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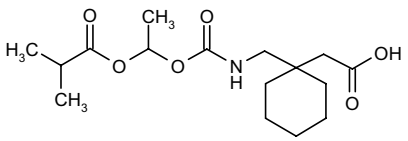
Gabapentin Enacarbil

Prop INN

Treatment of Restless Legs Syndrome
Treatment of Postherpetic Neuralgia
Treatment of Neuropathic Pain

XP-13512

(±)-2-[1-[1-(Isobutyryloxy)ethoxycarbonylaminomethyl]cyclohexyl]acetic acid



$C_{16}H_{27}NO_6$
Mol wt: 329.3887

CAS: 478296-72-9

EN: 332087

Abstract

Gabapentin enacarbil is a prodrug of the widely used anticonvulsant and analgesic agent gabapentin. Gabapentin itself has limited and variable bioavailability, thought to be due to its dependence on a low-capacity amino acid transporter expressed in the upper small intestine. Gabapentin enacarbil was designed to be recognized by high-capacity transport proteins expressed all along the intestinal tract, making it suitable for sustained-release formulation for colonic absorption. Clinical studies have shown that sustained-release gabapentin enacarbil has improved efficacy over the parent compound for the treatment of sleep loss in patients with restless legs syndrome. Preliminary results also indicate improvements in the treatment of pain associated with postherpetic neuralgia.

Synthesis

Gabapentin enacarbil can be prepared by several related methods.

1) Gabapentin (I) is acylated with 1-chloroethyl chloroformate (II) by means of chlorotrimethylsilane and triethylamine to give the corresponding carbamate (III), which is then condensed with isobutyric acid (IV) in the presence of triethylamine to afford the target gabapentin prodrug (1, 2). Alternatively, gabapentin enacarbil is obtained by direct condensation of gabapentin (I) with either 1-(isobutyryloxy)ethyl 4-nitrophenyl carbonate (V) (3, 4) or 1-(isobutyryloxy)ethoxycarbonyloxy succinimide (VI) (5). Scheme 1.

The acylating reagents (V) and (VI) can be obtained as follows:

1-Chloroethyl 4-nitrophenyl carbonate (VII), prepared from 1-chloroethyl chloroformate (II) and *p*-nitrophenol, is reacted with sodium iodide in acetone to give the 1-iodoethyl carbonate (VIII), which is condensed with silver isobutyrate (IX) in hot toluene to yield 1-(isobutyryloxy)ethyl 4-nitrophenyl carbonate (V) (3, 4). Alternatively, 1-chloroethyl chloroformate (II) is treated with a variety of thiol compounds, including MeSH, EtSH, *t*-BuSH and PhSH, in the presence of a tertiary amine to yield the respective thiocarbonate derivatives (Xa-d), which are subsequently condensed with isobutyric acid (IV), producing the corresponding *O*-[1-(isobutyryloxy)ethyl]thiocarbonates (XIa-d). The thiocarbonate esters (XI) are then displaced with *N*-hydroxysuccinimide (XII) utilizing different hydroperoxy reagents, such as peracetic acid, mCPBA, MgMPP, permaleic acid, etc., to furnish the target succinimidyl carbonate (VI) (5). Scheme 2.

2) In an alternative method, gabapentin (I) is previously protected as the corresponding benzyl (XV) or allyl ester (XVIII). The benzyl ester of gabapentin (XV) is prepared by protection of the amino group of (I) as the *N*-Boc derivative (XIII), followed by esterification of the carboxyl group with benzyl bromide and K_2CO_3, and deprotection of the resulting *N*-Boc amino ester (XIV) with HCl in dioxane. Gabapentin benzyl ester (XV) is then condensed with 1-chloroethyl chloroformate (II) in the presence of NMM to provide the carbamate (XVI), which is condensed with isobutyric acid (IV) by means of NMM to give the benzyl ester of gabapentin enacarbil (XVII). This is finally debenzylated by catalytic hydrogenation over Pd/C (6). Alternatively, gabapentin (I) is esterified with allyl alcohol employing $SOCl_2$ to afford the allyl ester (XVIII), which is condensed with 1-chloroethyl chloroformate (II), followed by displacement of the obtained chloroethyl carbamate (XIX) with isobutyric acid (IV), to produce the allyl ester of

