg/m²) basis.

426

427 In rats, gabapentin enacarbil was tested at doses of 500, 2,000, or 5,000 mg/kg/day for up to
428 97 weeks in mid-dose males, 90 weeks in high-dose males, and 104 weeks in females. The
429 plasma exposures (AUC) for gabapentin at these doses are approximately 10, 38, and 75 times,
430 respectively, that in humans at the RHD. Increases in the incidence of pancreatic acinar adenoma
431 and carcinoma were found in mid-dose males and high-dose males and females.

432

433 In 2-year dietary carcinogenicity studies of gabapentin, no evidence of drug-related
434 carcinogenicity was observed in mice treated at doses up to 2,000 mg/kg/day. In rats, increases in
435 the incidence of pancreatic acinar cell adenoma and carcinoma were found in male rats receiving
436 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,
437 the plasma AUC for gabapentin is estimated to be approximately 25 times that in humans at the
438 RHD.

439

440 Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis
441 in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro*

442 and thus may be acting as a tumor promoter by enhancing mitogenic activity. It is not known
443 whether gabapentin has the ability to increase cell proliferation in other cell types or in other
444 species, including human.

445
446 **Mutagenesis:** Gabapentin enacarbil was negative in *in vitro* bacterial reverse mutation (Ames)
447 and *in vivo* rat micronucleus assays. In an *in vitro* human lymphocyte assay, there was an
448 increase in the number of chromosomal aberrations with gabapentin enacarbil. This *in vitro*
449 response was attributed to acetaldehyde released by hydrolysis of gabapentin enacarbil during
450 the incubation period. Acetaldehyde is known to cause chromosome aberrations *in vitro*, but is
451 readily metabolized *in vivo*. The small quantity of acetaldehyde formed from gabapentin
452 enacarbil *in vivo* is rapidly cleared by normal metabolic activity.

453
454 **Impairment of Fertility:** Oral administration of gabapentin enacarbil (doses of 0, 200, 1,000, or
455 5,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in
456 females up to day 7 of gestation resulted in no adverse effects on fertility. The highest dose
457 tested is approximately 80 times the RHD on a mg/m² basis.

458 **14 CLINICAL STUDIES**

459 460 **14.1 12-Week Pivotal Studies**

461 The effectiveness of HORIZANT in the treatment of moderate-to-severe primary RLS was
462 demonstrated in two 12-week clinical studies in adults diagnosed with RLS using the
463 International Restless Legs Syndrome Study Group diagnostic criteria. Key diagnostic criteria
464 for RLS are: an urge to move the legs usually accompanied or caused by uncomfortable and
465 unpleasant leg sensations, symptoms begin or worsen during periods of rest or inactivity such as
466 lying or sitting, symptoms are partially or totally relieved by movement such as walking or
467 stretching at least as long as the activity continues, and symptoms are worse or occur only in the
468 evening or night. Patients were required to have a total score of ≥ 15 on the International Restless
469 Legs Syndrome (IRLS) Rating Scale at baseline. Patients with RLS secondary to other
470 conditions (e.g., pregnancy, renal failure, iron deficiency anemia) were excluded. In study 1,
471 patients were randomized to receive 1,200 mg of HORIZANT (N = 112) or placebo (N = 108)
472 taken once daily at about 5 PM with food. In study 2, patients were randomized to receive
473 600 mg of HORIZANT (N = 114), 1,200 mg of HORIZANT (N = 111), or placebo (N = 96)
474 taken once daily at about 5 PM with food.

475
476 Efficacy was evaluated using the IRLS Rating Scale and Clinical Global Impression of
477 Improvement (CGI-I) scores. The IRLS Rating Scale contains 10 items designed to assess the
478 severity of sensory and motor symptoms, sleep disturbance, daytime somnolence/sedation, and
479 impact on activities of daily living and mood associated with RLS. The range of scores is 0 to 40,
480 with 0 being absence of RLS symptoms and 40 the most severe symptoms. The CGI-I Scale

481 allows the investigator to rate the patient’s overall change in RLS symptoms since baseline,
 482 whether or not in the opinion of the investigator the change is related to study drug treatment.
 483 The change from baseline in the IRLS Rating Scale at Week 12 and the proportion of responders
 484 on the CGI-I Scale defined as a rating of “much improved” or “very much improved” at
 485 Week 12 were co-primary outcomes in these studies.

486
 487 In these 2 studies, the mean age of patients studied was 50 years (range: 18 to 81 years); 59% of
 488 the patients were female. The racial distribution for these studies was as follows: Caucasian,
 489 95%; black, 2%; and other, 3%.

