New Drug Review: Gabapentin enacarbil extended release (Horizant™) – A new formulation on the horizon

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ABSTRACT

Gabapentin enacarbil was approved by the Food and Drug Administration (FDA) in April of 2011. This article reviews clinically significant aspects of this new drug including: the FDA-approved indications, mechanism of action, administration, drug interactions, adverse effects, clinical trial evidence, innovative properties and place in therapy.

KEYWORDS

Gabapentin enacarbil, Horizant, restless legs syndrome

GR is a 57-year-old female who is not sleeping well due to her Restless Legs Syndrome. She reports strong, irresistible urges to move her legs when she is watching TV at night, and these worsen when she lies in bed and tries to fall asleep. She currently takes ropinirole 4mg PO 2 hours before bedtime with some improvement in her symptoms, but she would like an even greater benefit from her medication. She has taken levodopa/carbidopa in the past for her restless legs, but she reported that the symptoms were occurring earlier in the day and were migrating into her arms while she was on it. GR would like to know if there are any additional treatments for her restless legs that may offer additional symptom relief.

WHAT IS THE FDA APPROVED INDICATION FOR GABAPENTIN ENACARBIL?

Gabapentin enacarbil (Horizant™) extended release tablets received FDA approval in April 2011 for the treatment of moderate-to-severe primary Restless Legs Syndrome in adults.[1] Gabapentin immediate release (Neurontin) was first approved by the FDA in 1994 for the adjunct treatment of partial seizures and is also FDA approved for the treatment of post-herpetic neuralgia. Gabapentin immediate release has also been used for many off-label indications, including treatment of migraine headache, fibromyalgia and neuropathic pain, and anxiety.

WHAT IS THE MECHANISM OF ACTION OF GABAPENTIN ENACARBIL?

Gabapentin enacarbil is a prodrug of gabapentin that is absorbed throughout the entire GI tract. The ability of gabapentin enacarbil to be absorbed in the large intestine differs from traditional gabapentin and contributes to its long-acting nature. Gabapentin enacarbil undergoes extensive 1st-pass hydrolysis by non-specific carboxylesterases to form gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid.[1] The precise mechanism by which gabapentin is efficacious in Restless Legs Syndrome is unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation. In vitro studies have shown that gabapentin binds with high affinity to the $\alpha 2\delta$ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin enacarbil in RLS is unknown.[1]

HOW IS GABAPENTIN ENACARBIL DOSED AND HOW SHOULD IT BE ADMINISTERED?

Gabapentin enacarbil is supplied in 600 mg extended release tablets. The recommended dose is 600 mg daily at 5pm with food. Gabapentin enacarbil tablets should be swallowed whole and should not be cut, crushed, or chewed. A dose of 1,200 mg once daily provided no additional benefit compared with the 600 mg dose, and caused an increase in adverse reactions.[1] If the dose of gabapentin enacarbil is not taken at the recommended time, the next dose should be taken the following day as prescribed. Gabapentin enacarbil can be abruptly

discontinued in patients taking the 600 mg once daily dose. If this dose is exceeded, the dose should be tapered to 600 mg daily for one week prior to discontinuation. The package labeling states that gabapentin enacarbil is not interchangeable with any other forms of gabapentin due to differing pharmacokinetic profiles.[1]

ARE THERE ANY CLINICALLY SIGNIFICANT DRUG-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 and no significant pharmacokinetic interactions were observed.[1] When taken in the fed state, gabapentin enacarbil appears to exhibit a longer Tmax compared with gabapentin immediate release (7.3-9.8 hours vs. 2.7-3.3 hours, respectively).[2] Other disposition properties of gabapentin, including the elimination half-life and oral or renal clearance, are not affected with the use of the gabapentin enacarbil delivery method. Apparent oral clearance was decreased in moderate and severe renally-impaired patients. Dosage reduction in patients with renal dysfunction is necessary. For patients on hemodialysis, treatment with gabapentin enacarbil is not recommended.[1]

WHAT ADVERSE EFFECTS SHOULD I DISCUSS WITH MY PATIENT?