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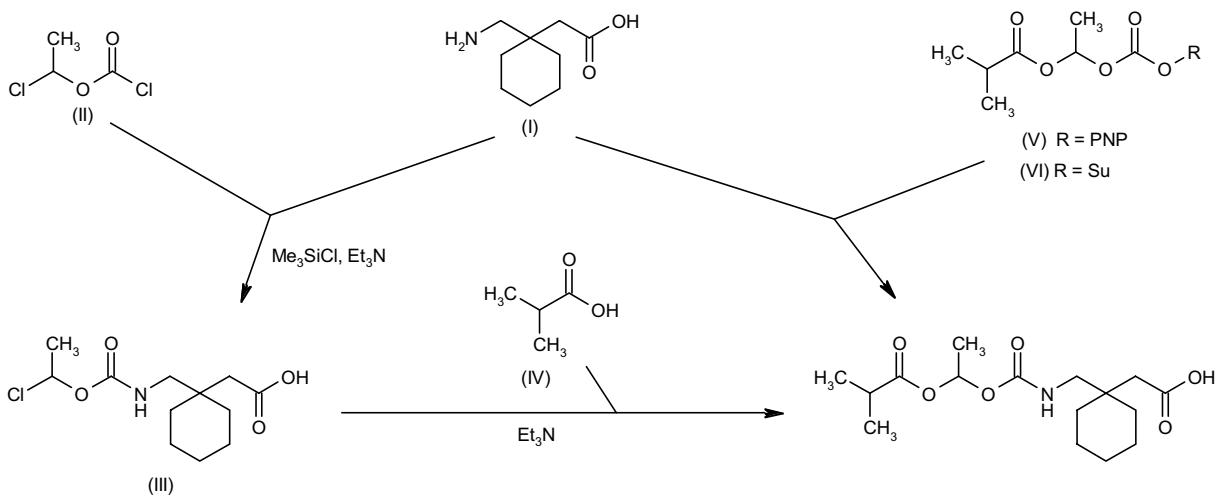
Scheme 1: Synthesis of Gabapentin Enacarbil



gabapentin enacarbil (XX). The allyl ester group of (XX) is finally removed by transfer hydrogenation in the presence of ammonium formate and Pd/C (2). Scheme 3.

Background

Restless legs syndrome (RLS) is an uncontrollable urge to move the legs in order to stop painful or odd sensations in the legs. Many people experience symptoms during prolonged periods of physical inactivity, such as when they try to sleep, and although moving or massaging the legs relieves the sensation for a while, the disruption to sleep can be a major contributor to the poor quality of life of RLS sufferers. The condition has a prevalence of 3-15% of the general population in the U.S. and Europe, and the National Institute of Neurological Disorders and Stroke (NINDS) estimates that RLS is the third largest sleep disorder in the U.S. (7-9).

