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REVIEW

Gabapentin enacarbil for the treatment of moderate to severe primary restless legs syndrome (Willis-Ekbom disease): 600 or 1,200 mg dose?

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Abstract: Gabapentin enacarbil is a prodrug of the anticonvulsant gabapentin. The efficacy and safety of gabapentin enacarbil for the treatment of moderate to severe primary restless legs syndrome (RLS) has been evaluated in several clinical trials in the United States and Japan. Although most clinical trials assessed gabapentin enacarbil at doses greater than 600 mg/day and demonstrated the overall safety and efficacy (defined as improvements in the coprimary endpoints of the international RLS rating scale [IRLS] total score and Clinical Global Impression-Improvement response), the US Food and Drug Administration approved the 600 mg once-daily dosage because doses higher than 600 mg/day were considered to provide no additional benefits and were associated with higher rates of adverse events, such as somnolence and dizziness. Nonetheless, the results of clinical trials and post hoc meta-analyses have indicated that the 1,200 mg once-daily dosage was the most validated gabapentin enacarbil treatment for not only subjective RLS symptoms but also severe sleep disturbance associated with RLS. A Japanese dose-finding study showed that 900 mg/day, the intermediate dose between 600 and 1,200 mg, failed to show a significant improvement in IRLS total score, probably because many of the patients who discontinued treatment did so early, suggesting that a half-landing dose may cause more adverse effects than favorable ones in some RLS patients early in the treatment. Gabapentin enacarbil may have two distinct therapeutic doses for the treatment of RLS: 600 mg/day or lower doses for the treatment of subjective RLS symptoms and 1,200 mg/day or higher doses for the treatment of both subjective RLS symptoms and associated problems such as severe sleep disturbances.

Keywords: gabapentin enacarbil, restless legs syndrome, meta-analysis, dose-finding

Introduction

Restless legs syndrome (RLS) or Willis-Ekbom disease is a sleep-related movement disorder characterized by an irresistible urge to move, which usually involves the legs, although other parts of the body could also be involved.[1,2] The four essential criteria used for the diagnosis of RLS are an urge to move the legs with or without abnormal sensations, worsening of symptoms at rest, improvement in symptoms with activity, and worsening of symptoms in the evening/night.[2] Typically, patients with RLS report gradual worsening of symptoms with age, family history of RLS, and periodic limb movements (PLM) during sleep.[2] Most patients are diagnosed with primary RLS, although some have secondary RLS, which is caused by various factors including iron deficiency, pregnancy, renal failure, peripheral neuropathy,

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or certain medications.[2–7] RLS is twice as common in women as in men, and it may affect any age, including children.[8,9] It is more common in older adults than in younger adults.[8,9] It occurs with a lower prevalence in African, Asian, and South Eastern European populations than in Northern European and North American populations.[10,11] Although the reported prevalence varies and the exact rate is controversial, the estimated prevalence in Western countries ranges from 4% to 15%.[11] In the United States, it is estimated that approximately 2%–3% of adults have moderate to severe RLS.[12,13] In Japan, the reported prevalence of RLS is 1%–4% in the general population,[14–16] and 13.5% of these patients are thought to have severe disease.[15]

Patients with mild symptoms do not require treatment, but RLS should be treated when symptoms impair quality of life, daytime or social functioning, or sleep.[17–22] There are multiple therapeutic options for the treatment of RLS. Dopamine agonists are generally considered first-line agents for treatment of moderate to severe RLS.[17–22] Polysomnographic studies of patients on dopamine agonists show dramatic improvement in PLM during sleep, but neither ropinirole nor pramipexole has demonstrated improved sleep architecture.[23–25] Moreover, the adverse effects of dopamine agonists often limit their use. Some patients report augmentation of RLS symptoms with long-term dopaminergic treatment.[26,27] Augmentation results in an earlier onset and possible intensification of symptoms.[26,27] Other medications used for the treatment of RLS include levodopa, opioids, benzodiazepines, and anticonvulsants such as gabapentin.[17–22]

Gabapentin is a gamma aminobutyric acid (GABA) analog used in the treatment of seizures and pain syndrome. The mechanism of action of gabapentin in epilepsy and neurogenic pain remains unclear. Despite its structural similarity to GABA, gabapentin does not interact directly with GABA receptors. Instead, it binds with high affinity to the alfa-2-delta subunit of the voltage-activated calcium channels.[28–30] It is unclear how this binding of gabapentin is linked to its therapeutic effects. However, it is believed that this binding results in inhibition of calcium entry through voltage-dependent calcium channels, which in turn leads to normalization of the release of neurotransmitters, including the excitatory neurotransmitter glutamate.[29,30] A recent evidence-based review considered gabapentin efficacious treatment for RLS.[31] Furthermore, four randomized controlled clinical studies demonstrated that gabapentin was significantly superior to placebo and was as effective as ropinirole and levodopa in improving symptoms in primary and uremic RLS.[32–35] This drug might be useful for patients who have the secondary form of RLS associated with polyneuropathy, who report their sensory discomfort as pain.[18,19] Because large multicenter clinical trials for gabapentin in RLS are lacking, its use in RLS is off-label. Unfortunately, gabapentin has an unfavorable pharmacokinetic profile that limits its use in clinical practice. The gabapentin absorption pathway in the upper intestine is prone to saturation at high doses; thus, its plasma level is not dose-dependent.[36,38] The expression level of gabapentin transporter varies widely among individuals, which explains the difference in plasma gabapentin levels between patients, and gabapentin has a short plasma half-life, requiring frequent dosing.[36,37]

To overcome the pharmacokinetic limitations of gabapentin, the prodrug formulation gabapentin enacarbil has been developed. In April 2011, the US Food and Drug Administration (FDA) approved gabapentin enacarbil 600 mg once daily for the treatment of moderate to severe primary RLS in adults. The Japan Ministry of Health, Labor and Welfare also approved gabapentin enacarbil at the same dosage for the treatment of moderate to severe primary RLS in January 2012. In June 2012, the FDA also approved gabapentin enacarbil 1,200 mg/day (600 mg twice daily) for the management of postherpetic neuralgia. At present, a randomized, double-blind, placebo-controlled clinical trial is being conducted at 42 sites in the United States to compare the efficacy and safety of gabapentin enacarbil at lower doses (450 and 300 mg/day) in addition to the already approved dose of 600 mg versus placebo for the treatment of subjects with moderate to severe primary RLS.[40] This study is a postmarketing commitment and a condition of the approval of gabapentin enacarbil in the United States. At this time, the United States and Japan are the only countries that have approved gabapentin enacarbil. So far, gabapentin enacarbil has been used for the treatment for RLS for more than 1 year. The results of the majority of Phase II and III clinical trials have already been published, and several meta-analyses using those data have also been reported in the literature. The purpose of this article is to review past clinical trials and discuss risks and benefits of gabapentin enacarbil treatment for RLS to identify the appropriate dosage and administration of gabapentin enacarbil in patients with RLS.

Data source

A literature search of the MEDLINE and EMBASE 2004–2013 databases was conducted using the terms "gabapentin enacarbil" and "restless legs syndrome." All English-based articles and abstracts retrieved from these databases were reviewed. Additional information was

obtained from references cited in the articles, clinical trial registries, and Web sites of regional regulatory agencies and the manufacturers.