490
 491 Statistically significant differences ($P < 0.05$) between the treatment groups receiving 600 and
 492 1,200 mg of HORIZANT and the group receiving placebo were observed at Week 12 for both
 493 the mean change from baseline in the IRLS Scale total score and the proportion of responders
 494 (“much improved” or “very much improved”) on the CGI-I Scale as described in Table 4.

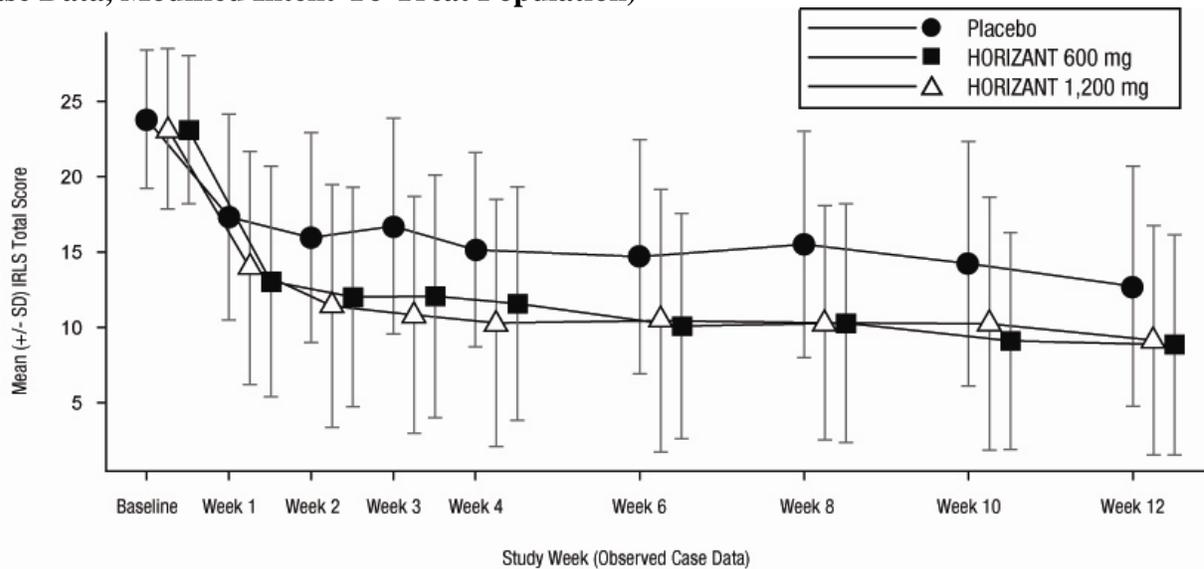
495
 496 **Table 4. Mean Change in IRLS Scale Total Score and Proportion of Responders on CGI-I**
 497 **Scale at Week 12**

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%

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

499
 500 Figure 1 presents the improvement in mean IRLS Rating Scale total score in patients treated with
 501 placebo or 600 or 1,200 mg of HORIZANT over the 12 weeks of treatment in study 2.
 502

503 **Figure 1. Study 2, Mean (\pm SD) IRLS Rating Scale Total Score Over 12 Weeks (Observed**
 504 **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

505
506

507 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

510

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

514 300 mg: NDC 0173-0832-13: Bottles of 30

515 600 mg: NDC 0173-0806-01: Bottles of 30

516

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

519 **17 PATIENT COUNSELING INFORMATION**

520 *See Medication Guide.*

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

524

525 **17.1 Effects on Driving**

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

530

531 **17.2 Somnolence/Sedation and Dizziness**

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

536

537 **17.3 Suicidal Behavior and Ideation**

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

543

544 **17.4 Drug Reaction With Eosinophilia and Systemic Symptoms**
545 **(DRESS)/Multiorgan Hypersensitivity**

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

549

550 **17.5 Lack of Interchangeability With Gabapentin**

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

553

554 **17.6 Dosing Instructions**

- 555
- 556 • Patients should be instructed to take HORIZANT only as prescribed.
 - 557 • HORIZANT should be taken once daily with food at about 5 PM.
 - 558 • If the dose is not taken at the recommended time, the patient should take the next dose at
559 about 5 PM the following day.
 - 560 • Tablets should be swallowed whole and should not be cut, crushed, or chewed.

560

561 HORIZANT is a trademark of GlaxoSmithKline.

562

563 Manufactured by:

564 Patheon Inc.

565 Research Triangle Park, NC 27709

566

for:



GlaxoSmithKline
Research Triangle Park, NC 27709

567

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569

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

572 -----

573

MEDICATION GUIDE

574

HORIZANT™ [*ho-ri' zant*]

575

(gabapentin enacarbil)

576

Extended-Release Tablets

577

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

581

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

583

HORIZANT can cause serious side effects:

584

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.