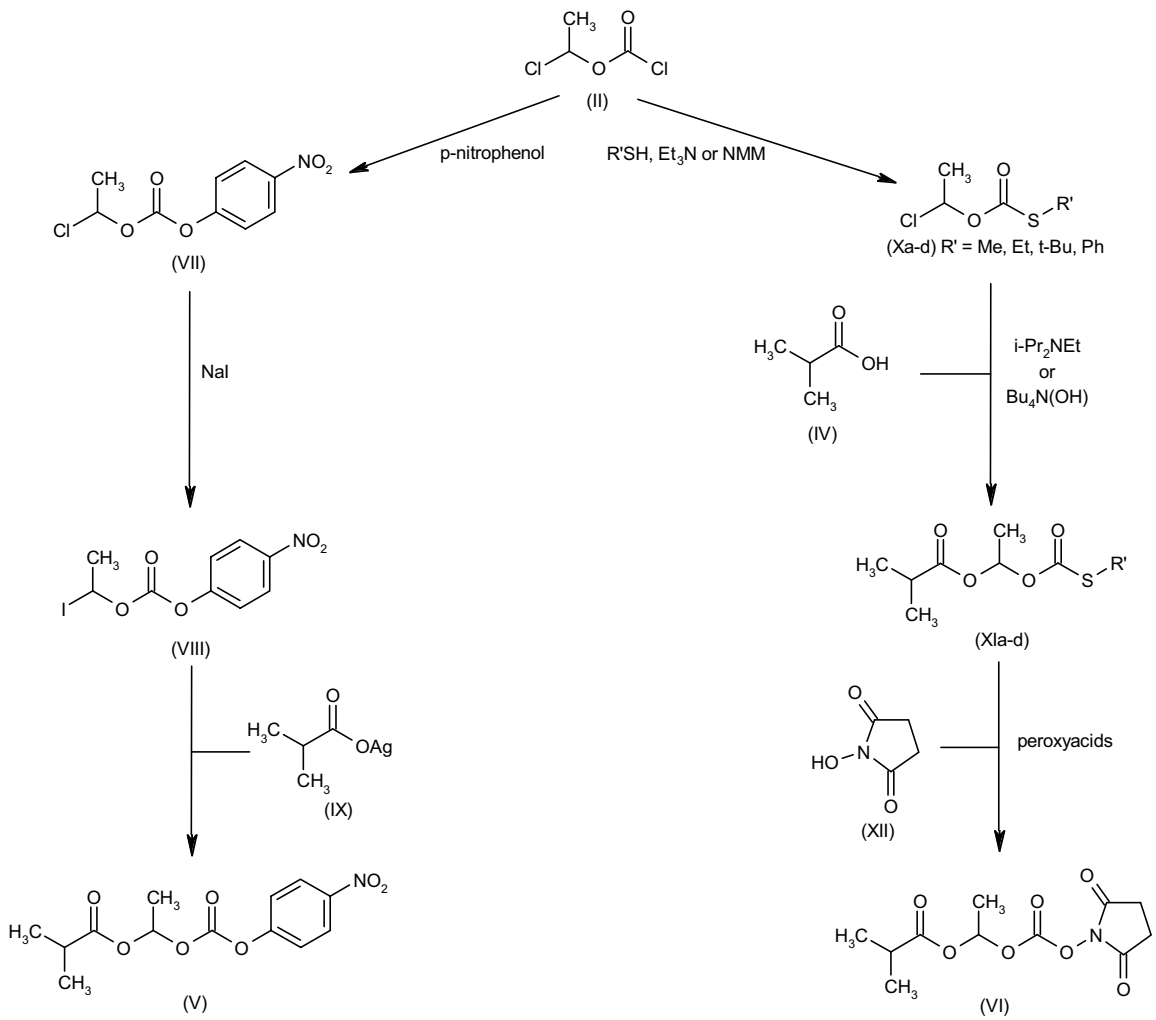
RLS is either primary or secondary. Primary, or idiopathic, RLS is associated with dopaminergic dysfunction and iron deficiency, and there is a high incidence of familial cases (25-75%), suggesting a genetic component to the disease. The onset of primary RLS is gradual and occurs at an earlier age than secondary RLS. Secondary RLS has a sudden onset, usually in people around 40 years of age, and is associated with hormonal changes, iron deficiency, peripheral neuropathies, some autoimmune disorders and certain antidepressants and antipsychotics. Treatment of the underlying condition that causes secondary RLS often eliminates the symptoms, although medication may be required for those whose RLS disrupts sleep. Current treatment options include dopamine agonists such as ropinirole for movement control, opioids for pain relief, benzodiazepines such as clonazepam to assist in staying asleep, and anticonvulsants such as gabapentin (8, 9).