Pharmacokinetics

The pharmacokinetics of oral gabapentin enacarbil have been evaluated in healthy volunteers, patients with RLS or postherpetic neuralgia, and patients with renal impairment.[28,41] Steady-state plasma concentrations of gabapentin are attained after 2 days of once-daily gabapentin enacarbil.[28] Gabapentin enacarbil is associated with approximately dose-proportional exposure to gabapentin over an extended period across a dose range of 300 to 6,000 mg (single or multiple doses) in healthy volunteers[39,42] and across a dosage range of 600 to 2,400 mg/day in patients with RLS.[43] Gabapentin enacarbil and the immediate-release formulation of gabapentin are not interchangeable because the same daily dose of each formulation results in different plasma concentrations of gabapentin, according to the US prescribing information.[28]

Gabapentin enacarbil is rapidly absorbed throughout the intestine via two high-capacity nutrient transporters, sodium-dependent multivitamin transporters and monocarboxylate transporter type 1, and subsequently undergoes extensive first-pass hydrolysis by nonspecific carboxylesterase, primarily in enterocytes and, to a lesser extent, in hepatocytes, to gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid.[28,44,45] The concentration of gabapentin enacarbil in the blood is low (≤2% of the corresponding plasma concentration of gabapentin) and transient.[28] The estimated mean bioavailability of the drug is approximately 75% in the feeding state and 42%–65% in the fasting state, as assessed by recovery of gabapentin in the urine.[28,46] Gabapentin shows minimal binding to plasma proteins (<3%).[28] The apparent volume of distribution of gabapentin is 76 L.[28] After conversion from the prodrug gabapentin enacarbil, gabapentin is primarily eliminated from the kidney as unchanged drug.[47] In healthy adult volunteers, 94.1% of radioactivity was recovered in the urine and 5.2% in the feces after a single, radiolabeled, 600 mg dose of gabapentin enacarbil; 85.9% of the dose was recovered in the urine within the first 24 hours.[47]

Renal excretion of gabapentin is thought to involve a component of active secretion via organic cation transporter 2.[28] The renal clearance of gabapentin after administration of gabapentin enacarbil is proportional to creatinine clearance (CL_{CR}).[48] The mean C/F value is decreased in patients with moderate (CL_{CR} 30–56 mL/minute) and severe (CL_{CR} <30 mL/minute) renal impairment compared with individuals with normal renal function.[28] Gabapentin enacarbil dosage adjustment is important in patients with renal impairment.[28] Gabapentin is removed from the plasma by hemodialysis, and thus, the drug is not recommended for patients with RLS receiving hemodialysis.[28] Recently, a meta-analysis of dose–exposure relationships for gabapentin after oral administration of gabapentin and gabapentin enacarbil was reported.[49] The study collected published pharmacokinetic data for gabapentin and gabapentin enacarbil from 35 identified studies conducted in at least 192–497 subjects. Several linear and nonlinear candidate models were tested, using the data from these studies. The E_{max} model best described the dose–exposure relationship for gabapentin, and the power model was the most suitable for gabapentin enacarbil. Simulations confirmed that these models accurately reflected the distribution of the respective data. The models allow pharmacokinetic bridging to project the likely therapeutic dose for the new gabapentin enacarbil from the recommended dose range of 900 to 1,800 mg/day for the established gabapentin.[49]

Efficacy

The efficacy of gabapentin enacarbil has been evaluated at doses ranging from 600 to 2,400 mg/day in patients with moderate to severe primary RLS in Phase II and III clinical trials. The results of ten trials and three meta-analyses have been published in the literature. Eight of these studies were double-blind, placebo-controlled randomized trials. The study characteristics, primary endpoints, and results of these trials are summarized in Table 1.

Phase II studies

XP021

The efficacy of gabapentin enacarbil in patients with moderate to severe primary RLS was evaluated during a 2-week period in XP021,[50] a randomized, double-blind, placebo-controlled, crossover trial. Thirty-eight drug-naive patients were treated for 2 weeks with either 1,800 mg/day of gabapentin enacarbil (600 mg orally at 5 pm and 1,200 mg 1 hour before bedtime) or placebo. The primary endpoint was the change from baseline in total score of the International Restless Legs Syndrome rating scale (IRLS) at day 14. The secondary endpoints were patient- and investigator-rated clinical global impression-improvement (CGI-I), subjective measures of sleep, parameters for the suggested immobilization test and the polysomnography. The mean change from baseline IRLS total score at day 14 was significantly greater after treatment with gabapentin enacarbil compared with placebo (−12.1 versus −1.9; $P<0.0001$). Improvement in IRLS total score was seen on day 7 (−11.7 with gabapentin enacarbil

Table 1 Published Phase II and III clinical trials for gabapentin enacarbil in patients with moderate to severe primary restless legs syndrome

Trial	Design	Setting	Duration	Participants	Dosage of GEn	Primary endpoints	Results	Adverse events
XP021 Kushida et al[50]	Randomized, DB, PC, crossover	9 US sites	14 days	38 (22 women, 34 white)	1,800 mg/day	IRLS score	Greater reduction in IRLS ($P<0.0001$)	Somnolence: 30.6% GEn, 2.8% placebo Dizziness: 27.8% GEn, 5.6% placebo
XP045 Walters et al[51]	Randomized, DB, PC	14 US sites	14 days	95 (59 women, 93 white)	600 mg/day, 1,200 mg/day	IRLS score for GEn 1,200 mg/day	Greater reduction in IRLS with GEn 1,200 mg/day ($P<0.0001$); no difference with GEn 600 mg/day	Somnolence: 36% GEn 1,200 mg, 14% GEn 600 mg, 15% placebo Dizziness: 18% GEn 1,200 mg, 14% GEn 600 mg, 3% placebo
XP081 Lal et al[43]	Randomized, DB, PC	21 US sites	12 weeks	217 (139 women, 208 white)	600 mg/day, 1,200 mg/day, 1,800 mg/day, 2,400 mg/day	NA	Dose-proportional exposure of gabapentin to GEn dose	Somnolence: 51% GEn 2,400 mg, 26% GEn 1,800 mg, 24% GEn 1,200 mg, 15% GEn 600 mg, 5% placebo Dizziness: 40% GEn 2,400 mg, 26% GEn 1,800 mg, 22% GEn 1,200 mg, 21% GEn 600 mg, 2% placebo
XP052 PIVOT RLS-I Kushida et al[52]	Randomized, DB, PC	22 US sites	12 weeks	222 (132 women, 214 white)	1,200 mg/day	IRLS score and CGI-I score	Greater reduction in IRLS ($P=0.0003$) and more treatment responders by CGI-I ($P<0.0001$)	Somnolence: 27% GEn, 7% placebo Dizziness: 20% GEn, 5% placebo
XP053 PIVOT RLS-II Lee et al[53]	Randomized, DB, PC	28 US sites	12 weeks	325 (189 women, 304 white)	600 mg/day, 1,200 mg/day	IRLS score and CGI-I score for GEn 1,200 mg/day	Greater reduction in IRLS ($P=0.0015$) and more treatment responders by CGI-I ($P<0.0001$) with GEn 1,200 mg/day; greater reduction in IRLS ($P=0.0001$) and more treatment responders by CGI-I ($P<0.0001$) with GEn 600 mg/day	Somnolence: 18.0% GEn 1,200 mg, 21.7% GEn 600 mg, 2.1% placebo Dizziness: 24.3% GEn 1,200 mg, 10.4% GEn 600 mg, 5.2% placebo
XP060 PIVOT RLS maintenance Bogan et al[54]	Randomized, DB, PC	27 US sites	24 weeks SB phase 12 weeks DB phase	194 (114 women, 184 white)	1,200 mg/day	Proportion of patients with RLS relapse during DB phase	Less relapse with GEn versus placebo (9% versus 23%; $P=0.02$)	SB phase: Somnolence: 29.8% Dizziness: 22.1% DB phase: Somnolence: 3% GEn, 1% placebo Dizziness: 2% GEn, 1% placebo
XP055 Ellenbogen et al[55]	Open-label, extension	67 US sites	52 weeks	573 (336 women, 552 white)	1,200 mg/day	NA	GEn was generally safe and well tolerated and improved RLS symptoms for up to 64 weeks	Somnolence: 19.7% Dizziness: 11.5%
RXP110908 Winkelman et al[56]	Randomized, DB, PC, crossover	23 US sites	4 weeks	131 with significant sleep disturbance (76 women, 120 white)	1,200 mg/day	WTDS	Greater reduction in WTDS (−26.00 min; $P<0.0001$)	Somnolence: 13% GEn, 2% placebo Dizziness: 20% GEn, 2% placebo

CL-0005 Inoue et al[60]	Open-label	Japanese sites	52 weeks	181 (93 women, all Asian)	1,200 mg/day	NA	GEn improved RLS symptoms in Japanese patients with an accepted safety profile	Somnolence: 41.2% (prevalence 37.4% at 0–4 weeks to 13.7% at week 52) Dizziness: 46.2% (prevalence 42.3% at 0–4 weeks to 9.2% at week 52)
CL-0003 Inoue et al[61]	Randomized, DB, PC	Japanese sites	12 weeks	469 (211 women, all Asian)	600 mg/day, 900 mg/day, 1,200 mg/day	IRLS score for GEn 1,200 mg/day	Greater reduction in IRLS with GEn 1,200 mg/day (P=0.011) No difference with GEn 600 or 900 mg/day (when excluding patients who discontinued the study because of adverse events: greater reduction in IRLS with GEn 600 mg/day [P=0.012], 900 mg/day [P=0.024] and 1,200 mg/day [P=0.006])	Somnolence: 32.5% GEn 1,200 mg, 26.9% GEn 900 mg, 19.2% GEn 600 mg, 17.2% placebo Dizziness: 28.9% GEn 1,200 mg, 25.2% GEn 900 mg, 25.0% GEn 600 mg, 6.9% placebo

Abbreviations: GEn, gabapentin enacarbil; DB, double-blind; PC, placebo-controlled; IRLS, International Restless Legs Syndrome rating scale; CGI-I, Clinical Global Impression-Improvement; RLS, restless legs syndrome; NA, not applicable; SB, single-blind; WTDS, wake time during sleep.

versus −3.7 with placebo). The percentage of responders to gabapentin enacarbil rated as "much improved" or "very much improved" on investigator-rated CGI-I on day 14 was 85.3% compared with 14.7% for placebo. Patients treated with gabapentin enacarbil showed improvement in the patient-rated CGI-I, time in RLS symptoms on 24-hour diaries, and the subject-rated postsleep questionnaire (PSQ), including overall quality of sleep, number of hours awake per night resulting from RLS symptoms, and number of awakenings per night resulting from RLS symptoms (an index of sleep fragmentation) compared with placebo. Polysomnography demonstrated that gabapentin enacarbil improved sleep architecture, including shortening of stage 1 sleep and extension of stage 3/4 (slow-wave) sleep.

