Gabapentin Enacarbil (Horizant®)

National Drug Monograph

March 2012

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

Gabapentin enacarbil (Horizant®) is a prodrug of gabapentin which binds with high affinity to the α2δ subunit of voltage-activated calcium channels in vitro studies. It is unknown how the binding of gabapentin enacarbil (GEn) to the α2δ subunit corresponds to the treatment of restless leg syndrome (RLS) symptoms.

- Indication: GEn is FDA approved for treatment of RLS.
- Pharmacokinetics: GEn is primarily excreted by the kidneys and neither gabapentin nor GEn is substrate, inhibitor, or inducer of the major CYP450 system. In addition, GEn is not an inhibitor or substrate of p-glycoprotein in vitro.
- Dose: The recommended dosage is 600 mg once daily taken with food at about 5 PM.
- Efficacy: Several studies examining GEn have shown efficacy over placebo in patients with RLS; improvement in RLS symptoms was observed within 7 days of starting treatment.[6-8, 12-14] Three studies demonstrated 1200 mg/day GEn significantly reduced International Restless Legs Syndrome (IRLS) scale total score and improved Clinical Global Impression–Improvement (CGI-I) scale compared with placebo.[6-8] Two studies demonstrated efficacy at lower dose of 600 mg/day GEn; however, another study did not.[7,12,13] These results are comparable to those seen with dopamine agonists.[8,12]
- Adverse Drug Events: Commonly reported adverse effects for the approved dose of 600 mg/day GEn are somnolence, sedation and dizziness. In clinical trials, doses as high as 1800 mg daily yielded other potential adverse effects occurring at a rate higher than placebo including nausea, dry mouth, flatulence, fatigue, irritability, peripheral edema, weight increase, increased appetite, vertigo, depression, and decreased libido.
- Warnings: Some common warnings for patients taking GEn include driving impairment, somnolence/sedation and dizziness, suicidal behavior and ideation, drug reaction with eosinophilia and systemic symptoms (DRESS) and carcinogenesis potential. Patients should also be advised to not substitute immediate release gabapentin with GEn due to differences in bioavailabilty between the two products.[1]
- There does not appear to be sufficient evidence to support the use of GEn as a first line agent due to limited comparative data to immediate release formulations and other dopamine agonists as well as long term safety and efficacy. There seems to be no pharmacokinetic advantage of the GEn 600 mg dose over the immediate release formulation as the bioavailabilty is similar at the 600-1200 mg ranges between both products. The association of an increased absorption rate with GEn is not seen until doses ≥ 1200 mg are employed.

- GEn may be considered in patients with moderate to severe RLS who have failed all other treatment options including gabapentin immediate release and dopamine agonists. Due to the lack of active comparator trials, there is no evidence to support superiority of GEn. Disadvantages of GEn include limited head to head trials looking at other possible treatment options for RLS. GEn at the FDA approved dose of 600 mg daily has not been proven superior to the currently available immediate release formulation of gabapentin and should only be considered after failure of all other currently available agents used to treat RLS.
- There is no evidence to support the preferential use of GEn over immediate release gabapentin or pregabalin in treatment of trigeminal neuralgia, neuropathic pain, seizure disorders, diabetic neuropathy and fibromyalgia.

Introduction[1,3,6]

Gababentin Enacarbil (GEn) is a prodrug of gabapentin. Gabapentin, the active metabolite of GEn, is FDA approved for use as an anticonvulsant and for pain relief in postherpetic neuralgia. This new formulation of gabapentin has been developed to aid in variable bioavailability demonstrated with oversaturation of gabapentin transporters in the intestine at high doses. The new formulation provides reliable drug absorption and provides consistent bioavailability.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating GEn for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics [1,2,4]

Gabapentin is an analog of neurotransmitter gamma aminobutyric acid. It has been shown *in vitro* to interact with the α2δ -1 of the nerve terminals' voltage-gated calcium channels to decrease the calcium influx from the presynaptic nerve terminals thereby inhibiting excitatory neurotransmission. Exact mechanism of action for relief of moderate-to-severe RLS symptoms is unknown. Gabapentin is absorbed by low-capacity transporters located in the upper region of the small intestine, which may become saturated at clinically relevant doses and as the dose is increased the bioavailability of gabapentin decreases from 60% at doses of 300mg to ≤40% at 1600–4800 mg. Intestinal transits as well as the expression of these transporters are variably expressed in patient population leading to an erratic absorption. The short half-life of gabapentin *in vivo* ranges from 5 to 7 hours requiring the patient to take 3 to 4 doses per day in order to provide therapeutic concentrations.