Eleven out of 163 patients (7%) treated with 600 mg of gabapentin enacarbil discontinued treatment due to adverse reactions compared with 10 of the 245 patients (4%) 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 were somnolence/sedation (20% on gabapentin enacarbil vs. 6% on placebo) and dizziness (13% vs. 4% on placebo).[1] The following adverse reactions were dose-related: somnolence/sedation, dizziness, feeling drunk, libido decreased, depression, headache, peripheral edema, and vertigo. Like all anti-epileptic drugs, gabapentin enacarbil carries the same FDA risk warning for increasing suicidal thoughts or behavior in patients taking these drugs for any indication. Gabapentin enacarbil is classified as Pregnancy Category C; however, there are no adequate and well-controlled studies with gabapentin enacarbil in pregnant women.[1]

HOW DID GABAPENTIN ENACARBIL PERFORM IN CLINICAL STUDIES?

The effectiveness of gabapentin enacarbil in the treatment of moderate-to-severe primary RLS was demonstrated in two 12-week randomized, placebo-controlled clinical studies in adults diagnosed with RLS using the International Restless Legs Syndrome Study Group diagnostic criteria.[3,4] Statistically significant differences ($P<0.05$) between the treatment groups receiving 600 and 1,200 mg of gabapentin enacarbil and the group receiving placebo were observed at Week 12. Patients treated with gabapentin enacarbil showed an improved international RLS (IRLS) total score (–13.2) in contrast to placebo group (–8.8) at 2 weeks. On the investigator-rated CGI (Clinical Global Impression), significantly more gabapentin enacarbil-treated patients (76.1%) responded than placebo (38.9%). At the end of study more than 50% of gabapentin enacarbil-treated patients showed no sign of RLS over the 24-hour assessment period compared with 18% of placebo patients. Long-term safety and efficacy of gabapentin enacarbil was evaluated in a 24-week multicenter single-blind placebo controlled trial.[5]

In this phase of the study, 194 of 221 patients (88%) reported they were either "much improved" or "very much improved" CGI scores. These patients were then entered into a 12-week randomized, double-blind phase. Patients were given gabapentin enacarbil for either 12 weeks (1200 mg/day PO) or for 2 weeks (600 mg/day PO) and then placebo for 10 weeks. For the extended trial, the primary end-point was number of patients who relapsed or had worsening symptoms. Gabapentin enacarbil treated group showed a statistically significant lower proportion of relapses than placebo, 9% versus 23% respectively. Other indications are being investigated for gabapentin enacarbil including post-herpetic neuralgia, painful diabetic neuropathy, and migraine prophylaxis.[6]

WHAT PLACE DOES GABAPENTIN ENACARBIL HAVE IN THE TREATMENT OF RESTLESS LEGS SYNDROME?

The efficacy of gabapentin enacarbil has not been compared in a controlled fashion to gabapentin immediate release nor to any other available treatments for Restless Legs Syndrome. Gabapentin enacarbil appears to offer more consistent dose-proportional bioavailability, a longer time to Tmax and decreased dosing frequency, when its pharmacokinetics are compared with those of the gabapentin immediate release formulation. It is unclear what benefit this may (or may not) lend to the treatment of restless legs syndrome. Horizant™ will cost approximately $120 per

month[7] as compared with generic gabapentin 600 mg tablets which cost approximately $31.00 per month[8] It is unclear how gabapentin enacarbil will compare with Gralise, an alternate gabapentin extended release formulation that was recently approved for the treatment of post-herpetic neuralgia.

Returning to our case and our patient, GR, since she is already at the maximum approved dose of a dopamine agonist and still experiencing restless legs symptoms, gabapentin may be a reasonable agent to add to her regimen. Gabapentin enacarbil represents a possible option for treatment of her refractory symptoms; however, it may be difficult to justify the significantly higher cost of gabapentin enacarbil before an adequate trial of traditional (immediate release) gabapentin has been completed.

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