Postherpetic neuralgia (PHN) is a painful neuropathic complication of herpes zoster, or shingles, caused by the reactivation of latent varicella-zoster virus. It affects zones of the skin served by the dorsal root ganglia. It is estimated that around 1 million individuals in the U.S. develop herpes zoster, 20% of whom go on to suffer from PHN. Current treatments include narcotics, tricyclic antidepressants and anticonvulsants (10).

Gabapentin, originally marketed as Neurontin® by Pfizer for the treatment of epilepsy and postherpetic neuralgia, is a 3-substituted analogue of the neurotransmitter GABA that has also demonstrated efficacy in RLS and several other disorders. It has been used for many years and has a good safety profile, although it has dose-limiting oral bioavailability: 60% of gabapentin is orally bioavailable at subtherapeutic doses, dropping to 35% or less at doses required for the treatment of neuropathic pain (11-14). Additionally, large interpatient variability in bioavailability makes dose optimization difficult, a factor which is thought to have contributed to a high rate of nonresponders (70%) to gabapentin therapy (12, 15). One possible reason for the poor pharmacokinetic properties of gabapentin is the apparent requirement for an L-amino acid transporter. This transporter has a low capacity, is localized specifically in the upper small intestine and has variable rates of expression from person to person (13).

Gabapentin enacarbil (XP-13512) is a prodrug of gabapentin designed to be absorbed by high-capacity nutrient transporters found all along the intestinal tract of humans, and rapidly converted to gabapentin. This is expected to result in a more efficient and consistent oral absorption of the drug and to allow colonic absorption of a sustained-release formulation. Gabapentin enacarbil is under clinical development for the treatment of RLS and neuropathic pain caused by PHN (1, 16-18).

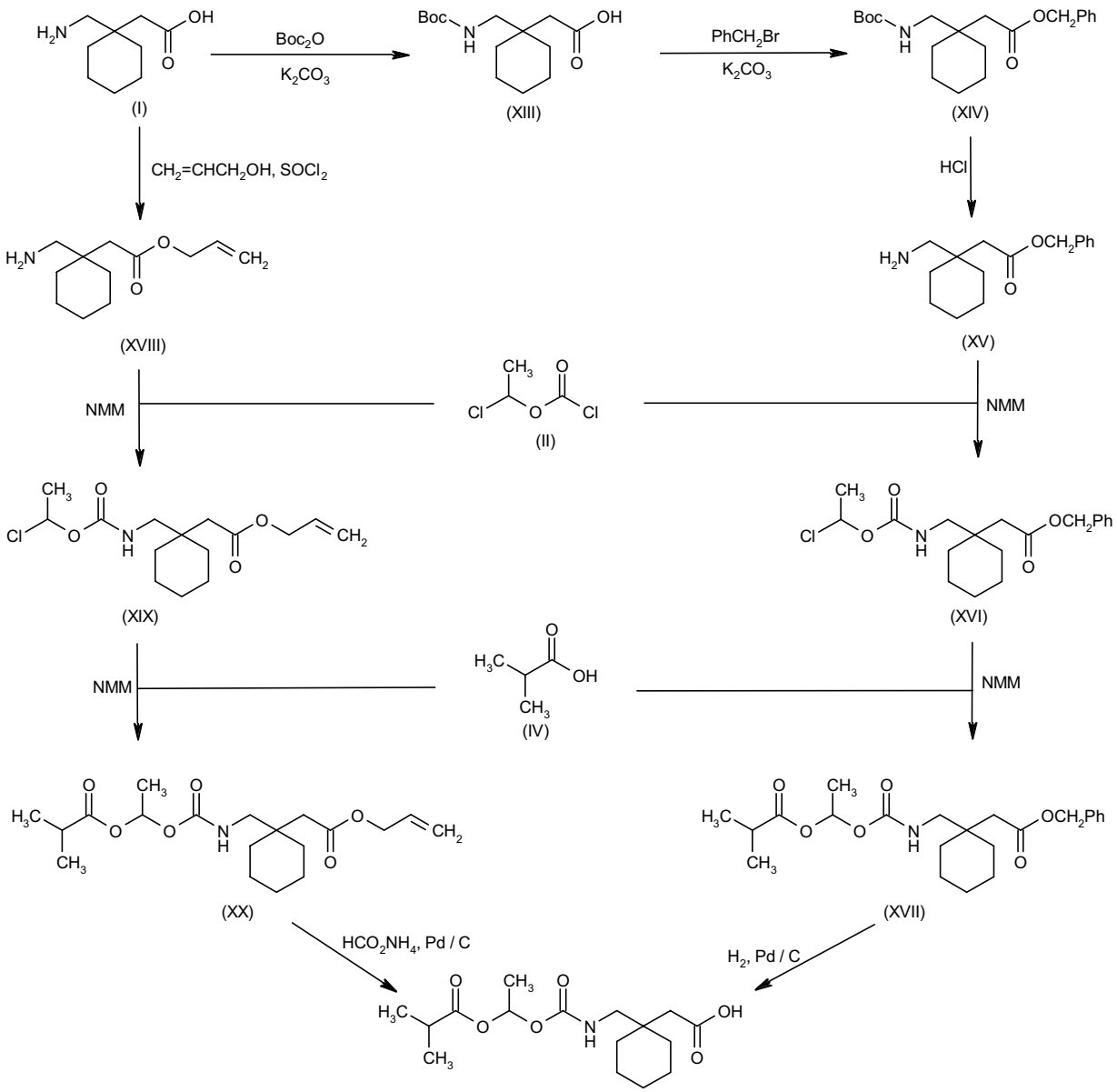
Scheme 2: Synthesis of Intermediates (V) and (VI)