585

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

590

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

591

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

593

594

• thoughts about suicide or dying

595

• attempt to commit suicide

596

• new or worse depression

597

• new or worse anxiety

598

• feeling agitated

599

• new or worse restlessness

600

• panic attacks

601

• new or worse trouble sleeping (insomnia)

602

• new or worse irritability

603

• acting aggressive, being angry, or violent

604

• acting on dangerous impulses

605

• an extreme increase in activity and talking (mania)

606

• other unusual changes in behavior or mood

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

- 608 • Pay attention to any changes, especially sudden changes, in mood,
609 behaviors, thoughts, or feelings.
610 • Keep all follow-up visits with your healthcare provider as scheduled.
611 • Call your healthcare provider between visits as needed, especially if you are
612 worried about symptoms.

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

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

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

- 621 • skin rash
622 • hives
623 • fever
624 • swollen glands that do not go away
625 • swelling of your lips or tongue
626 • yellowing of your skin or eyes
627 • unusual bruising or bleeding
628 • severe fatigue or weakness
629 • unexpected, severe muscle pain
630 • frequent infections

631
632 These symptoms may be the first signs of a serious reaction. A healthcare provider
633 should examine you to decide if you should continue taking HORIZANT.

634
635 **What is HORIZANT?**

636 HORIZANT is a prescription medicine used to treat adults with moderate-to-severe
637 primary Restless Legs Syndrome (RLS).

638 HORIZANT is not for people who need to sleep during the daytime and need to stay
639 awake at night.

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

642 It is not known if HORIZANT is safe and effective in children.
643

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

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

- 646 • have or have had kidney problems or are on hemodialysis.
- 647 • have or have had depression, mood problems, or suicidal thoughts or behavior.
- 648 • if you are pregnant or plan to become pregnant. It is not known if HORIZANT
- 649 will harm your unborn baby. Talk to your healthcare provider if you are pregnant
- 650 or plan to become pregnant while taking HORIZANT. You and your healthcare
- 651 provider will decide if you should take HORIZANT while you are pregnant.
- 652 • are breastfeeding or plan to breastfeed. Your body turns HORIZANT into another
- 653 drug (gabapentin) that passes into your milk. It is not known if this can harm
- 654 your baby. You and your healthcare provider should decide if you will take
- 655 HORIZANT or breastfeed.

656 **Tell your healthcare provider about all the medicines you take**, including

657 prescription and non-prescription medicines, vitamins, and herbal supplements.

658 Know the medicines you take. Keep a list of them and show it to your healthcare

659 provider and pharmacist when you get a new medicine.

660

661 **How should I take HORIZANT?**

- 662 • Take HORIZANT exactly as your healthcare provider tells you to take it.
- 663 • Take HORIZANT 1 time each day with food around 5 PM. If you miss your dose,
- 664 wait and take your usual dose the next day around 5 PM.
- 665 • Take HORIZANT tablets whole. **Do not** cut, crush, or chew your tablet.
- 666 • If you take too much HORIZANT, call your healthcare provider or go to the
- 667 nearest hospital emergency room right away.

668

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

- 670 • Do not take other medicines that make you sleepy or dizzy while taking
- 671 HORIZANT without first talking with your healthcare provider. Taking HORIZANT
- 672 with medicines that cause sleepiness or dizziness may make your sleepiness or
- 673 dizziness worse.
- 674 • Do not take other gabapentin drugs (for example, NEURONTIN or GRALISE)
- 675 while you take HORIZANT.

676

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

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

680 The most common side effects of HORIZANT include:

- 681 • sleepiness
682 • dizziness

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

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

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

689
690 **How should I store HORIZANT?**

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

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

696
697 **General Information about the safe and effective use of HORIZANT**

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

702 This Medication Guide summarizes the most important information about
703 HORIZANT. If you would like more information, talk with your healthcare provider.
704 You can ask your healthcare provider or pharmacist for information about
705 HORIZANT that was written for healthcare professionals.

706 For more information about HORIZANT, go to www.gsk.com or call 1-888-825-
707 5249.

708
709 **What are the ingredients in HORIZANT?**

710 **Active ingredients:** gabapentin enacarbil

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

715
716 **This Medication Guide has been approved by the U.S. Food and Drug**
717 **Administration.**

718
719 HORIZANT is a trademark of GlaxoSmithKline. The other brands listed are
720 trademarks of their respective owners and are not trademarks of GlaxoSmithKline.
721 The makers of these brands are not affiliated with and do not endorse
722 GlaxoSmithKline or its products.

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727

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730
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732 HZT: 2MG