XP045

The efficacy of gabapentin enacarbil 1,200 mg and 600 mg was assessed in 95 patients with moderate to severe primary RLS in XP045,[51] a 14-day, double-blind, randomized, placebo-controlled trial. Gabapentin enacarbil 1,200 mg/day significantly reduced the IRLS total score compared with placebo at day 14 (−16.1 versus −8.9; $P<0.0001$). CGI-I results showed that significantly more subjects responded to treatment with gabapentin enacarbil 1,200 mg/day, as rated by investigators (81.3% versus 48.5%; $P<0.001$) and by patients (81.3% versus 45.5%; $P<0.001$), than to treatment with placebo. PSQ indicated that gabapentin enacarbil 1,200 mg/day significantly improved overall sleep quality and resulted in fewer nights with RLS symptoms, fewer awakenings, and fewer hours awake per night compared with placebo. Although gabapentin enacarbil 600 mg/day showed a similar changes in IRLS total score, CGI-I responses, and results on PSQ, these changes were not significant compared with placebo.

XP081

XP081,[43] a randomized, 12-week, double-blind, placebo-controlled, parallel-group clinical trial was conducted to assess the pharmacokinetics and efficacy of gabapentin enacarbil in patients with moderate to severe primary RLS. In this study, 217 subjects were randomly allocated to a gabapentin enacarbil 600 mg group (n=48), a 1,200 mg group (n=45), a 1,800 mg group (n=38), a 2,400 mg group (n=45), or a placebo group (n=41). Exposure to gabapentin was proportional to gabapentin enacarbil dose. The mean reduction in IRLS total score from baseline to week 12 ranged from −12.9 to −13.9 for gabapentin enacarbil treatment groups versus −9.3 for placebo. The results indicated that

all four dose levels of gabapentin enacarbil provided efficacious drug exposure because all doses resulted in numerically greater relief of symptoms in subjects with RLS compared with placebo.

Phase III studies

XP052 (PIVOT [Patient Improvements in Vital Outcomes Following Treatment] RLS 1 study)

The 12-week, multicenter, randomized, double-blind, placebo-controlled XP052 clinical trial[52] evaluated the efficacy of gabapentin enacarbil 1,200 mg once daily at 5 pm after meal in 222 patients with moderate to severe primary RLS. The coprimary outcome measures were the mean change in IRLS total score from baseline to week 12 and the proportion of responders on the CGI-I scale at week 12. Treatment with gabapentin enacarbil resulted in improvement of IRLS total score compared with the placebo group (−13.2 versus −8.8) at week 12. On the investigator-rated CGI-I, significantly more gabapentin enacarbil-treated patients responded than patients treated with placebo (76.1% versus 38.9%; $P<0.0001$). At the end of the study, more than 50% of gabapentin enacarbil-treated patients showed no sign of RLS during the 24-hour assessment period compared with 18% of placebo patients. Subjects treated with gabapentin enacarbil also experienced a significant increase in RLS quality-of-life scores compared with placebo-treated patients (21.4 versus 14.1; $P<0.001$) and improved Medical Outcomes Study (MOS) sleep scale domains, such as daytime somnolence (−17.4 versus −9.6; $P=0.0018$) and sleep quantity (0.8 versus 0.4; $P=0.0084$).

XP053 (PIVOT RLS 2 study)

In XP053,[53] another multicenter, randomized, double-blind, placebo-controlled clinical trial, the therapeutic effects of gabapentin enacarbil at 1,200 and 600 mg/day were examined during a 12-week period (n=321). Both the IRLS total score and CGI-I scale improved after 12 weeks of both doses of gabapentin enacarbil compared with placebo. The improvement in IRLS total score was −13.8 and −13.0 for the 600 and 1,200 mg groups, respectively, compared with −9.8 with placebo. Significantly more subjects treated with gabapentin enacarbil 600 mg (72.8%) and 1,200 mg (77.5%) were rated as responders on the investigator-rated CGI-I scale compared with placebo (44.8%). PSQ revealed that gabapentin enacarbil at both doses significantly improved overall quality of sleep and resulted in improved ability to function, fewer nights with RLS symptoms, fewer awakenings and fewer hours awake per night compared with placebo.

XP060 (PIVOT RLS Maintenance Study)

XP060[54] is a multicenter, randomized, placebo-controlled clinical trial that evaluated the efficacy and long-term tolerability of gabapentin enacarbil in 327 patients with moderate to severe primary RLS. In the initial 24 weeks of the study (the single-blind treatment phase), subjects were treated with gabapentin enacarbil 1,200 mg/day at 5 pm with food. The initial phase was completed by 221 subjects, and 194 (88%) were considered responders with an IRLS total score reduction of 6 or more points and "much improved" or "very much improved" on the CGI-I scale. These 194 patients then entered a 12-week, double-blind, parallel-group phase in which they received gabapentin enacarbil 1,200 mg/day for 12 weeks or gabapentin enacarbil 600 mg/day for 2 weeks, followed by placebo for 10 weeks. The primary endpoint was the proportion of subjects with relapse during the double-blind phase, defined as an increase of 6 or more points in IRLS total score, a rating of "much worse" or "very much worse" on the investigator-rated CGI-I scale, or withdrawal because of lack of efficacy. A statistically significant lower percentage of gabapentin enacarbil-treated subjects relapsed during the double-blind phase compared with placebo (9.4% versus 22.7%; $P=0.02$).

XP055

The long-term efficacy of gabapentin enacarbil in patients with moderate to severe primary RLS was evaluated in XP055,[55] an open-label, multicenter, 52-week extension study that enrolled 573 participants who completed one of four short-term parent trials (XP052, XP053, XP081, XP063). All subjects received gabapentin enacarbil at 5 pm with food for up to 52 weeks. The titration comprised gabapentin enacarbil 600 mg at days 1–3 and 1,200 mg/day from day 4. Dosage increase to 1,800 mg/day and decrease to 600 mg/day were allowed at the investigator's discretion according to efficacy and tolerability. Efficacy evaluation included IRLS total scores and CGI-I scales at week 52 last observation carried forward (LOCF). The modal doses chosen by participants during the study were 600 mg/day by 17.1%, 1,200 mg/day by 55.1%, and 1,800 mg/day by 27.6%. The final doses chosen by participants were 600 mg/day by 18.3%, 1,200 mg/day by 52.2%, and 1,800 mg/day by 29.5%. At week 52 LOCF, the mean change from parent study baseline (23.2) in IRLS total score was −15.2, and 84.8% of subjects were CGI-I responders rated by investigators.

RXP110908

To evaluate the efficacy of gabapentin enacarbil in patients with moderate to severe RLS and associated sleep disturbance, RXP110908,[56] a randomized, double-blind, placebo-controlled, crossover polysomnographic study was conducted. The primary endpoint was the mean change from baseline at week 4 and 10 LOCF in wake time during sleep. The key secondary endpoint was the mean change from baseline at week 4 and 10 LOCF in PLM associated with arousal per hour of sleep. Thus, 136 subjects with significant sleep disturbance on IRLS item 4 and PLM during sleep index higher than 15 on actigraphy (average over 5 nights using both legs) were randomized 1:1 to a sequence of gabapentin enacarbil 1,200 mg:placebo or placebo:gabapentin enacarbil 1,200 mg, receiving each treatment for 4 weeks; 114 patients completed the study. Gabapentin enacarbil 1,200 mg significantly improved the sleep outcome compared with placebo at week 4 and 10 LOCF, including wake time during sleep (−26.0 minutes; $P<0.0001$), PLM associated with arousal per hour of sleep (−3.1 PLM with arousal/hour; $P=0.002$), stage N3 sleep time (12.1 minutes; $P<0.0001$), number of awakenings (−2.5; $P<0.0001$), and PLM associated with awakening per hour of sleep (−0.14; $P<0.001$).

