

Steroid Injections Ease Cluster Headaches

BY MARY ANN MOON

FROM THE LANCET

Serial suboccipital injections of steroids rapidly relieve cluster headaches as a transitional treatment while patients wait for long-term prophylactic drugs to take effect, according to a randomized, double-blind, controlled clinical trial.

Compared with placebo injections,

cortivazol injections reduced the number of headaches per day during the first 4 days of treatment, decreased the total number of attacks over 15 days while patients waited for verapamil to kick in, and shortened the interval until remission, reported Dr. Elizabeth Leroux of the Emergency Headache Centre, Lariboisière Hospital, Paris, and her associates.

Cluster headache is characterized by attacks of strong periorbital pain with ip-

ilateral autonomic signs, which recur up to eight times a day. Episodic cluster headaches occur in phases for weeks or months separated by long remissions. In 10% of patients, episodic cluster headaches evolve into chronic cluster headaches.

Most patients are managed with a combination of acute therapy and prophylactic treatment. Transitional treatment is used to suppress attacks at the onset of a

cluster while awaiting the delayed efficacy of preventive drugs such as verapamil or lithium. Oral steroids are widely used in this setting, but they can induce rebound attacks when patients are weaned off them and can cause serious adverse effects even when used briefly.

Suboccipital steroid injections have been proposed as an alternative to systemic steroids, but only one small, randomized, controlled trial on this ap-

BRIEF SUMMARY

HORIZANT™ (gabapentin enacarbil)

Extended-Release Tablets

The following is a brief summary only; see full Prescribing Information for complete product information.

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Effects on Driving

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

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

Somnolence/Sedation and Dizziness

HORIZANT causes somnolence/sedation and dizziness (see Table 2). Patients should be advised not to drive a car or operate other complex machinery until they have gained sufficient experience on HORIZANT to assess whether HORIZANT impairs their ability to perform these tasks.

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

Lack of Interchangeability With Gabapentin

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

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

Suicidal Behavior and Ideation

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

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

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

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. 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

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

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

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

Discontinuation of HORIZANT

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

Tumorigenic Potential

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

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

ADVERSE REACTIONS

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

Clinical Trials Experience

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

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

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

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

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

proach has been published. Dr. Leroux and her colleagues, who have used suboccipital cortivazol injections for 10 years in their clinic, assessed their safety and efficacy when added to usual care. (Cortivazol is not available in the United States.)

During an 8-month period, the investigators enrolled 43 adults who presented to the Emergency Headache Center with frequent daily cluster headaches, including 28 with episodic and 15 with chronic cluster headache. The study subjects were randomly assigned to receive three suboccipital injections containing either cortivazol (21 patients) or saline (22 patients),

given singly every 48-72 hours.

The injections were made under the occipital bone at the medial third between theinion and mastoid process, ipsilateral to the attack. Each injection was aimed in three directions: upward, at a 45-degree angle to the left, and at a 45-degree angle to the right.

Acute treatment with sumatriptan or oxygen was given as needed. Patients continued on any prophylactic agents they had been taking before the attack or were started on verapamil.

The study subjects completed daily diaries in which they recorded cluster

headache attacks, medication use, and adverse effects for 90 days. All were telephoned after 3-11 months to assess their satisfaction with treatment.

The study's primary end point was to reduce the mean number of daily attacks to two or fewer on the second, third, and fourth days after the final injection. In all, 20 of 21 patients (95%) who received steroid injections reached this end point, compared with 12 of 22 controls (55%) who received placebo injections.

This significant benefit with active injections was the same for both episodic and chronic cluster headaches, reported

the investigators (Lancet 2011 Sept. 7 [doi:10.1016/S1474-4422(11)70186-7]).

Patients given steroid injections also had fewer attacks during the first 15 days of the study than did those given placebo, and achieved remission a mean of 7 days earlier. Cortivazol also lowered the need for sumatriptan injections during the first 15 days of the study and reduced the need for verapamil in patients with the episodic type of cluster headache.

In addition, patients' scores of satisfaction with therapy were higher for steroid than for placebo injections.

In a post hoc analysis, 7 of 21 patients (33%) given cortivazol remained pain free from 4 days after the first injection until day 30, while only 2 of 22 control subjects (9%) did. Eleven (52%) in the cortivazol group remained pain free after the last injection to day 30, compared with only 4 (18%) in the control group.

The injections were safe and well tolerated. Adverse events – chiefly neck pain at the injection site and headache other than cluster headache – developed in 18 (86%) of the cortivazol group and 14 (64%) of the control group.

This study received no industry funding. Dr. Leroux and her associates reported ties to numerous industry sources, including Sanofi-Aventis, maker of the prefilled cortivazol syringes used in this study. ■

Table 2 (continued). Incidence of Adverse Reactions in 12-Week RLS Studies Reported in ≥2% of Patients Treated With 600 or 1,200 mg of HORIZANT and Numerically Greater Than Placebo

Body System/ Adverse Reaction	Placebo ^a (N = 245) %	HORIZANT 600 mg/day ^b (N = 163) %	HORIZANT 1,200 mg/day ^c (N = 269) %
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

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

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

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

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

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

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*.

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) of full prescribing information*].

USE IN SPECIFIC POPULATIONS

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.

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

In a published study, gabapentin (400 mg/kg/day) was administered by intraperitoneal injection to neonatal mice during the first postnatal week, a period of synaptogenesis in rodents (corresponding to the last trimester of pregnancy in humans). Gabapentin caused a marked decrease in neuronal synapse formation in brains of intact mice and abnormal neuronal synapse formation in a mouse model of synaptic repair. Gabapentin has been shown *in vitro* to interfere with activity of the α2δ subunit of voltage-activated calcium channels, a receptor involved in neuronal synaptogenesis. The clinical significance of these findings is unknown.

Labor and Delivery

The effect of HORIZANT on labor and delivery is unknown.

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

Gabapentin is known to be almost exclusively excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, the frequency of dosing may need to be adjusted based on calculated creatinine clearance in these patients [see *Dosage and Administration (2.2) of full prescribing information*].

Renal Impairment

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

OVERDOSAGE

Human Overdose Experience

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

Overdosage Management

In the event of an overdose, the patient should be treated supportively with appropriate monitoring as necessary. Gabapentin derived from gabapentin enacarbil can be removed by hemodialysis. Standard hemodialysis procedures result in significant clearance of gabapentin.

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

PATIENT COUNSELING INFORMATION

See *Medication Guide*.

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

Effects on Driving

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

Somnolence/Sedation and Dizziness

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

Suicidal Behavior and Ideation

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

Lack of Interchangeability With Gabapentin

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

Dosing Instructions

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

HORIZANT is a trademark of GlaxoSmithKline.

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Research Triangle Park, NC 27709

For:

 GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park, NC 27709

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Robust, Long-Awaited Data

The study by Dr. Leroux and Ther colleagues provides “long-awaited evidence in support of” suboccipital steroid injections for cluster headache, said Dr. David W. Dodick.

“Leroux and colleagues have provided the clinical and academic community with the largest and most robust controlled trial to date showing efficacy of suboccipital steroid injections for short-term transitional treatment of cluster headache,” he said.

The three-injection strategy used in the study is somewhat cumbersome. It remains to be seen if this strategy could potentially be replaced with a single injection of steroid and local anesthetic, as has been shown in several smaller studies, he noted.

DR. DODICK is in the department of neurology at the Mayo Clinic, Phoenix. He reported no financial conflicts of interest. These remarks were taken from his commentary accompanying Dr. Leroux's report (Lancet 2011 Sept. 7 [doi:10.1016/S1474-4422(11)70197-1]).

