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Pregabalin
In the Treatment of Postherpetic Neuralgia

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Contents

Abstract

▲ Pregabalin, the pharmacologically active *S*-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid, has a similar pharmacological profile to that of its developmental predecessor gabapentin, but showed greater analgesic activity in rodent models of neuropathic pain.

▲ The exact mechanism of action of pregabalin is unclear, although it may reduce excitatory neurotransmitter release by binding to the α_2-δ protein subunit of voltage-gated calcium channels.

▲ Oral pregabalin 150–600 mg/day, administered twice or three times daily, was superior to placebo in relieving pain and improving pain-related sleep interference in three randomised, double-blind, placebo-controlled, multicentre studies of 8–13 weeks' duration in a total of 776 evaluable patients with postherpetic neuralgia (PHN).

▲ Weekly mean pain scores (primary endpoint; assessed in all three studies) and weekly mean sleep interference scores (assessed in two studies) were significantly improved at 1 week. In two studies, significant improvements in daily mean pain scores were apparent on the first or second day of treatment with pregabalin administered three times daily.

▲ Pregabalin was generally well tolerated when force-titrated over 1 week to fixed dosages (maximum 600 mg/day) in clinical trials that enrolled mostly elderly PHN patients. Dizziness, somnolence and peripheral oedema of mild-to-moderate intensity were the most common adverse events.

Features and properties of pregabalin (Lyrica®, CI-1008)	
Indication	
Postherpetic neuralgia	
Putative mechanism of action	
Binds to the α_2-δ protein subunit of voltage-gated calcium channels and reduces excitatory neurotransmitter release	
Dosage and administration	
Recommended dosage	150–600 mg/day
Route of administration	Oral
Frequency of administration	2 or 3 times daily
Mean pharmacokinetic parameters (1–300mg single oral dose in healthy volunteers)	
Bioavailability	≈90% (no plasma protein binding)
Peak plasma concentration	0.04–9.46 mg/L
Time to peak plasma concentration	1.3h
Area under the plasma concentration-time curve	0.2–66.3 mg • h/L
Metabolism and elimination	Negligible hepatic metabolism, with primarily renal elimination (98% as unchanged drug)
Elimination half-life	4.6–6.8 hours
Adverse events	
Most frequent	Dizziness, somnolence and peripheral oedema

Herpes zoster infection ('shingles') leads to a characteristic vesicular dermatomal rash that is typically accompanied – and usually preceeded – by pain. Postherpetic neuralgia (PHN) refers to pain that lasts beyond a defined (e.g. 3 months), but as yet not universally accepted, interval after rash onset or healing.[1] As many as 1 million people in the US may be affected by this condition,[2] which can be physically and socially debilitating, and is commonly associated with allodynia.[1] The risk of developing PHN increases with advancing age; ≈50% of patients over the age of 70 years have pain that persists for 12 months after healing.[1]

As with other forms of neuropathic pain, the management of PHN relies mainly on pharmacological control of pain symptoms in conjunction with nonpharmacological approaches (e.g. physical therapy, psychosocial interventions).[1,2] Recommended (first-line) treatments include tricyclic antidepressants (TCAs; e.g. nortryptyline, desipramine),[1-3] controlled-release opioid analgesics (e.g. oxycodone, morphine sulphate)[1-3] the topical lidocaine (lignocaine) patch,[1-3] gabapentin[1-3] and pregabalin[3] (Lyrica®)[1] – the subject of this profile. Drawbacks with some of these agents include: a slow onset of analgesic action (TCAs); a potentially limiting adverse effect profile, especially in elderly patients (the predominant PHN population) [TCAs and opioids]; and lack of suitability for long-term use (lidocaine). Moreover, patients commonly require a combination of therapies for adequate pain relief, which increases the risk of drug-related adverse events.[2,4] Alternative rapidly acting, effective and safe treatments are therefore desirable. To date, only the 5% lidocaine patch and gabapentin have been approved by the US FDA for use in this indication;[2] pregabalin (3-isobutyl GABA), the pharmacologically active *S*-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid,[5] has also received an approvable letter[6] (see section 6).

Developed as a follow-up compound to gabapentin, pregabalin has been shown to be effective in the treatment of several disorders, including neuropathic pain [PHN and painful diabetic peripheral neuropathy [DPN]), epilepsy (add-on treatment of partial seizures) and generalised anxiety disorder.[5] This profile, however, focuses on the efficacy and tolerability of oral pregabalin in the treatment of PHN.