Meta-analyses studies

Dose–response relationship

The efficacy of individual dose groups and placebo was compared statistically using an integrated post hoc analysis of three 12-week, randomized, double-blind, placebo-controlled trials (XP052/XP053/XP081) on subjects with moderate to severe primary RLS.[57] In total, 760 subjects were included in the pooled analysis (placebo, n=245; gabapentin enacarbil 600 mg, n=163; 1,200 mg, n=269; 1,800 mg, n=38; 2,400 mg, n=45). The adjusted mean change in IRLS total score from baseline to week 12 LOCF was −13.6 for gabapentin enacarbil 600 mg compared with −9.3 for placebo ($P<0.0001$). Similar treatment benefits were noted for the three higher doses, and the adjusted mean reduction in IRLS total score was significantly greater compared with placebo for all gabapentin enacarbil treatment groups (−13.2 for 1,200 mg [$P<0.0001$]; −13.7 for 1,800 mg [$P<0.0062$]; −12.5 for 2,400 mg [$P<0.0329$]). With gabapentin enacarbil 600 mg, 70.2% of subjects were rated as investigator-rated CGI-I responders compared with 42.2% of subjects treated with placebo ($P<0.0001$). The proportion of investigator-rated CGI-I responders was also significantly greater with gabapentin enacarbil 1,200 mg (75.3%; $P<0.0001$), 1,800 mg (73.0%; $P=0.0006$), and 2,400 mg (81.8%; $P<0.0001$) compared with placebo. This integrated analysis demonstrated that the lowest dose of gabapentin enacarbil evaluated (600 mg) significantly improved RLS symptoms and global outcomes, as demonstrated by improvements in IRLS total score and the investigator-rated CGI-I scale compared with both placebo and higher doses of gabapentin enacarbil.

Population pharmacokinetic-pharmacodynamic models

Using plasma gabapentin concentration data obtained after administration of gabapentin enacarbil in 12 Phase I–III trials involving healthy adults (n=95) and patients with RLS (n=994; dose range, 300–2,400 mg/day), a population pharmacokinetic model was developed by nonlinear mixed-effect modeling using the software NONREM.[58] Population pharmacokinetic-pharmacodynamic (PK-PD) models were also evaluated using gabapentin exposure and change from baseline in IRLS total score and investigator-/patient-rated CGI-I. A simple E_{max} model adequately fitted the relationship between gabapentin enacarbil dose/gabapentin $AUC_{SS,\,24}$ (area under the curve at steady state, 0–24 hour) and change from baseline in IRLS total score at week 12. A logistic regression model was used to fit the relationship between gabapentin enacarbil dose/gabapentin $AUC_{SS,\,24}$ and investigator- and patient-rated CGI-I responses. The predicted probability of investigator- and patient-rated CGI-I responses increased with increasing gabapentin enacarbil dose up to 2,400 mg/day, whereas the IRLS total score was similar at all exposures tested.

Effect on sleep quality

To assess the subjective and novel sleep endpoints in patients with moderate to severe primary RLS (relative to the severity of sleep disturbances at baseline), the results of two 12-week, randomized, double-blind, placebo-controlled trials (XP052/XP053) were analyzed.[59] The modified intent-to-treat population included 427 subjects (gabapentin enacarbil 1,200 mg, n=223; placebo, n=204). Subjects were divided into two subgroups (very severe to severe sleep disturbance or moderate to no sleep disturbance) on the basis of their response to IRLS item 4 at baseline. Gabapentin enacarbil significantly improved all MOS sleep scale domain scores relative to baseline compared with placebo ($P<0.05$) in both subgroups. Compared with placebo, gabapentin enacarbil-treated subjects with very severe to severe sleep disturbance reported higher overall quality of sleep, fewer nighttime awakenings, and fewer hours awake per night resulting

from RLS symptoms at week 12 on PSQ (all $P<0.001$), and sleep quality was the only significant item in those with moderate to no sleep disturbance ($P<0.0001$). Evaluation of sleep endpoints based on the novel 24-Hour RLS Symptom Diary and the conventional Pittsburgh Sleep Diary yielded similar results.

Japanese trials

CL-0005

To evaluate the long-term efficacy of gabapentin enacarbil in an Asian RLS population, CL-0005,[60] an open-label, multicenter, 52-week clinical trial, was conducted in Japanese subjects with moderate to severe primary RLS. In this study, 181 patients received gabapentin enacarbil once daily after an evening meal at an initial dose of 600 mg/day for 3 days that was then increased to 1,200 mg/day for a total treatment period of 52 weeks. The dose could be increased to 1,500 mg/day or decreased to 900 mg/day based on efficacy and tolerability. Efficacy was assessed by IRLS total scores and investigator-rated and patient-rated CGI-I. The majority (83.4%) of subjects selected 1,200 mg/day as the final dose in this study. Four individuals (2.2%) increased the daily dose to 1,500 mg because of insufficient efficacy. The dose was reduced to 900 mg/day in 18 patients (9.9%) because of adverse events. The mean IRLS total score decreased from 24.4 at baseline to 6.3 at week 52. Investigator- and patient-rated CGI-I responders rate were 87.1% and 87.1%, respectively.

CL-0003

In CL-0003,[61] a 12-week, randomized, double-blind, placebo-controlled, parallel-group clinical trial, the efficacy of three doses of gabapentin enacarbil (600, 900, and 1,200 mg/day) was evaluated compared with placebo in 469 Japanese patients with moderate to severe primary RLS. The primary outcome was a change in IRLS total score, and the secondary outcomes included investigator- and patient-rated CGI-I. The mean change in IRLS total score relative to baseline at the final observation was −8.96 for placebo versus −11.10, −10.26, and −11.38 for 600, 900, and 1,200 mg gabapentin enacarbil, respectively. William's multiple comparison test using LOCF analysis showed that only 1,200 mg gabapentin enacarbil was superior to placebo ($P=0.011$). However, when patients who discontinued treatment early in the study were excluded from analysis, the improvement in each gabapentin enacarbil group was significantly superior to that in the placebo group ($P=0.012$ in the 600 mg group, $P=0.024$ in the 900 mg group, and $P=0.006$ in the 1,200 mg group).

The discrepancy in these findings is probably multifactorial. For example, many of the patients who discontinued treatment in this study did so early, often before gabapentin enacarbil had the opportunity to improve IRLS scores, and most discontinued at the 900 mg dose. The median duration of administration in those who discontinued the study was 50.0 days in the 600 mg group (n=8), 14.5 days in the 900 mg group (n=6), and 27.0 days in the 1,200 mg group (n=8). Therefore, LOCF analysis may bias data toward a poorer outcome, particularly in the 900 mg group. The responders rate of investigator-rated CGI-I was significantly higher in all three gabapentin enacarbil groups compared with the placebo group (65.8% [$P<0.001$] for the 600 mg group, 52.9% [$P=0.014$] for the 900 mg group, and 62.8% [$P=0.003$] for the 1,200 mg group compared with 44.8% for the placebo group). The patient-rated CGI-I responders rates were also significantly higher in all three gabapentin enacarbil groups than in the placebo group (65.8% [$P<0.001$] for the 600 mg group, 52.1% [$P=0.012$] for the 900 mg group, and 61.9% [$P=0.003$] for the 1,200 mg group compared with 44.0% in the placebo group).