GEn was engineered to overcome these variances in absorption. It is a prodrug of gabapentin absorbed from high-capacity nutrient transporters (monocarboxylate transporter type 1 and the sodium-dependent multivitamin transporter) found throughout the gastrointestinal tract. GEn is then primarily metabolized by nonspecific, enterocyte carboxylesterases and to a lesser extent by the liver into gabapentin isobutyric acid, acetaldehyde, and carbon dioxide in equimolar concentrations. Unlike conventional gabapentin, the transporters associated with GEn are not saturated at therapeutic doses producing a proportional dose of gapabentin that is derived from GEn. Upon hydrolysis of 600 mg GEn, 312 mg gabapentin is produced. Neither gabapentin nor GEn is substrate, inhibitor, or inducer of the major CYP450 system. In addition, GEn is not an inhibitor or substrate of p-glycoprotein *in vitro*.

The pharmacokinetic parameters of GEn and gabapentin are shown in Table 1.[1]

- Absorption:
    - Tmax 7.3 hrs with food

  - Bioavailability: 75% with food
  - Effects of food: increases bioavailability and delayed Tmax
- Distribution:
  - Vd: 76L
  - Protein binding: less than 3%
- Metabolism:
  - Intestinal tract: primary; lesser extent, liver
  - Metabolite, gabapentin (active drug) not appreciably metabolized
- Excretion:
  - Renal clearance: 5 to 7 L/hr
  - Renal excretion: 94%
  - Fecal elimination: 5%
  - Dialyzable: Yes, significant
  - Total body clearance: 6 to 9.3 L/hr
- Elimination half-life:
  - 5.1 to 6 hrs

Table 1 - Pharmacokinetic parameters of GEn and gabapentin[1,3,5]

Parameter	Gabapentin Enacarbil	Gabapentin
Bioavailability (%)		
Fasting	600 mg: 42 to 65	900 mg: 60
		1200 mg: 47
		2400 mg: 34
		3600 mg: 33
		4800 mg: 27
Fed	75	Increase 14% AUC
Tmax (hr)		
Fasting	5	2.7 to 3.3
Fed	7.3	N/A
Protein Binding	<3%	<3%
Metabolism	First-pass hydrolysis by enterocytes (primary); liver (lesser)	Not metabolized
Elimination (%)	Renal: 94 (unchanged); Feces: 5	Renal: 76 to 81 (unchanged); Feces: 10 to 23
Half-Life (hr)	5.1 to 6	5 to 7

FDA Approved Indication(s)

GEn is FDA approved for treatment of RLS and .

Potential Off-label Uses[2,5]

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

There are studies underway looking at GEn in the treatment of neuropathic pain and migraine prophylaxis.[2]

Current VA National Formulary Alternatives

Current formulary agents for treatment of restless leg syndrome are gabapentin immediate release and carbidopa/levodopa which are being used off-label and ropinirole which is FDA approved for the treatment of RLS.

Dosage and Administration[1]

For moderate-to-severe RLS
Dose for moderate-to-severe RLS is 600 mg daily taken with food. Patients who took higher dose of 1200 mg experienced more adverse reactions, but gained no additional benefit. GEn tablets should be swallowed whole and not split, crushed, or chewed.

For post herpetic neuralgia
The recommended dosage is 600 mg twice daily. GEn should be initiated at a dose of 600 mg in the morning for 3 days of therapy, and then increased to 600 mg twice daily (1,200 mg/day) on day four. In the 12-week principal efficacy study, additional benefit of using doses greater than 1,200 mg a day was not demonstrated, and these higher doses resulted in an increase in adverse reactions

Hepatic impairment
No adjustments are required for hepatic impairment.

Renal impairment
Clearance of gabapentin is approximately proportional to creatinine clearance. Dose adjustment is not necessary for patients with creatinine clearance (CrCl) ≥60 mL/min. For patients with CrCl 30-59 mL/min, the recommended initial dose is 300 mg per day and may be increased to 600 mg per day as needed. When CrCl is 15-29 mL/min, the recommended dose is 300 mg daily and 300 mg every other day when CrCl is <15 mL/min.

Hemodialysis
GEn is not recommended for patients on hemodialysis.

Elderly patients
The manufacturer states that dose adjustments based solely on age are not required, but dose may need to be adjusted based on age-related decline in renal function.

Drug Interactions[1,3]

- No known drug interactions found. GEn is not substrate, inhibitor, or inducer of the major CYP450 system. In addition, GEn is not an inhibitor or substrate of p-glycoprotein *in vitro*.
- From drug interaction studies conducted with GEn versus cimetidine and naproxen, there appears to be no significant pharmacokinetic interactions.
- No drug interactions are anticipated between GEn and substrates of the organic cation transporter type 2 (OCT2) or monocarboxylate transporter type 1 (MCT-1).

Drug-Lab Interactions

- No drug-lab interactions have been identified.