Pharmacokinetics and Metabolism

In vitro experiments showed that gabapentin enacarbil is stable at physiological pH, but is rapidly converted to gabapentin by nonspecific esterases in rat, dog, monkey and human intestinal, kidney and liver tissues. The prodrug was not a substrate or inhibitor of the major cytochrome P-450 isoforms. Gabapentin enacarbil showed a pH-dependent passive permeability and preferential apical to basolateral permeability across cultured intestinal cell monolayers. In an analysis of transport mechanisms, cells expressing either the monocarboxylate transporter type-1 (MCT-1) or the sodium-dependent multivitamin transporter (SMVT) took up gabapentin enacarbil. These proteins are high-capacity solute transporters found throughout the human intestinal tract, suggesting an improved bioavailability and colonic absorption following administration of the prodrug over gabapentin itself (1). These predictions were borne out in animal studies. In rats, the prodrug was essentially completely converted to gabapentin (> 99%), with a $t_{1/2}$ of 5 min (*vs.* 1.8 h for gabapentin) following i.v. administration (16). Also in rats, the oral bioavailability of gabapentin following administration of the prodrug was consistently high (57.5%-71.2%), whereas following gabapentin it decreased from 83.8% after a dose of 25 mg/kg p.o. to 47.5% after a dose of 200 mg/kg; > 95% of an oral dose of [^{14}C]-gabapentin enacarbil was excreted in the urine in 24 h as gabapentin. In monkeys, the oral bioavailability of gabapentin was 84.2% following administration of the prodrug as capsules compared with 25.4% for an equimolar dose of gabapentin capsules. The bioavailability of gabapentin following intracolonic gabapentin enacarbil was also higher in rats and monkeys than a comparable dose of gabapentin, suggesting that gabapentin enacarbil may be suitable for extended-release formulation (16).