Safety and tolerability

According to the US prescribing information,[28] 1,201 patients with RLS (age, 18–82 years; 60% women; 95% white) were treated with gabapentin enacarbil, including 613 patients treated for at least 6 months and 371 treated for at least 1 year. Eleven (7%) of 163 patients treated with the recommended dosage of 600 mg/day of gabapentin enacarbil discontinued treatment because of adverse events compared with 10 (4%) of the 245 patients of the placebo group. The most commonly observed adverse events (≥5% and at least twice the rate in the placebo group) during the 12-week trial were somnolence and dizziness. Somnolence was reported by 20% of patients treated with 600 mg/day dose compared with 6% of patients receiving placebo. Somnolence persisted during treatment in about 30% of patients, with symptoms resolving within 3–4 weeks in the remaining patients. Dizziness was reported by 13% of the patients treated with the 600 mg/day dose compared with 4% of patients in the placebo group. Dizziness persisted during treatment in about 20% of patients. Somnolence and dizziness led to treatment withdrawal in 2% and 1% of patients treated with 600 mg/day gabapentin enacarbil, respectively. The rates of these adverse events were higher in the 1,200 mg/day group (somnolence: 600 mg, 20%, and 1,200 mg, 27%; dizziness: 600 mg, 13%, and 1,200 mg, 22%). Other treatment-related adverse effects that were considered dose-related were

headache (600 mg, 12%, and 1,200 mg, 15%), feeling drunk (1% versus 3%), decreased libido (<1% versus 2%), depression (<1% versus 3%), peripheral edema (<1% versus 3%), and vertigo (1% versus 3%).

A pooled analysis of three 12-week trials (XP052/XP053/XP081) evaluated the safety and tolerability of gabapentin enacarbil treatment across a dose range of 600 to 2,400 mg.[57] The two most common adverse events were somnolence and dizziness, and higher rates of those events were observed with higher doses of gabapentin enacarbil (somnolence: placebo, 5%; 600 mg, 20%; 1,200 mg, 23%; 1,800 mg, 26%; 2,400 mg, 51%; dizziness: placebo, 4%; 600 mg, 13%; 1,200 mg, 22%; 1,800 mg, 26%; 2,400 mg, 40%). The majority of those events were mild or moderate in intensity, occurred on dose initiation, and usually resolved spontaneously within 1–2 weeks.

An integrated analysis of two 12-week trials (XP052/XP053) examined sleep-related tolerability of gabapentin enacarbil 1,200 mg/day in subjects with moderate to severe primary RLS with and without severe sleep disturbance.[59] Somnolence and sedation were summarized for both subgroups, including those patients who withdrew from the studies. The proportion of subjects who experienced somnolence was similar between the subgroups (very severe to severe sleep disturbance, gabapentin enacarbil, 25%, and placebo, 7%; moderate to no sleep disturbance, gabapentin enacarbil, 29%, and placebo, 5%). Few subjects withdrew because of somnolence: one from the very severe to severe sleep disturbance group and three from the moderate to no sleep disturbance group. None of the subjects of the placebo group withdrew because of somnolence.

In this study, the change from baseline in Epworth Sleepiness Scale (ESS) total score was assessed for each subgroup. For subjects with very severe to severe sleep disturbance at baseline, there was a treatment benefit for the 1,200 mg/day dose relative to placebo for the change in ESS total score at week 12 (−1.3; P=0.0349). For subjects with moderate to no sleep disturbance at baseline, the change in ESS total score was not significant at any time. There was a trend for a larger improvement in ESS total score in subjects of the 1,200 mg/day dose group with very severe to severe sleep disturbance at baseline compared with those with moderate to no sleep disturbance.

A 1-year, open-label Japanese clinical trial analyzed the incidence and the prevalence of somnolence and dizziness in each 4-week period of the study in 182 subjects, the majority of whom (83.4%) were treated with gabapentin enacarbil 1,200 mg/day.[60] In most patients, somnolence and dizziness occurred early during the treatment period, usually within 4 weeks after starting treatment. The incidence of these two adverse events gradually fell with study progression. The rates of new-onset somnolence and dizziness were 37.4% and 42.3%, respectively, in the first 4 weeks of treatment, then decreased later to 0.0%–1.4% and 0.0%–2.4%, respectively. The prevalence of these events gradually decreased over time (somnolence, 37.4% at 0–4 weeks to 13.7% at week 52; dizziness, 42.3% at 0–4 weeks to 9.2% at week 52).

In a 2-week simulated driving study in patients with RLS, a daily single 1,200 mg dose of gabapentin enacarbil resulted in significant impairment in lane position variability within 2 hours and for up to 14 hours after dosing.[62] The impairment was similar to that caused by the active control, a single oral dose of diphenhydramine 50 mg. The 600 mg/day dose of gabapentin enacarbil was not included in the simulated driving study.

The clinical significance of increased incidence of pancreatic acinar cell adenoma and carcinoma found in rats treated with gabapentin enacarbil is unknown.[63] The possible mechanism of tumorigenesis is that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells in vitro, which may cause gabapentin to act as a tumor promoter by enhancing mitogenic activity. At this stage, there is no information on whether gabapentin increases cell proliferation in human cells. In addition, the FDA noted the difficulty in extrapolating such risk in humans because acinar cell tumors are rare and the majority of human pancreatic cancers are ductal in origin.[62] In this regard, the published clinical trials did not report any cases of pancreatic cancer. Epidemiological data from two electronic medical records in a US cohort with up to 12 years of follow-up and a UK cohort with up to 15 years of follow-up did not report any carcinogenic effect for gabapentin, although the wide variability of some confidence intervals makes it difficult to exclude the carcinogenic effect with confidence.[64]

Benefit–risk assessment

Therapeutic effects

The overall clinical development program of gabapentin enacarbil for the treatment of moderate to severe primary RLS reviewed here indicates that the 1,200 mg once-daily dose is the most validated treatment in relieving subjective RLS symptoms and maintaining improvement for up to 64 weeks. The efficacy of the 1,200 mg dose was confirmed in four (three in the United States and one in Japan) 12-week trials as statistically significant improvement in the coprimary endpoints of IRLS total score and the investigator-rated

CGI-I responders rate compared with placebo. Interestingly, significant treatment effects for the 1,200 mg dose for both coprimary measures were identified at week 1.

Population PK-PD analysis using the entire clinical trials data indicated that the predicted probability of investigator- and patient-rated CGI-I response increased with an increasing dose of gabapentin enacarbil, up to 2,400 mg/day, whereas the IRLS total score was similar at all doses tested. The IRLS and its total score have become the gold standard in assessment of severity in RLS research, especially in clinical drug trials. Nonetheless, it was argued that the IRLS relates to high average scores at baseline in most clinical trials but also to a barrier of about 10 points at the end of therapy,[65] even under highly effective treatments, as assessed by other efficacy variables.[66] The IRLS does not include any specific assessment of time of onset of RLS symptoms during the day. Moreover, item 3 of the IRLS assesses relief with movement, which is one of the diagnostic criteria, and does not contribute to scale factors. The answers to the items for the scale are set up to carry identical weight, ranging from none to very severe, but the nature of the questions makes these categorical responses somewhat arbitrary and internally consistent. Thus, the scale may have properties that tend to inflate rather than substantiate the psychometrics.[65] The CGI is a global instrument and is not very specific to RLS. The regulatory authorities have recommended CGI as a coprimary endpoint to patient-based severity scales in RLS clinical trials.[63] When used in RLS clinical trials, all efficacy items of the CGI were highly sensitive for treatment differences.[67] Therefore, the efficacy of gabapentin enacarbil may actually increase dose-dependently at a dose range between zero and 2,400 mg/day, as suggested by the CGI-I results on the population PK-PD analysis.

Treatment with gabapentin enacarbil 1,200 mg/day also improves secondary endpoints such as PSQ, MOS sleep domain, and RLS quality-of-life scores compared with placebo.[52] Long-term maintenance of the efficacy with the 1,200 mg dose was confirmed, as a significantly smaller proportion of patients treated with gabapentin enacarbil experienced relapse compared with patients treated with placebo.[54] Polysomnography conducted in subjects with moderate to severe primary RLS and associated sleep disturbance demonstrated that treatment with gabapentin enacarbil 1,200 mg significantly reduced the wake time during sleep and PLM associated with arousal per hour of sleep compared with placebo.[56] Gabapentin enacarbil 1,200 mg also significantly increased the time in slow-wave sleep compared with placebo.

Integrated analysis of two 12-week trials (XP052/XP053) showed that gabapentin enacarbil 1,200 mg significantly improved time awake during the night and ESS total score compared with placebo only in patients with very severe to severe sleep disturbances.[59]

Because sleep disturbance is the single most troublesome symptom of RLS and the primary reason for seeking medical assistance, improvement in this parameter is highly relevant to the optimal treatment of RLS sufferers. Although dopamine agonists are efficacious in RLS, these agents frequently do not extend sleep duration, reduce nocturnal awakenings, or normalize sleep architecture, necessitating the concomitant use of sleep-promoting agents in at least some patients.[23–25] Gabapentin enacarbil 1,200 mg once daily is confirmed as highly effective in improving sleep disturbance associated with RLS.