Efficacy[6-7]

Efficacy Measures

Restless Legs Syndrome:

Primary Measure

- International Restless Legs Severity (IRLS) Scale - investigator administered, patient rated severity of RLS by answering 10 questions regarding RLS symptoms. Each question has a set of five response options graded from no RLS impact (score =0) versus severe RLS impact (score=4). Overall score can range from 0-40. Higher scores signifying severe disease.
- Clinical Global Impression of Improvement (CGI-I) Scale - Investigator rated total improvement in symptoms from drug therapy on a scale of 0 – 7: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7= very much worse.
    - Relapse - worsening of RLS symptoms when IRLS score increases 6 points or more from IRLS baseline score of ≥15 and a rating of "much worse" or "very much worse" on the Clinical Global Impression of Change (CGI-C) Scale on 2 consecutive visits at least 1 week apart or withdrawal because of lack of efficacy.
    - Responders - subjects who have an IRLS total score ≤15 points at the end of study period, which decreased by 6 points from baseline and have an assessment of "much approved" or very much improved" based on the CGI-I scale.

Secondary Measures

- CGI-C Scale - investigator rated assessment of change on a scale of 0 – 7 of global clinical status, which is defined as a sense of well-being and ability to function in daily activities.
- Medical Outcomes Sleep (MOS) Scale - six item assessment of sleep disturbance, sleep adequacy, somnolence, quantity of sleep, snoring and/or awakening short of breath, or awakening with a headache.
- Investigator Designed Post-Sleep Questionnaire (PSQ) - queried sleep quality, next-day functioning, number of nights with RLS symptoms, number of nighttime awakening from RLS symptoms and duration of time awake from RLS symptoms over a time span.
- RLS quality of life (QoL) questionnaire - assesses the impact of RLS on daily life, emotional well-being, social and work life on a 0-100 point scale.
- Pittsburgh Sleep Diary (PghSD) - quantifies subjectively reported sleep and wake behaviors.
- Epworth Sleepiness Scale (ESS) - investigator administered assessment of severity of daytime sleepiness based on responses to 8 questions. Each question is scored on a scale of 0-3 (0= no chance of dozing, 1= slight chance of dozing, 2= moderate chance of dozing, 3= high chance of dozing) based on responses to 8 questions. Score ≥10 signified excessive daytime sleepiness.
- 24 Hour RLS Sleep Diary
- Polysomnography
- Adverse Events

Pivitol Trials: [7,8]

In a study performed by Kushida et al, subjects were randomized to receive 1200 mg GEn or placebo taken once daily. The purpose of the study was to assess the efficacy and tolerability of GEn in adults with moderate to severe primary RLS. Co-primary endpoints assessed during the study consisted of mean change from baseline IRLS total score and the proportion of investigator rated responders (very much improved or much improved on the CGI-I). The secondary endpoints assessed the tolerability of the medication by looking at clinical laboratory data, adverse events, vital signs and the post-sleep

questionnaire (PSQ) which was a tool designed by the investigators to assess sleep quality in patients suffering from RLS symptoms. CGI-I, PghSD, RLS pain scale, RLSQoL and MOS sleep scale were also assessed as secondary endpoints. Men and women aged 18 years or older with a diagnosis of moderate to severe primary RLS symptoms 15 days during the month prior to screening were included in the study. Patients presenting with evidence of secondary RLS, body mass index 34 kg/m^2 or greater, being treated for moderate to severe depression, primary sleep disorders, or neurologic disease, movement disorders, history of RLS symptom augmentation, end-of-dose rebound with previous dopaminergic treatment or pregnant patients were excluded from the study. Originally patients with daytime RLS symptoms were excluded, but later included to aid in the generalizability of the study. A sample size of 105 patients per treatment group was determined with a power of 81% to detect a significant difference of -4.0 in the IRLS scale in the two groups. Upon completion of the study, GEn was determined to be superior to placebo for both co-primary endpoints by week 1 and throughout the remainder of the 12 week trial.[8]

Lee et al conducted a 12-week, randomized, double-blind, placebo-controlled, multicenter study in the United States to assess the efficacy and tolerability of GEn 1200 mg and 600 mg compared to placebo. The co-primary outcome measures were the mean change in IRLS total score from baseline to 12 weeks and the proportion of responders rated as "much improved" or "very much improved" in the CGI-I scale.[7] The study consisted of 322 subjects randomized 1:1:1 to receive GEn 1200 mg (111 patients), GEn 600 mg (115 patients) or placebo (97 patients) once daily. IRLS score significantly improved in the GEn 1200 mg group compared to placebo. Week 12 IRLS last observation carried forward (LOCF) for the GEn 1200 mg group was (baseline: 23.2 [5.32]); week 12: 10.2 [8.03]; with mean change from baseline of -13.0 [9.12]. Placebo (baseline: 23.8 [4.58]; week 12: 14.0 [7.87]; mean change from baseline of -9.8 [7.69]. The adjusted mean treatment difference (AMTD) for change from baseline was -3.5 (95% CI: -5.6, -1.3; P=0.0015). Based on the investigator rated CGI-I scores at week 12, 77.5% of the patients in the GEn 1200 mg group were responders ("much" or, "very much improved") versus 44.8% of the placebo group; adjust OR: 4.3 (95% CI: 2.34, 7.86; P<0.0001).[7]

