Gabapentin enacarbil Improves Restless Legs Syndrome (RLS) Symptoms and Subjective Measures of Sleep in Subjects with Primary RLS with and without Severe Sleep Disturbance: Secondary Analyses from Two Studies

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Introduction
− Symptoms of Restless Legs Syndrome (RLS) negatively impact sleep, with more than 75% of patients with RLS reporting at least one sleep-related symptom. Many patients with RLS report performance-related effects, possibly resulting from sleep disruption (e.g., daytime sleepiness, difficulty concentrating).
− Gabapentin enacarbil (GE) is a transport-prodrug of gabapentin under investigation for the treatment of moderate-to-severe primary RLS.
− GE is absorbed throughout the large and small intestine by high-capacity nutrient transporters and provides sustained, dose-proportional gabapentin exposure.

Methods
Study Design
Data were integrated for the GE 1200-mg and PBO treatment groups from two studies:
− LanePort, Inc. protocols 10350 and 10360 (ClinicalTrials.gov NCT00989003 and NCT00983032). Subjects were randomized to receive GE 1200 mg (± 600 mg extended-release tablets) or matching PBO once daily at 5 pm with food for 12 weeks.
− As GE 600 mg was only assessed in study 10350, it was not included in the analysis.
− Subjects were divided into two subgroups based on the Internal Restless Legs Scale (IRLS) at baseline: severe/very severe sleep disturbance at moderate-to-no sleep disturbance.

Assessment
− Coprimary endpoints at Week 12 LOCF:
− mean change from baseline in IRLS total score
− proportion of responders (patients who improved 40% or ‘very much’) as defined in the Investigated Clinical Global Improvement Improvement [6] study.
− Secondary endpoints to assess sleep disturbances Week 12 LOCF:
− Medicos Outcomes Study (MOS) Sleep Scale: mean change from baseline in the four domains of sleep disturbances, sleep quantity, sleep quality, sleep adequacy, and daytime dysfunction.
− Post-Sleep Questionnaire (PSQ): responses on the three items specifically related to sleep disturbances were analyzed at baseline and Week 12 LOCF: overall quality of sleep over the past week, number of nighttime awakenings from RLS symptoms, and time awake due to RLS symptoms.
− Tolerability assessments included treatment-emergent adverse events (TEAEs) and serious AEs.

Statistical Analyses
− Safety data were summarized for the safety population, which comprised all subjects who received at least one dose or portion of a dose of study medication.
− Efficacy outcomes were performed on the modified intent-to-treat (mITT) population, which comprised all subjects in the safety population who also had baseline and at least one post-baseline PBO assessment.
− Robust outcomes were analyzed as:
− change from baseline data using an ANCOVA model, adjusted for baseline IRLS score, pooled sites, study, and treatment

Results
Subjects
− Overall, 432 subjects were randomized (GE 1200 mg = 227; PBO = 205) and 427 subjects (GE 1200 mg = 223; PBO = 204) completed the study.
− The mITT population comprised 427 subjects (GE 1200 mg = 223; PBO = 204).
− Subject demographics and baseline characteristics were similar across treatment group (Table 1).

Conclusions
− Interim analyses from two PBO-controlled studies indicate that GE 1200 mg once daily significantly improves RLS symptoms compared with PBO in subgroups of subjects with moderate-to-severe primary RLS with either severe/very severe or moderate-to-no sleep disturbance.
− Significant improvements in subjective sleep outcomes were observed with GE 1200 mg compared with PBO for IRLS scores in subjects with either severe/very severe to moderate-to-no sleep disturbance, and on the PSG in subjects with severe/very severe sleep disturbance.
− GE 1200 mg is generally well tolerated.

Tolerability
− The most commonly reported AE was somnolence (GE 1200 mg: 31%; PBO: 15%), dizziness (GE 1200 mg: 21%; PBO: 10%), and headache (GE 1200 mg: 14%; PBO: 10%).
− Twenty-six subjects withdrew due to an AE (GE 1200 mg: 17%; PBO: 9).
− The majority of AEs were rated as mild or moderate in intensity.

Disclosures
The authors were compensated by Henning Inc., Quest Diagnostics, Research Triangle Park, NC, and completed the investigational studies described above. The authors, and their immediate family members, have received compensation from Allergan, GlaxoSmithKline, Impax Pharmaceuticals, Novartis, and Schwatz. EB has received compensation from GlaXoSmithKline. WG O has received compensation from GlaXoSmithKline. CA K has received compensation from Stanford University, GlaXoSmithKline, XenoPort, Merck, Pacific Medico, and Ventus. NW, ST K and CKC are employees of GlaXoSmithKline.

References

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