Recently, gabapentin enacarbil 1,200 mg/day (600 mg twice daily) was approved in the United States for the management of postherpetic neuralgia. Not a few patients with RLS express their subjective symptoms as "pain".[1,2,9] In general practice, the differential diagnosis of RLS or neurogenic pain may sometimes be difficult. Elderly patients with RLS often accompany with neurogenic pain in the back and legs. Patients with polyneuropathy sometimes have both typical neurogenic pain and typical RLS symptoms in their legs.[6] In such cases, gabapentin enacarbil 1,200 mg/day may provide analgesic effects in addition to its effect on RLS symptoms, thus improving the overall subjective symptoms better than the gabapentin enacarbil 600 mg once-daily treatment.

Sedative effects

Somnolence and dizziness during treatment with gabapentin enacarbil and gabapentin are thought to be related to the sedative effects of the drugs; these effects are generally dose-dependent. The sedative effects of gabapentin enacarbil may cause serious drug adverse reactions in some patients, but such effects could become beneficial, rather than adverse reactions, in those patients who suffer from severe insomnia or excessive anxiety during the night. In clinical practice, the appropriate dose of dopamine agonists or gabapentin in the management of RLS is usually determined by weighing both the benefits and risks on a case-by-case basis, and even on visit-by-visit basis in the same patient. In one 1-year, open-label trial (XP055), patients were treated first with gabapentin enacarbil 1,200 mg once daily and then, as in clinical practice, given the choice to increase to 1,800 mg or decrease to 600 mg throughout the study, on the basis of the residual symptoms or adverse effects.[55]

Interestingly, 55% of the patients used 1,200 mg/day as the modal dose, whereas 28% chose 1,800 mg/day. In comparison, only 17% of the patients selected 600 mg/day during most of the study period. These results suggest that more than 80% of patients preferred to use a 1,200 mg/day or higher dose as the maintenance dose. The Japanese 1-year, open-label trial (CL-0005) also found that 86% of patients used a 1,200 mg/day or higher dose at the end of the study.[60] Thus, the long-term clinical trials indicated that 1,200 mg once-daily dose was most frequently chosen by the patients and was the validated dosage used in the treatment of moderate to severe primary RLS. It is interesting that in the Japanese parallel-group, dose-finding trial, patients in the 1,200 mg group showed statistically significant improvement in IRLS total score compared with placebo group, but the 900 mg dose, an intermediate dose between 600 and 1,200 mg, failed to show a significant improvement in IRLS total score.[61] Many of the patients who discontinued treatment in that study did so early, often before gabapentin enacarbil had the opportunity to improve IRLS scores, and most discontinued at the 900-mg dose. This finding suggests that a half-landing dose may cause more adverse effects, such as somnolence or dizziness, than favorable effects on RLS symptoms in the early treatment period in some patients, but an adequately high dose brings about favorable sedative effects during the night leading to a better quality of sleep in addition to improvements in the subjective RLS symptoms.

Regulatory concerns

Although most clinical trials assessed gabapentin enacarbil at doses greater than 600 mg/day and demonstrated the overall safety and efficacy, the FDA approved the 600 mg once daily dosage because doses higher than 600 mg/day were considered to provide no additional benefits and could increase the likelihood of adverse reactions. However, only four clinical trials (XP045, XP081, XP053, CL-0003) used a treatment group with a 600-mg once-daily dose. Three (XP045, XP081, CL-0003) of these trials failed to show improvement in RLS by 600 mg treatment compared with placebo, although the integrated post hoc analysis of three 12-week trials (XP052/XP053/XP081) demonstrated statistically significant improvements in IRLS total score and the investigator-rated CGI-I response with gabapentin enacarbil 600 mg compared with placebo. Furthermore, no study to date has included the 600-mg dose in the primary endpoint. Therefore, the efficacy of gabapentin enacarbil 600 mg for the treatment of moderate to severe primary RLS needs to be confirmed by specifically designed studies, one of which is the ongoing postmarketing commitment trial.

It is possible that a similar magnitude of improvement in IRLS total score can be obtained with a gabapentin enacarbil dose lower than 600 mg/day. Lower doses could minimize the safety risk of gabapentin enacarbil, such as a dose-dependent increase in somnolence and dizziness events and potential carcinogenicity. Future assessment of the efficacy and safety of lower doses, such as 300 and 450 mg/day, may justify the use of a dose lower than 600 mg/day as the maintenance dose for the treatment of moderate to severe primary RLS.

One of the reasons why the FDA approved only the 600 mg dose for the treatment of moderate to severe primary RLS is concern about potential pancreas carcinogenicity.[63] A 25-fold safety margin for carcinogenicity between plasma exposure used in animal studies and that in humans was agreed on by regulatory authorities.[68] In the 2-year carcinogenicity study of gabapentin conducted in rat, gabapentin 1,000 mg/kg/day was determined to be a no-effect dose.[68] The AUC of gabapentin in 1,000 mg/kg/day was 1,300 μg·hour/mL, and it was just 25-fold of that (51.4 μg·hour/mL) after a gabapentin enacarbil 600 mg dose in humans.[68] The AUC of gabapentin after a gabapentin enacarbil 700 mg dose (53.0 μg·hour/mL) was also comparable to the gabapentin AUC (56.6 μg·hour/mL) after a gabapentin dose of 1,200 mg/day, a standard antiepilepsy dose.[69] A recent meta-analysis study of 35 pharmacokinetic studies on gabapentin and gabapentin enacarbil included an accurate conversion graph of the two drugs and suggested that the therapeutic effects of 900 to 1,800 mg of gabapentin were comparable to the same dose range of gabapentin enacarbil.[49] If this is correct, one can apply the safety data of gabapentin to gabapentin enacarbil at least by 1,800 mg/day and confidently reduce the potential risk for pancreatic acinar cell tumor in patients treated with gabapentin enacarbil, similar to that with gabapentin.

The FDA has also indicated that gabapentin could be approved for the treatment of patients with refractory epilepsy, despite the potential risk for pancreatic cancer. However, gabapentin enacarbil cannot be approved for RLS patients because the disease is not comparable to poorly controlled epilepsy in both severity and clinical outcome and the FDA had already approved two dopamine agonists (three at present) for RLS.[69] However, the impact of RLS on patients often brings about serious sleep and mood problems and a decrease in functioning of daily activities, leading to a significant impairment of QOL that is comparable with that encountered in patients with type 2 diabetes mellitus and myocardial infarction.[9] Recent epidemiological studies

have suggested that RLS is a potential risk factor for cardiovascular events.[70,71] Thirty percent to 50% of patients treated with dopamine agonists developed augmentation, and many of those had to stop dopamine agonists.[26,27] A proportion of patients with severe RLS do not respond to treatment with dopamine agonists, whereas others stop such treatment because of serious adverse effects such as gambling or increased sexual desire.[72–74] They are assessed as refractory RLS, and several treatment guidelines recommend treatment with alfa-2-delta ligands or opioids for such patients,[17–22] among which only gabapentin enacarbil is approved for RLS in the United States and Japan.

Since the approval of gabapentin enacarbil for RLS, more published data have pointed to the superior effects of gabapentin enacarbil 1,200 mg relative to 600 mg.[56–59,61] The clinical significance of RLS has also emerged through various clinical research studies including gabapentin enacarbil trials and several epidemiological studies.[50,70,71] Huge amounts of pharmacokinetic data have been collected on gabapentin enacarbil, and more accurate pharmacokinetic profiles have been published,[49] which may allow extrapolation of the 15-year gabapentin experience to the new treatment with gabapentin enacarbil.

The clinical trials on gabapentin enacarbil reviewed here confirmed that the 600 mg once-daily treatment is the treatment of choice to improve RLS symptoms with the lowest risk for sedative adverse reactions. However, the same clinical trials also indicated that the 1,200 mg once-daily dose is the most validated and well-tolerated treatment for moderate to severe primary RLS, particularly in patients with severe sleep disturbances. At this time, only 600 mg once daily is approved for the treatment of moderate to severe primary RLS in adults by the regulatory authorities. Such a high-level decision by the multidisciplinary experts was probably based on a tradeoff of expected clinical benefits and potential risks in the entire patient populations with RLS, including children, elderly patients, and patients with various comorbid disorders.