Similar results were seen with the GEn 600 mg group. Mean IRLS total score at week 12 LOCF (baseline: 23.1 [4.83]; week 12: 9.3 [7.77]; change from baseline to week 12 LOCF: -13.8 [8.09]) and when compared to placebo, AMTD for change from baseline was -4.3 (95% CI: -6.4, -2.3; P<0.0001). Based on the CGI-I, investigator rated 72.8% of the patients from GEn 600 mg group as responders at week 12 compared to placebo 44.8% of patients: adjusted OR: 3.3 (95% CI: 1.84, 5.99; P<0.0001). GEn 1200 mg also showed statistical significant in regards to MOS Sleep Scale with improvements in sleep disturbances, sleep quantity, sleep adequacy, and daytime somnolence. All 5 PSQ sleep outcomes significantly improved with GEn 1200 mg and 600 mg when compared to placebo. The adverse effects most commonly seen with the GEn treatment groups were dizziness and somnolence, but none were significant.[7]

Bogan et al conducted a 24 week single-blinded phase followed by a 12 week randomized double-blinded placebo controlled phase study. The trial was conducted in the United States and employed GEn titrated to 1200 mg daily. Pertinent inclusion criteria were a diagnosis of RLS based on the International RLS Study Group Criteria (Appendix 1), IRLS score ≥15 at baseline, RLS symptoms for ≥15 nights in the month before screening, symptomatic RLS ≥4 nights during the 7-day screening period and creatinine clearance of ≥60 ml/min. Patients were required to discontinue dopamine agonists or gabapentin or any other RLS treatments for 2 weeks or more prior to baseline. Pertinent exclusion criteria were evidence of secondary RLS, body mass index of ≥34, moderate or severe major depressive disorder and sleep

disorders, neurologic disease, or movement disorders other than RLS. Primary outcome was relapse of RLS.[6]

In the single-blinded treatment phase, 311 patients received GEn titrated to 1200 mg. Ninety patients withdrew from the study (38 adverse events, 24 withdrew consent, 13 lack of efficacy, 5 lost to follow-up, 6 noncompliance, 3 other, 1 death); 221 patients completed the single-blinded study and there was an improvement in IRLS total score with mean (SD) change from baseline to week 24 of -15.5 (9.16). Seventy-eight (25.1%) of the 311 patients received a score of "much improved" and 170 (54.7%) of 311 received "very much improved" on the CGI-I scale. Out of the 221 patients who completed the study, 194 were responders to GEn, and were entered into the 12 week parallel-group, double-blinded phase (96 in the GEn group and 98 in the placebo group).[6] Significantly smaller proportion of GEn patients experienced relapse in the double-blinded phase compared to the placebo (9% [9/26] versus 23% [22/97]; OR, 0.35 (95% CI: 0.2-0.8; P=0.02).[6]

At week 36, patients in the treatment group had significantly smaller mean changes of RLS symptoms from baseline compared to the placebo group based on the MOS Sleep Scale: sleep disturbance (2.3 [18.32] versus 10.2 [19.02]; adjusted mean treatment difference (AMTD), -7.0; P=0.007); sleep adequacy (-4.3 [22.28] versus -11.6 [24.01]; AMTD, 7.7; P=0.02). There was no statistical difference with daytime somnolence and sleep quantity between the GEn group and placebo. PSQ showed significantly greater proportion of patients in the treatment group reporting fewer nights with RLS (P=0.05), fewer night-time awakenings (P=0.04), and fewer hours awake per night due to RLS symptoms (P=0.02). There was no statistical difference in daytime somnolence or sleep quality. RLS QoL questionnaire showed no statistical significance in overall life-impact score. Assessment of safety and tolerability showed no statistical significance in adverse events between the two groups, but most common side effect with GEn was somnolence and dizziness.[6]

Overall, GEn 1200 mg was generally well-tolerated and improved RLS symptoms compared with placebo. However, the 1200 mg GEn dose is not currently approved by the FDA and the two studies reviewed here did not include the 600 mg dose in the primary endpoint. One of the studies did show statistical significance in improving RLS symptoms in comparison with placebo as a secondary endpoint.[6]

Long Term Safety and Efficacy Study[12]

Ellenbogen et al conducted an open label, multicenter, 52-week extension study assessing the long term safety and efficacy of GEn.[12] The study involved subjects from 4 previously randomized, double-blind placebo controlled studies of subjects who received either 12 months of GEn or placebo.[6-8, 11] All patients received 52-weeks of GEn 600-1800 mg; dose was at the discretion of the investigators based on efficacy and tolerability. Subjects were stratified in 1 of 2 groups: GEn naïve (those who were never exposed to GEn in the previous studies) and non-naïve groups. Efficacy was determined by mean change in IRLS score from the original studies' baseline and those who were responders on the investigator rated CGI-I scale at week 52. Safety assessment included incidences and severity of treatment associated adverse events.