1. Pharmacodynamic Profile

- Pregabalin has a similar pharmacological profile to that of gabapentin.[7,8] It demonstrated antiallodynic and antihyperalgesic activities in various rodent models of neuropathic pain, including: vincristine-,[9] streptozocin-[10] and nerve injury-induced[11-13] mechanical allodynia; formalin-,[14] carrageenan-,[14,15] substance P-,[16] NMDA-,[16] and thermal injury-induced[17,18] hyperalgesia; and surgically-induced mechanical allodynia.[19] The effective dosages of pregabalin in these models were 2- to 4-fold lower than those of gabapentin.[7]

- The exact mechanism of action of pregabalin is unclear.[5] It is a structural analogue of GABA, like gabapentin, although neither compound interacts with GABA-A or -B receptors, or influences GABA uptake.[8,20]

- Pregabalin (and gabapentin) may, however, modulate the presynaptic release of excitatory neurotransmitters, such as glutamate and noradrenaline (norepinephrine), by selectively binding with high affinity to α_2-δ protein, an auxiliary subunit of voltage-gated calcium channels[21-23] (see also review by Lauria-Horner and Pohl[7]). Recent structure-activity studies as well as results with a mutant mouse model of neuropathic pain indicate that binding to α_2-δ protein is a prerequisite for the analgesic actions of pregabalin.[24]

- Both pregabalin and gabapentin modulated the release of the sensory neuropeptides substance P and calcitonin gene-related peptide from rat spinal tissues, but only under conditions that correspond to significant inflammation-induced sensitisation of the spinal cord.[25]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

2. Pharmacokinetic Profile

Pharmacokinetic data pertaining to oral administration of pregabalin in healthy volunteers is only available as abstracts,[26-28] whereas that in patients with PHN,[29] or in otherwise healthy subjects with various degrees of renal function or end-stage renal failure (ESRF),[30] has been published in full. Additional information is available from earlier reviews of the drug,[5,7] as well as a recent summary of pharmacokinetic studies published as an abstract.[31] Mean pharmacokinetic parameters are reported throughout this section.

- Pregabalin was rapidly absorbed and displayed linear pharmacokinetics after oral administration in a total of 86 healthy volunteers.[27,28] The time to peak plasma concentration (C_{max}), was 1.3 hours.[28] Both C_{max} and the area under the plasma concentration-time curve (AUC) increased in proportion to the dose following single rising (1–300mg) or multiple rising (25–300mg every 8 hours then 300mg every 12 hours) doses.[27] Values for C_{max} and the AUC following a single 1–300mg dose are listed in the Features and Properties table.
- The oral bioavailability of pregabalin was ≈90%.[28] Food delayed the rate, but not extent, of pregabalin absorption.[31] The drug does not undergo substantial metabolism after oral administration in healthy volunteers, nor does it bind to plasma proteins.[5,15] The lack of hepatic metabolism (and of pregabalin activity at cytochrome P450 enzymes) was reflected in an absence of pharmacokinetic drug-drug interactions in relevant studies.[31] However, no further details are available.[5,15,31]
- Renal excretion is the primary route of elimination of pregabalin; 98% of the administered dose is eliminated as unchanged drug in the urine.[31] Urinary recovery of pregabalin was independent of the dose, although it was slightly higher after multiple- than single-dose administration.[27] The elimination half-life ($t_{1/2}$) was ≈6 hours (range, 4.6–6.8 hours following a single 1–300mg dose[28]), and was independent of the dose.[27]

The pharmacokinetics of a single 50mg oral dose of pregabalin have been investigated in 26 otherwise healthy subjects aged 18–75 years with various degrees of renal function.[30] For the purposes of making pregabalin dosage recommendations, subjects were stratified according to the following creatinine clearance (CL_{CR}) groups: >60 mL/min (n = 11); 30–60 mL/min (n = 7); 15–29 mL/min (n = 7); and <15 mL/min (n = 1). An additional 12 subjects with ESRF (urinary output ≤200 mL/24 hours) who were stable on three-times-weekly haemodialysis were also studied; pregabalin was administered ≈24 hours before the next scheduled dialysis session.[30]

- Pregabalin oral clearance was directly proportional to CL_{CR} in patients not on dialysis; it was 56.5, 30.6, 16.7 and 8.3 mL/min in the >60, 30–60, 15–29 and <15 mL/min CL_{CR} groups, respectively. In line with this, $t_{1/2}$ was prolonged and $AUC_{0-\infty}$ was increased. Pregabalin was effectively cleared in patients with ESRF undergoing dialysis, with each 4-hour haemodialysis session removing ≈50–60% of the amount of drug initially present in the circulation.[30]

The pharmacokinetics of pregabalin were further studied as part of an 8-week, randomised, double-blind, placebo-controlled, multicentre clinical trial in 173 patients with PHN[29] (section 3). To achieve equivalent pregabalin exposure, treatment was stratified according to CL_{CR}; hence, 59 patients with a CL_{CR} of >60 mL/min received pregabalin 200mg three times daily, whereas 30 patients with a CL_{CR} of >30 to ≤60 mL/min received pregabalin 100mg three times daily.