Conclusion

Gabapentin enacarbil has already been used during the last 1–2 years for the treatment of RLS. The approved dosage is 600 mg orally once daily with food at about 5 pm because doses higher than 600 mg are thought to provide no additional benefits and increase the chance of adverse reactions. Nonetheless, the overall clinical development program reviewed here indicates that 1,200 mg/day of gabapentin enacarbil is the most validated treatment in relieving RLS symptoms and maintaining improvements. The 1,200-mg once-daily treatment also improves severe sleep disturbance associated with RLS. Meta-analyses studies indicated that the IRLS total score was similar at all doses tested, whereas the CGI-I response increased with increasing the doses up to 2,400 mg/day, suggesting two distinct therapeutic doses of gabapentin enacarbil: 600 mg/day or lower doses for the treatment of subjective RLS symptoms and 1,200 mg/day or higher doses for the treatment of both subjective RLS symptoms and associated problems, such as severe sleep disturbances. The ongoing postmarketing commitment trial may propose a dose lower than 600 mg/day as a new therapeutic dose for RLS in the future. In contrast, the recent approval of gabapentin enacarbil 1,200 mg/day (600 mg twice daily) for the management of postherpetic neuralgia provides us the opportunity to treat RLS patients who have comorbid postherpetic neuralgia with gabapentin enacarbil 1,200 mg/day, the most validated dose for RLS treatment.

The two most common adverse effects, somnolence and dizziness, are dose-dependent and usually occur early in the course of treatment. Administration of a half-landing dose of gabapentin enacarbil may bring about more adverse effects than favorable ones in some RLS patients, leading to early discontinuation of the treatment. Therefore, starting with a low dose and carefully increasing it to the maintenance dose would be appropriate to prevent adverse events and avoid withdrawals. Based on personal experience, the alternative approach for successful introduction of gabapentin enacarbil in patients with moderate to severe primary RLS can include initiation of treatment using a 300-mg tablet once daily with food early in the evening for 1–7 days, followed by increasing the dose to 600 mg once daily, although this approach has not been tested in the clinical trials.

For the time being, physicians should perform treatment of RLS patients with gabapentin enacarbil at 600 mg once daily, but we should always keep in mind that the 1,200 mg once daily may be more beneficial and that we may have something more to do in addition to the use of gabapentin enacarbil at 600 mg for improvement of the whole set of problems encountered at least in some patients with RLS, such as severe sleep disturbance, pain, or mood changes.

Disclosure

Dr Kume was a principal investigator for CL-0003 and received speaker's honoraria from Astellas.

References

1. Ekbom KA. Restless legs. *Acta Med Scand*. 1945;158(Suppl):1–123.
2. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J; Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health; International Restless Legs Syndrome Study Group. 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):101–119.

3. Tunç T, Karadağ YS, Doğulu F, Inan LE. Predisposing factors of restless legs syndrome in pregnancy. *Mov Disord*. 2007;22(5):627–631.
4. Allen RP, Earley CJ. The role of iron in restless legs syndrome. *Mov Disord*. 2007;22(Suppl 18):S440–S448.
5. Gigli GL, Adorati M, Dolso P, et al. Restless legs syndrome in end-stage renal disease. *Sleep Med*. 2004;5(3):309–315.
6. Gemignani F, Brindani F, Negrotti A, Vitetta F, Alfieri S, Marbini A. Restless legs syndrome and polyneuropathy. *Mov Disord*. 2006;21(8): 1254–1257.
7. Manconi M, Govoni V, De Vito A, et al. Restless legs syndrome and pregnancy. *Neurology*. 2004;63(6):1065–1069.
8. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med*. 2005;165(11):1286–1292.
9. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med*. 2004;5(3):237–246.
10. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. *Sleep Med Rev*. 2012;16(4): 283–295.
11. Innes KE, Selfe TK, Agarwal P. Prevalence of restless legs syndrome in North American and Western European populations: a systematic review. *Sleep Med*. 2011;12(7):623–634.
12. Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. *Mov Disord*. 2011;26(1):114–120.
13. Allen RP, Stillman P, Myers AJ. Physician-diagnosed restless legs syndrome in a large sample of primary medical care patients in western Europe: Prevalence and characteristics. *Sleep Med*. 2010;11(1): 31–37.
14. Nomura T, Inoue Y, Kusumi M, et al. Email-based epidemiological surveys on restless legs syndrome in Japan. *Sleep Biol Rhythm*. 2008;6: 139–145.
15. Nomura T, Inoue Y, Kusumi M, Uemura Y, Nakashima K. Prevalence of restless legs syndrome in a rural community in Japan. *Mov Disord*. 2008;23(16):2363–2369.
16. Mizuno S, Miyaoka T, Inagaki T, Horiguchi J. Prevalence of restless legs syndrome in non-institutionalized Japanese elderly. *Psychiatry Clin Neurosci*. 2005;59(4):461–465.
17. Garcia-Borreguero D, Kohnen R, Silber MH, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. *Sleep Med*. 2013;14(7):675–684.
18. Silber MH, Ehrenberg BL, Allen RP, et al; Medical Advisory Board of the Restless Legs Syndrome Foundation. An algorithm for the management of restless legs syndrome. *Mayo Clin Proc*. 2004;79(7): 916–922.
19. Oertel WH, Trenkwalder C, Zucconi M, et al. State of the art in restless legs syndrome therapy: practice recommendations for treating restless legs syndrome. *Mov Disord*. 2007;22(Suppl 18):S466–S475.
20. Trenkwalder C, Hening WA, Montagna P, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *Mov Disord*. 2008;23(16):2267–2302.
21. Hening WA. Current guidelines and standards of practice for restless legs syndrome. *Am J Med*. 2007;120(1 Suppl 1):S22–S27.
22. Vignatelli L, Billiard M, Clarenbach P, et al; EFNS Task Force. EFNS guidelines on management of restless legs syndrome and periodic limb movement disorder in sleep. *Eur J Neurol*. 2006;13(10):1049–1065.
23. Bliwise DL, Freeman A, Ingram CD, Rye DB, Chakravorty S, Watts RL. Randomized, double-blind, placebo-controlled, short-term trial of ropinirole in restless legs syndrome. *Sleep Med*. 2005;6(2):141–147.
24. Allen R, Becker PM, Bogan R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. *Sleep*. 2004;27(5):907–914.
25. Partinen M, Hirvonen K, Jama L, et al. Efficacy and safety of pramipexole in idiopathic restless legs syndrome: a polysomnographic dose-finding study – the PRELUDE study. *Sleep Med*. 2006;7(5):407–417.
26. García-Borreguero D, Allen RP, Benes H, et al. Augmentation as a treatment complication of restless legs syndrome: concept and management. *Mov Disord*. 2007;22(Suppl 18):S476–S484.
27. García-Borreguero D, Williams AM. Dopaminergic augmentation of restless legs syndrome. *Sleep Med Rev*. 2010;14(5):339–346.
28. Horizant® (gabapentin enacarbil) [prescribing information]. Santa Clara, CA: XenoPort, Inc.; revised May 2013.
29. Hendrich J, Van Minh AT, Heblich F, et al. Pharmacological disruption of calcium channel trafficking by the alpha2delta ligand gabapentin. *Proc Natl Acad Sci U S A*. 2008;105(9):3628–3633.
30. Dooley DJ, Taylor CP, Donevan S, Feltner D. Ca2+ channel alpha2delta ligands: novel modulators of neurotransmission. *Trends Pharmacol Sci*. 2007;28(2):75–82.
31. Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, et al; European Federation of Neurological Societies; European Neurological Society; European Sleep Research Society. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. *Eur J Neurol*. 2012;19(11):1385–1396.
32. Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. *Am J Kidney Dis*. 2001;38(1):104–108.
33. Happe S, Sauter C, Klösch G, Saletu B, Zeitlhofer J. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. *Neuropsychobiology*. 2003;48(2):82–86.
34. Micozkadioglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M. Gabapentin versus levodopa for the treatment of Restless Legs Syndrome in hemodialysis patients: an open-label study. *Ren Fail*. 2004;26(4):393–397.
35. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology*. 2002;59(10): 1573–1579.
36. Neurontin® (gabapentin) [prescribing information]. New York: Pfizer, Inc.; revised Dec 2012.
37. Gidal BE, Radulovic LL, Kruger S, Rutecki P, Pitterle M, Bockbrader HN. Inter- and intra-subject variability in gabapentin absorption and absolute bioavailability. *Epilepsy Res*. 2000;40(2–3):123–127.
38. Stewart BH, Kugler AR, Thompson PR, Bockbrader HN. A saturable transport mechanism in the intestinal absorption of gabapentin is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma. *Pharm Res*. 1993;10(2):276–281.
39. Lal R, Sukbuntherng J, Luo W, et al. Pharmacokinetics and tolerability of single escalating doses of gabapentin enacarbil: a randomized-sequence, double-blind, placebo-controlled crossover study in healthy volunteers. *Clin Ther*. 2009;31(8):1776–1786.
40. XenoPort, Inc. Gabapentin Enacarbil (GSK1838262) Adult Restless Legs Syndrome Post Marketing Commitment Study (CONCORD). Available from: http://clinicaltrials.gov/ct2/show/NCT01668667?term=concord&rank=1. Accessed: January 6, 2014.
41. Lal R, Sukbuntherng J, Luo W, et al. Clinical pharmacokinetics of gabapentin after administration of gabapentin enacarbil extended-release tablets in patients with varying degrees of renal function using data from an open-label, single-dose pharmacokinetic study. *Clin Ther*. 2012;34(1):201–213.
42. Cundy KC, Sastry S, Luo W, Zou J, Moors TL, Canafax DM. Clinical pharmacokinetics of XP13512, a novel transported prodrug of gabapentin. *J Clin Pharmacol*. 2008;48(12):1378–1388.
43. Lal R, Ellenbogen A, Chen D, et al. A randomized, double-blind, placebo-controlled, dose-response study to assess the pharmacokinetics, efficacy, and safety of gabapentin enacarbil in subjects with restless legs syndrome. *Clin Neuropharmacol*. 2012;35(4):165–173.
44. Cundy KC, Annamalai T, Bu L, et al. XP13512 [(±)-1-([(alpha-isobutanoyloxyethoxy)carbonyl] aminomethyl)-1-cyclohexane acetic acid], a novel gabapentin prodrug: II. Improved oral bioavailability, dose proportionality, and colonic absorption compared with gabapentin in rats and monkeys. *J Pharmacol Exp Ther*. 2004;311(1): 324–333.