A total of 573 subjects participated in the study; 197 GEn naïve and 376 GEn non-naïve. Overall, 386 patients completed the 52 week study; 71 and 116 subjects from the GEn naïve and non-naïve groups, respectively, withdrew from the study. Mean baseline IRLS score from the four studies and in the GEn naïve and non-naïve groups was 23.2. At 52-weeks, mean change in IRLS score from baseline was -15.2 [8.85]. Mean change in IRLS score at 52-weeks was -14.8 [8.64] and –15.4 [8.96] in the GEn naïve and

non-naïve groups, respectively. In addition, 84.8% of all subjects and 82.2% and 86.2% of GEn naïve and non-naïve patients were responders on the CGI-I scale, respectively. Four hundred and fifty-nine (80.1%) patients experienced ≥1 adverse events (AE) (GEn naïve, 82.2%; GEn non-naïve, 79.0%). Similar to previous studies, the most commonly reported AEs were somnolence (113 subjects [19.7%]) and dizziness (66 subjects [11.5%]). Incidences of somnolence and dizziness were higher in the GEn naïve group 54 [27.4%] and 39 [19.8%], respectively, versus the non-naïve group 59 [15.7%] and 27 [7.2%]. A total of 64 subjects withdrew from the study because of AEs. Twenty subjects reported severe AEs, none of which were considered treatment related by the investigators. Other reported AEs include headaches, fatigue and nausea. Overall, the study showed GEn 600-1800 mg to be well tolerated and efficacious for up to 52 weeks in patients in GEn naïve and non-naïve patients with RLS.[12]

Phase 2 Trial[13,14]

In a phase 2b randomized, double-blind, placebo-controlled trial by Walters et al, treatment-naive individuals aged 18 to 69 years with a diagnosis of moderate-to-severe primary RLS were given either GEn 600 mg, 1200 mg or placebo. A total of 95 subjects were selected and randomized to receive GEn 1200 mg (n = 33), GEn 600 mg (n = 29), or placebo (n=33). IRLS score change from baseline at day 7, CGI-I score, PSQ and SD were used to determine efficacy of the trial medication with the change from baseline IRLS score at day 14 as the primary endpoint. Upon completion of the trial, the 1200 mg dose showed efficacy with significant improvement at both day 7 and day 14 on the IRLS score (GEn: -14.2, placebo: -7.8 at day 7 and GEn: -16.1, placebo: -8.9 at day 14). The 600 mg GEn on the other hand did not significantly improve symptoms on the IRLS score when compared with placebo (GEn: -9.1, placebo: -8.9). GEn 1200 mg was also found to be efficacious when compared with placebo on the CGI-I scale (GEn: 81.3% vs. placebo 48.5%; P<0.0001), whereas GEn 600 mg was not (GEn 58.6% vs. placebo 48.5%).[13]

In another phase 2 study by Kushida et al, patients were randomized to receive 1800 mg per day GEn or placebo in a double-blinded, placebo-controlled, crossover fashion. Patients were included with a primary RLS diagnosis and were treatment-naïve. GEn 1800 mg daily was shown to be efficacious on both the IRLS and CGI-I scales (GEn -12.1 vs. placebo - 1.9; (P<0.0001) and GEn 79.5% vs. placebo 14.7% (P<0.0060) using the adjusted p-value (adjustments in p-value were done using the Holm-Bonferroni methodology).[14] (See Appendix 2)

Use in Post Herpetic Neuralgia

Only one study assessing the use of GEn in the use of post herpetic neuralgia (PHN) was found. Included in the study were 221 adults, aged 23–87, with diagnosis of herpes zoster infection and concomitant PHN. The study consisted of 116 patients who received gabapentin treatment and 101 patients were randomized and received at least one dose of either GEn 1200 mg (n = 47) or placebo twice daily (n = 54). After a 7 day baseline period, all participants received 11-days of gabapentin then entered in a double-blind, randomized design to receive 1200 mg GEn or placebo twice a day. Efficacy was measured using patient diaries rating their pain from 1 to 10, where 10 being the worst pain imaginable. After patient randomization, a significant improvement was seen in pain in the GEn group when compared with placebo (P = 0.0112). This was more of a hypothesis generating study as all patients received 11 days of gabapentin prior to the randomization stage and the length of the trial was only 14 days. The dose used in the trial was also much larger than the current FDA recommended dose for treatment of RLS.

Adverse Events (Safety Data)[8,13,14]