Scheme 3: Synthesis of Gabapentin Enacarbil



In a double-blind phase I study, healthy subjects (n=8/group) were randomized to ascending single doses of oral immediate-release gabapentin enacarbil (350, 700, 1400, 2100 and 2800 mg) or placebo. After a 1-week washout period, patients received an equimolar dose of gabapentin. Gabapentin enacarbil was rapidly absorbed and converted to gabapentin following oral administration. The oral bioavailability of gabapentin following gabapentin enacarbil was in the range of 70-85%, independent of dose, and AUC values were dose-proportional. In contrast, the bioavailability of gabapentin showed a dose-dependent decrease from 65% at 200 mg to 27% at 1200 mg and above, and AUC values were non-dose-proportional, indicating saturation of the transporter. In a second double-blind phase I study, doses of 350, 700, 1400 and 2100 mg of immediate-release gabapentin enacarbil were administered orally twice a day for 7 days (n=10/group). The mean steady-state pharmacokinetic parameters were dose-proportional, and oral bioavailability was consistently > 70% (19).

A sustained-release formulation of gabapentin enacarbil was assessed in a randomized, crossover phase I study in 12 healthy volunteers in which groups 1 and 2 received 1200 mg gabapentin enacarbil (equivalent to 625 mg gabapentin) with or without food, and group 3 received 600 mg gabapentin without food. When administered with food, the sustained-release prodrug provided a 2-fold greater gabapentin AUC and an almost 3-fold delay in t_{max} compared to an equimolar dose of gabapentin. The bioavailability of gabapentin from the prodrug form was 73.7% in fed subjects and 46.5% in fasted subjects compared to 37.7% for oral gabapentin capsules (20).

Clinical Studies

In a multicenter, randomized, double-blind, placebo-controlled, crossover phase IIa trial (Study XP021), 36 RLS patients were administered oral sustained-release gabapentin enacarbil (600 mg at 5:00 pm and a further 1200 mg 1 h before bedtime) or placebo for 2 weeks. The primary endpoint was an improvement in the International Restless Legs Scale (IRLS) upon drug treatment. A significant change from baseline was observed for those on gabapentin enacarbil (–12.1 *versus* –1.9 for placebo). Secondary endpoints of Clinical Global Impression (CGI) of Change, subjective measures of sleep and Suggested Immobilization Tests (SIT; a measure of leg discomfort) were also significantly improved. Polysomnographic measurement indicated that gabapentin enacarbil-treated patients gained 25.2 min of total sleep time, 21.3 min of stage 3 and 4 sleep time and had 28.2 min less wake time after persistent sleep onset compared to placebo. There were also fewer awakenings (3.8 *versus* 5.9 for placebo) and fewer periodic limb movements with arousal (29.3 *versus* 46.3 for placebo). The drug was well tolerated, with no serious adverse effects. The most common adverse effects were somnolence and dizziness (21). The results of this and several of the following studies are summarized in Table I.

Another multicenter, double-blind, placebo-controlled phase IIb trial (Study XP045) enrolled 95 previously untreated patients diagnosed with RLS who were randomized to receive sustained-release gabapentin enacarbil 600 or 1200 mg or placebo once daily at 5:00 p.m. with food for 2 weeks. At the end of the treatment period, the higher dose was associated with a significant improvement in the IRLS score (–16.1 *versus* –8.9 for placebo). The secondary endpoints of patient and investigator CGI of Change, subjective measures of sleep, including overall quality of sleep, the number of awakenings and the number of hours awake per night due to RLS symptoms, and the severity of RLS symptoms in the evening were all significantly improved. Those in the lower dose treatment group showed no improvement over placebo. Gabapentin enacarbil was generally well tolerated, there were no serious adverse events, and the most common adverse events were somnolence and dizziness (22).