45. Cundy KC, Branch R, Chernov-Rogan T, et al. XP13512 [(±)-1-([(alpha-isobutanoyloxyethoxy)carbonyl] aminomethyl)-1-cyclohexane acetic acid], a novel gabapentin prodrug: I. Design, synthesis, enzymatic conversion to gabapentin, and transport by intestinal solute transporters. *J Pharmacol Exp Ther*. 2004;311(1):315–323.
46. Lal R, Sukbuntherng J, Luo W, Huff FJ, Zou J, Cundy KC. The effect of food with varying fat content on the clinical pharmacokinetics of gabapentin after oral administration of gabapentin enacarbil. *Int J Clin Pharmacol Ther*. 2010;48(2):120–128.
47. Lal R, Sukbuntherng J, Ho J, Cundy KC. A phase I, single-dose study of the disposition of 14C-radiolabeled gabapentin enacarbil in healthy male volunteers. *Int J Clin Pharmacol Ther*. 2011;49(2):109–115.
48. Lal R, Sukbuntherng J, Luo W, et al. Clinical pharmacokinetics of gabapentin after administration of gabapentin enacarbil extended-release tablets in patients with varying degrees of renal function using data from an open-label, single-dose pharmacokinetic study. *Clin Ther*. 2012;34(1):201–213.
49. Chen C. Meta-analyses of dose-exposure relationships for gabapentin following oral administration of gabapentin and gabapentin enacarbil. *Eur J Clin Pharmacol*. 2013;69(10):1809–1817.
50. Kushida CA, Walters AS, Becker P, et al; XP021 Study Group. A randomized, double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients with primary restless legs syndrome. *Sleep*. 2009;32(2):159–168.
51. Walters AS, Ondo WG, Kushida CA, et al; XP045 Study Group. Gabapentin enacarbil in restless legs syndrome: a phase 2b, 2-week, randomized, double-blind, placebo-controlled trial. *Clin Neuropharmacol*. 2009;32(6):311–320.
52. Kushida CA, Becker PM, Ellenbogen AL, Canafax DM, Barrett RW; XP052 Study Group. Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. *Neurology*. 2009;72(5):439–446.
53. Lee DO, Ziman RB, Perkins AT, Poceta JS, Walters AS, Barrett RW; XP053 Study Group. 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(3):282–292.
54. Bogan RK, Bornemann MA, Kushida CA, Trân PV, Barrett RW; XP060 Study Group. Long-term maintenance treatment of restless legs syndrome with gabapentin enacarbil: a randomized controlled study. *Mayo Clin Proc*. 2010;85(6):512–521.
55. Ellenbogen AL, Thein SG, Winslow DH, et al. A 52-week study of gabapentin enacarbil in restless legs syndrome. *Clin Neuropharmacol*. 2011;34(1):8–16.
56. Winkelman JW, Bogan RK, Schmidt MH, Hudson JD, DeRossett SE, Hill-Zabala CE. Randomized polysomnography study of gabapentin enacarbil in subjects with restless legs syndrome. *Mov Disord*. 2011;26(11):2065–2072.
57. VanMeter SA, Kavanagh ST, Warren S, Barrett RW. Dose response of Gabapentin Enacarbil versus placebo in subjects with moderate-to-severe primary restless legs syndrome: an integrated analysis of three 12-week studies. *CNS Drugs*. 2012;26(9):773–780.
58. Lal R, Sukbuntherng J, Luo W, Tovera J, Lassauzet ML, Cundy KC. Population pharmacokinetics and pharmacodynamics of gabapentin after administration of gabapentin enacarbil. *J Clin Pharmacol*. 2013;53(1):29–40.
59. Bogan RK, Ellenbogen A, Becker PM, et al. Gabapentin enacarbil in subjects with moderate to severe primary restless legs syndrome with and without severe sleep disturbance: an integrated analysis of subjective and novel sleep endpoints from two studies. *J Parkinsonism Restless Legs Syndrome*. 2013;3:31–40.
60. Inoue Y, Uchimura N, Kuroda K, Hirata K, Hattori N. Long-term efficacy and safety of gabapentin enacarbil in Japanese restless legs syndrome patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;36(2):251–257.
61. Inoue Y, Hirata K, Uchimura N, Kuroda K, Hattori N, Takeuchi M. Gabapentin enacarbil in Japanese patients with restless legs syndrome: a 12-week, randomized, double-blind, placebo-controlled, parallel-group study. *Curr Med Res Opin*. 2013;29(1):13–21.
62. Center for Drug Evaluation and Research. Application number: 022399Orig1s000 Medical Review. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022399Orig1s000MedR.pdf. Accessed: January 6, 2014.
63. Center for Drug Evaluation and Research. Application number: 022399Orig1s000 Summary Review. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022399Orig1s000SumR.pdf. Accessed: January 6, 2014.
64. Irizarry MC, Webb DJ, Boudiaf N, et al. Risk of cancer in patients exposed to gabapentin in two electronic medical record systems. *Pharmacoepidemiol Drug Saf*. 2012;21(2):214–225.
65. Kohnen R, Allen RP, Benes H, et al. Assessment of restless legs syndrome – methodological approaches for use in practice and clinical trials. *Mov Disord*. 2007;22(Suppl 18):S485–S494.
66. Stiasny-Kolster K, Benes H, Peglau I, et al. Effective cabergoline treatment in idiopathic restless legs syndrome. *Neurology*. 2004;63(12):2272–2279.
67. Fulda S, Wetter TC. Where dopamine meets opioids: a meta-analysis of the placebo effect in restless legs syndrome treatment studies. *Brain*. 2008;131(4):902–917.
68. Center for Drug Evaluation and Research. Application number: 022399Orig1s000 Pharmacology Review. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022399Orig1s000PharmR.pdf. Accessed: January 6, 2014.
69. Center for Drug Evaluation and Research. Application number: 022399Orig1s000 Cross Discipline Team Leader Review. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022399Orig1s000CrossR.pdf. Accessed: January 6, 2014.
70. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. *Circulation*. 2012;126(14):1689–1694.
71. Innes KE, Selfe TK, Agarwal P. Restless legs syndrome and conditions associated with metabolic dysregulation, sympathoadrenal dysfunction, and cardiovascular disease risk: a systematic review. *Sleep Med Rev*. 2012;16(4):309–339.
72. Tippmann-Peikert M, Park JG, Boeve BF, Shepard JW, Silber MH. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. *Neurology*. 2007;68(4):301–303.
73. Driver-Dunckley ED, Noble BN, Hentz JG, et al. Gambling and increased sexual desire with dopaminergic medications in restless legs syndrome. *Clin Neuropharmacol*. 2007;30(5):249–255.
74. Voon V, Schoerling A, Wenzel S, et al. Frequency of impulse control behaviours associated with dopaminergic therapy in restless legs syndrome. *BMC Neurol*. 2011;11:117.