Table 2 - Common adverse events separated by study and dose

	Kushida neurology 2009[8]		Kushida Sleep 2009[14]		Walter 2009[13]		
	1200 mg (%)	placebo (%)	1800 mg (%)	placebo (%)	600 mg (%)	1200 mg (%)	placebo (%)
somnolence	26.5	7.4	30.6	2.8	14	36	15
dizziness	19.4	4.6	27.8	5.6	14	18	3
headache	14.2	11.1	5.6	2.8	10	0	3
fatigue	9.7	1.9	5.6	0			
nausea	7.9	2.8	5.6	0			
nasopharyngitis	6.2	5.6	0	8.3			
feeling abnormal	4.4	0.9					
irritability	4.4	0					
sedation	4.5	0			0	9	0
dyspepsia	3.6	2.8					
muscle spasms	3.6	0.9					
myalgia	3.6	0					
sinus congestion	3.5	1.9					
vertigo	3.6	0					
vomiting	3.6	1.8					
back pain	2.7	1.8					
cough	2.7	1.9					
dry eye	2.7	0					
flatulence	2.7	0					
increased appetite	2.7	0.9					
insomnia	2.7	3.7	5.6	0	0	6	0
lethargy	2.7	0					
libido decreased	2.7	0.9					
pain	2.7	2.8					
rash	2.7	0.9					
URI	2.7	6.5					
Any			77.8	38.9			
balance disorder			8.3	0	0	6	0
dry mouth			5.6	0			
hypoesthesia			5.6	0			
diarrhea					3	6	0

Table 3 - Common adverse events separated by study and dose

Adverse Effects	Bogan (Single-blind)[6]	Bogan (Double-blind)[6]	Lee[7]	Ellenbogan[12]
Somnolence %				
600 mg			21.7	
1200 mg	29.8	3	18	
Placebo		1	2.1	
Naïve				27.4
Non-naive				15.7
Dizziness %				
600 mg			10.4	
1200 mg	22.1	2	24.3	
Placebo		1	5.2	
Naïve				19.8
Non-naive				7.2
Headaches %				
600 mg			14.8	
1200 mg	12.6	4	13.5	
Placebo		2	8.3	
Naïve				7.6
Non-naive				6.9
Fatigue %				
600 mg			5.2	
1200 mg			2.7	
Placebo			5.2	
Naïve				7.6
Non-naive				4.4
Nausea %				
600 mg			5.2	
1200 mg	6.4	3	5.4	
Placebo		2	4.2	
Naïve				5.1
Non-naive				5.3
Nasopharyngitis %				
600 mg			11.3	
1200 mg	8.9	3	9.9	
Placebo		5	7.3	
Naïve				4.1
Non-naive				5.3

Deaths and Other Serious Adverse Events

There were no reported deaths directly related to GEn use.

Contraindications[1]

None

Warnings and Precautions[1,9]

The most common warnings and precautions for GEn use are somnolence, sedation and driving impairments. Patients are warned not to drive until they have used the medication long enough to determine if use of the medication will impair their ability to drive. Patients should also be warned that GEn and gabapentin products are not interchangeable. Additional warnings exist regarding suicidal thoughts or behaviors that might occur while on GEn as these symptoms have been noted in patients taking gabapentin. Patients should be monitored for these types of behaviors or thoughts. During animal studies, there was a high incidence of acinar pancreatic cancer found in male but not female rats. After a review by the FDA it was determined that acinar pancreatic cancer was very rare in humans and acinar pancreatic cancer can appear spontaneously in rats and was determined not be a significant concern for humans.

Sentinel Events

No data

Look-alike / Sound-alike (LASA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

LASA for generic name <*Gabapentin enacarbil*>: <*gabapentin, Gabitril*>
LASA for trade name <*Horizant*>: <*Hyzaar, Hilzentra*>

The potential for medication errors may be increased due to overlapping labeled and off label uses associated with gabapentin, pregabalin and gabapentin enacarbil.

Pharmacoeconomic Analysis

There is no pharmacoeconomic data currently available.

Conclusions[5-8, 12-14]

Several studies of GEn have shown efficacy over placebo in patients with RLS. Improvement in RLS symptoms was observed within 7 days of starting treatment. Three studies demonstrated 1200 mg/day GEn significantly reduced IRLS total score and improved CGI-I compared with placebo. The 600 mg dose was shown efficacious in 2 studies, but in one phase 2 trial it failed to prove efficacy when compared with placebo. These results are similar to those seen with dopamine agonists, although there are currently no head-to-head trials comparing GEn and any dopamine agonists. The new gabapentin delivery system (GEn) is unique and does have certain advantages over the current gabapentin formulation including higher bioavailability and consistent serum concentrations at higher doses, although there are no studies showing its superiority in the treatment of RLS when compared to other therapeutic options.

There does not appear to be sufficient evidence to support the use of GEn as a first line agent due to limited comparative data to immediate release formulations and other dopamine agonists as well as long term safety and efficacy. There seems to be no pharmacokinetic advantage of the GEn 600 mg dose over the immediate release formulation as the bioavailabilty is similar at the 600-1200 mg ranges between both products. The association of an increased absorption rate with GEn is not seen until doses ≥ 1200 mg are employed. GEn may be considered in patients with moderate to severe RLS who have failed all other treatment options including gabapentin immediate release and dopamine agonists. Due to the lack of active comparator trials, there is no evidence to support superiority of GEn. Disadvantages of GEn include limited head to head trials looking at other possible treatment options for RLS. GEn is also very expensive and the research supporting the FDA approved dose of 600 mg daily has not been proven superior to the currently available immediate release formulation of gabapentin and should only be considered after failure of all other currently available agents used to treat RLS. There is no evidence to support the preferential use of GEn over immediate release gabapentin or pregabalin in treatment of trigeminal neuralgia, neuropathic pain, seizure disorders, diabetic neuropathy and fibromyalgia.