Gabapentin enacarbil has also been evaluated in a phase IIa clinical study for the treatment of pain associated with PHN. In this randomized, double-blind, placebo-controlled study, 101 PHN patients with a pain score of at least 4 on a scale of 0-10 and with pain for > 3 months after the herpes zoster skin rash had healed were first treated with 600 mg gabapentin t.i.d. for 10 days, and were then switched to either 1200 mg gabapentin enacarbil or placebo b.i.d. for 14 days. Pharmacokinetic analysis showed a mean increase of 17% in the plasma concentration of gabapentin at the end of gabapentin enacarbil treatment compared to at the end of gabapentin treatment in the same patient. Patients in the gabapentin enacarbil treatment arm had a significantly lower mean daily pain score over the last week of treatment compared to the last week of treatment with gabapentin itself (differ-

Table I: Clinical studies of gabapentin enacarbil (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Restless legs syndrome	Randomized Double-blind Crossover Multicenter	Gabapentin enacarbil, 600 mg [at 5 PM] + 1200 mg [1 h before bed] x 2 wks Placebo	36	Gabapentin enacarbil reduced restless legs syndrome symptoms and improved sleep	21
Restless legs syndrome	Randomized Double-blind Multicenter	Gabapentin enacarbil, 600 mg o.d. x 2 wks Gabapentin enacarbil, 1200 mg o.d. x 2 wks Placebo	95	International Restless Legs Scale total scores were significantly improved after 2 weeks on the higher dose of gabapentin enacarbil compared to placebo	22
Neuralgia, postherpetic	Randomized Double-blind Multicenter	Gabapentin, 600 mg p.o. t.i.d. → Gabapentin enacarbil, 1200 mg b.i.d. x 14 d (n=47) Gabapentin, 600 mg p.o. t.i.d. → Placebo n=54)	101	Gabapentin enacarbil was well tolerated and increased gabapentin exposure, with significant pain reduction in subjects with postherpetic neuralgia	23
Restless legs syndrome	Randomized Double-blind	Gabapentin enacarbil, 1200 mg p.o. o.d. x 12 wks Placebo	210	A phase III study will evaluate the safety and efficacy of gabapentin enacarbil for the treatment of restless legs syndrome	25
Restless legs syndrome	Randomized Double-blind	Gabapentin enacarbil o.d. Placebo	300	This phase III study, which began in April 2006, will assess the long-term safety profile and efficacy of gabapentin enacarbil in patients with restless legs syndrome	27

ence = –0.4). Of these responders, a subgroup of patients whose mean plasma concentrations increased by more than 30% upon being switched to gabapentin enacarbil showed a more pronounced difference in the mean pain score (difference = –0.9 compared to treatment with gabapentin itself in the same patient). This effect was not seen in those whose average gabapentin concentration increased by < 20% upon being switched to gabapentin enacarbil (difference = –0.2). Improvements were also seen in sleep interference scores, quality of life scores and mood states upon gabapentin enacarbil treatment. Gabapentin enacarbil was well tolerated in this study, the most common adverse effect being dizziness (23).

Four phase III trials are planned or under way for gabapentin enacarbil in the treatment of RLS (24). Study XP052 is a randomized, double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of 1200 mg of gabapentin enacarbil administered once a day at approximately 5:00 pm for 12 weeks. This trial is anticipated to enroll approximately 200 patients and results are expected in the first half of 2007 (25). Study XP053 is a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of 600 and 1200 mg of gabapentin enacarbil administered once a day at approximately 5:00 pm for 12 weeks (26). A third trial (Study XP060) will evaluate the long-term efficacy of gabapentin enacarbil using a placebo-controlled, randomized withdrawal to evaluate the relapse of RLS symptoms in gabapentin enacarbil- or placebo-treated patients who had previously achieved clinical improvement while taking 1200 mg of gabapentin enacarbil for 24 weeks (27). Finally, an open-label extension of up to 12 months is also planned (Study XP055), which, together with the other phase III studies, will provide further safety and efficacy data on gabapentin enacarbil (28).

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XenoPort, Inc. (US); licensed to Astellas Pharma for Japan and certain other Asian countries.

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