References:

1. Product information. Horizant (gabapentin enacarbil). Research Triangle Park, NC: GlaxoSmithKline, December 2011.
2. Backonja MM, Canafax DM, et al. Efficacy of gabapentin enacarbil vs placebo in patients with postherpetic neuralgia and a pharmacokinetic comparison with oral gabapentin. Pain Medicine. 2011; 12:1098-1108.
3. Product information. Neurontin (gabapentin). New York City, NY: Pfizer, September 2011.
4. Yaltho TC and Ondo WG. The use of gabapentin enacarbil in the treatment of restless legs syndrome. Thr Adv Neurol Disord. 2010; 3(5):269-275.
5. Hayes WJ, Lemon MD, Farver DK. Gabapentin enacarbil for treatment of restless legs syndrome in adults. Ann Pharmacother. 2012; 46:229-39.
6. Bogan RK, Bornemann MA, Kushida CA, et al. Long-term maintanence treatment of restless legs syndrome with gabapentin enacarbil: a randomized controlled study. Mayo Clin Proc. 2010;85:512-21.
7. Lee DO, Ziman RB, Perkins AT, et al. A randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of gabapentin enacarbil in subjects with restless legs syndrome. J Clin Sleep Med 2011;7:282-92
8. Kushida CA, BeckerPM, Ellenbogen AL, et al. Randomized, double blind, placebo controlled study of XP13512/GSK1838262 in patients with RLS. Neurology 2009;32:311-20.
9. Center For Drug Evaluation And Research. Summary review document for gabapentin enacarbil. www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022399Orig1s000SumR.pdf (Accessed 2/1/12)
10. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med.2003;4(2):101-19.
11. Zomorodi K, Lal R, Atluri H, et al. A randomized, double-blind, placebo controlled, dose-response study to assess the pharmacokinetics and tolerability of gabapentin enacarbil in subjects with restless legs syndrome. J Clin Pharmacol 2009:49:1122.

12. Ellenbogen AL, Thein SG, Winslow DH, et al. A 52-week study of gabapentin enacarbil in restless legs syndrome. Clin Neuropharmacol 2011;34:8-16.
13. Walters AS, Ondo WG, Kushida CA, et al. Gabapentin enacarbil in restless legs syndrome: a phase 2b, 2-week, randomized, double-blind, placebo-controlled trial. Clin Neuropharmacol 2009;32:311-20.
14. Kushida CA, Walters AS, Becker P, Thein SG, Perkins AT, Roth T, et al. A randomized,double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients with primary restless legs syndrome. Sleep. 32: 159-168.

Prepared March/2012 by Meeta Patel, PharmD, BCPS, CDE; Ryan Wiest PharmD, MBA; Andrea Matsuda PharmD; Yenh Long PharmD

Appendix: Clinical Trials

Appendix 1[10]

- Four criteria are essential to the diagnosis of primary RLS based on the International RLS Study Group Diagnostic Criteria for RLS:
    - An urge to move the legs:
        - Usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs.
    - The urge to move or unpleasant sensations:
        - Begin or worsen during periods of rest or inactivity such as lying or sitting
        - Are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
        - Are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present

Appendix 2 Randomized, placebo controlled trials

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Measurements	Efficacy Results	Author's conclusions
Kushida (2009)[14] **Crossover** R, DB, PC, C Phase 2 trial 9 US clinical sites	Inclusion criteria: Men and women with Dx of RLS with no prior treatment for RLS.	GEn 1800 mg or placebo nightly	38 (22 female), average age 50.1 years	IRLS score change from baseline at day 7, CGI-I score, PSQ, SD, polysomography	IRLS: GEn-12.1± 6.5 vs placebo -1.9 ± 6.3; P<0.0001 CGI-I: GEn vs. placebo "much improved" (79.5% vs 14.7%; adjusted P<0.0060) , "very much improved" (85.3% vs 14.7%; adjusted P<0.0059)	GEn proved efficacious on both the IRLS and CGI-I measurements vs. placebo at the earliest time point examined. IRLS scores showed improvement only after 2 days at target dose of GEn which implies that lower doses might be beneficial and should be explored.
Kushida (2009)[8] **FDA Trial** R, DB, PC Phase 3 trial 22 US clinical sites	Inclusion criteria: Men and women with Dx of moderate to severe primary RLS with symptoms 15 days during the month prior to screening	GEn 1200 mg or placebo daily	222 (132 female), average age 51.1 years	IRLS score, CGI-I score RLSQol, SD, PSQ, MOS, PghSD, RLS pain scale	IRLS: At week 12, baseline change in IRLS score was GEn –13.2, placebo -8.8 (p=0.0003) CGI-I: Percent responders ("much improved or very much improved") GEn 76.1%; placebo 38.9% (p<0.0001)	Patients showed significant improvement in the IRLS and CGI-I scores while taking GEn when compared with placebo. These results were similar when compared with mean changes on the IRLS score observed with ropinirole (0.25 mg to 4 mg) and pramipexole (0.25 mg, 0.5 mg, and 0.75 mg).
Bogan (2010) [6] Long term safety/efficacy R, SB, DB, PC 27 US clinical sites	Inclusion criteria: men and non-pregnant women ≥18 years old, with Dx of moderate to severe primary RLS, IRLS score ≥15 at baseline and with symptoms ≥15 days during the month prior to screening and CrCl of ≥60 ml/min	SB: All patients received GEn titrated to 1200 mg DB: Responders in the SB randomized to continue GEn 1200 mg or receive placebo	194 (114 female). average age GEn, 50.7 years; placebo, 52.7 years	SB: IRLS score, CGI-I score, CGI-C score, RLSQoL, MOS sleep scale, PSQ DB: Relapse of RLS, IRLS score, CGI-I score, MOS sleep scale, PSQ, RLSQoL	Relapse: GEn 9%, placebo 23% (P = 0.02) IRLS: GEn -3.2, placebo -1.4 (P=0.03) CGI-I: GEn 75%. placebo 67%	Patients had lower rates of relapse with GEn compared to placebo. GEn is efficacious and was shown to have long-term tolerability (36 weeks).
Lee (2011)[7] Phase 3 R, DB, PC 28 US clinical sites	Inclusion criteria: men and non-pregnant women ≥18 years old, with Dx of moderate to severe primary RLS, IRLS score ≥15 at baseline and with symptoms ≥15 days during the month prior to screening and CrCl of ≥60 ml/min	GEn 1200 mg, GEn 600 mg or placebo	325 (192 female), average age GEn 1200 mg, 49.5 years; GEn 600 mg, 48.3 years; Placebo 49.1 years	IRLS, CGI-I, MOS, PSQ	IRLS: GEn 1200 mg -13.0, (p=0.0015); GEN 600 mg -13.8, (p<0.0001); placebo -9.8. CGI-I: GEn 1200 mg 77.5%, (p<0.0001); GEN 600 mg 72.8%, (p<0.0001); placebo 44.8%.	Compared to placebo, GEn 1200 mg and 600 mg significantly improved RLS symptoms after 12 weeks of treatment. Adverse effects commonly seen were somnolence and dizziness but this was not statistically significant.

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Measurements	Efficacy Results	Author's conclusions
Ellengoban (2011)[12] R, DB, E	Inclusion criteria: includes all 4 parent studies: men and non-pregnant women ≥18 years old, with Dx of moderate to severe primary RLS, IRLS score ≥15 at baseline and with symptoms ≥15 days during the month prior to screening and CrCl of ≥60 ml/min	GEn 600-1800 mg	573 (336 female), average age 50.2 years	AEs, IRLS score, CGI-I score	IRLS:change from baseline, CGI-I naïve,-14.8; CGI-I non-naïve -15.4 CGI-I: GEn naïve 82.2%; GEn non-naïve 86.2% AEs: 80.1% patients experienced ≥1 AE (GEn naïve, 82.2%; GEn non-naïve 79.0%). Non-naïve patients had higher rates of somnolence, dizziness, fatigue and headaches.	Study showed GEn doses of 600-1800 mg are generally tolerated and efficacious for up to 52 weeks in patients who have RLS who are GEn naïve and non-naïve.
Walters (2009)[13] R, DB, PC Phase 2b trial 14 US clinical sites	Inclusion Criteria: treatment-naive aged 18 to 69 with a moderate-to-severe Dx of primary RLS and an IRLS total score of 15 or higher at the end of baseline.	GEn 600 mg, 1200 mg or placebo	95 (59 female) average age 50.5 years	IRLS, CGI-I score, PSQ and SD, change from baseline IRLS score at day 14 as the primary endpoint.	IRLS: GEn 1200 mg -14.2, placebo -7.8 at day 7; GEn -16.1, placebo -8.9 at day 14; GEn 600 mg -9.1, placebo -8.9 CGI-I: GEn 1200 mg 81.3% (P<0.0001), placebo 48.5%; GEn 600 mg 58.6%, placebo 48.5%	Study showed evidence of short-term efficacy of GEn at 1200 mg in treating moderate-to-severe primary RLS, but failed to show efficacy on both the IRLS and CGI-I scales for the 600 mg dose.

GEn=Gabapentin Enacarbil; PC = placebo-controlled ;DB = double-blind; E = extension; IRLS = International Restless Legs Syndrome scale; C = crossover; CGI-C = Clinical Global Impression of Change; CGI-I = Clinical Global Impression–Improvement scale, MOS = Medical Outcomes Study; PghSD = Pittsburgh sleep diary; PGIT = Patient Global Impression of Therapy; PSQ = post-sleep questionnaire; R = randomized; RLS = restless legs syndrome; RLSQoL = Johns Hopkins RLS quality of life questionnaire, SB = single-blind; SD = subject diary