- Dosage adjustment based on CL_{CR} resulted in similar plasma pregabalin concentrations in the two groups. Patients in the >30 to ≤60 mL/min CL_{CR} group had plasma concentrations of the drug in the range 2.4–4.8 mg/L, as observed 1.00–6.67 hours after dosing, and a predicted average plasma concentration of 6.64 (range 4.05–14.4) mg/L. By comparison, patients in the >60 mL/min CL_{CR} group had plasma concentrations in the range 0.244–18.6 mg/L (seen 0.75–17.8 hours post-dose) and a predicted average plasma concentration of 8.36 (range 3.45–15.7) mg/L. Across all patients, the pregabalin volume of distribution and clearance ranged from 29.8–34.2L and 42.7–52.2 mL/min, respectively.[29]

3. Therapeutic Trials

The efficacy of pregabalin in the treatment of PHN has been evaluated in three randomised, double-blind, placebo-controlled, multicentre studies of 8–13 weeks' duration.[29,32-35] Relevant data from two of these trials (n = 173[29] and 238[32]) have been published in full papers[29,32] and/or in an abstract,[36] whereas data from the third trial (n = 370[33-35]) have been reported in abstracts only.[33-35] Also available as an abstract is an analysis of six follow-on, open-label extensions of randomised, double-blind, placebo-controlled clinical trials in patients with neuropathic pain (PHN or DPN).[37]

Patients aged ≥18 years with PHN (defined as pain present for >3 months after healing of a herpes zoster skin rash) were considered eligible if: (i) they had completed at least four daily pain diaries and had a minimum daily score of ≥4 on an 11-point numerical pain rating scale[38] (0 = no pain to 10 = worst possible pain) during the baseline week preceeding randomisation; and (ii) they had pain equivalent to ≥40mm on the 100mm visual analogue scale (VAS) of the Short-form McGill Pain Questionnaire (SF-MPQ) at baseline and randomisation visits.[29,32,33]

Exclusion criteria included CL_{CR} ≤30 mL/min or failure to respond to previous treatment with gabapentin ≥1200 mg/day and prior neurolytic or neurosurgical therapy for PHN.[29,32,33] All three trials enrolled mostly elderly patients (mean age 70.5–73.2 years).[29,32,33] In two trials, the mean duration of PHN was 33.3–40.7 months.[29,32]

The primary efficacy parameter was the endpoint weekly (i.e. averaged over the preceeding 7 days) mean pain score on the 11-point numerical rating scale[38] from patients' daily pain diaries.[29,32,33] A supplementary analysis of the primary efficacy parameter was the responder rate (i.e. proportion of patients with a ≥30% and ≥50% reduction in mean pain score from baseline to endpoint).[29,32,33]

Secondary efficacy measures common to two or more of the three studies included: SF-MPQ VAS;[29,32] daily sleep interference score (averaged over the preceeding 7 days on an 11-point numerical rating scale: 0 = no interference to 10 = complete interference);[29,32,33] Medical Outcomes Study (MOS) sleep problem index;[29,33] and Patient Global Impression of Change (PGIC).[29,32] Another secondary efficacy parameter, health-related quality of life (HRQoL), was assessed using self-administered instruments, namely the SF-36 Health Survey (two trials[29,32]) or the EuroQol Health State Profile (EQ-5D; one trial[35]).

Pregabalin dosages of 150 and 300 mg/day were administered twice daily[33] or three times daily,[32] in two separate studies. Likewise, pregabalin 600 mg/day was administered twice daily[33] or three times daily[29] in two separate studies. Patients assigned to the 600 mg/day dosage groups received pregabalin 600 mg/day only if their CL_{CR} was >60 mL/min; those with a CL_{CR} of >30 to ≤60 mL/min received a clinically equivalent dosage of pregabalin 300 mg/day.[29,33] Pregabalin was force-titrated to the final fixed dosage over a 1-week period.[29,32,33]

Presented below are the results of efficacy analyses performed on the intent-to-treat (ITT) population, defined as all patients who received at least one dose of study medication.[29,32,33] The ITT populations were 87, 98 and 90 for the pregabalin 150, 300 and 600 mg/day twice daily groups (vs 93 for placebo) in one study;[33] 80 and 76 for the pregabalin 150 and 300 mg/day three times daily groups (vs 80 for placebo) in a second study;[32] and 88 for the pregabalin 600 mg/day three times daily group (vs 84 for placebo) in a third study.[29]

- Pregabalin 150–600 mg/day was superior to placebo in relieving pain associated with PHN. Moreover, analyses of the primary efficacy parameter across all three studies appeared to show a dose-dependent effect.[29,32,33] The endpoint least squares (LS) mean pain scores were as follows: 4.81, 4.72 and 4.07 with pregabalin 150, 300 and 600 mg/day twice daily ($p \leq 0.01$ vs placebo [5.74]; all values estimated from a graph);[33] 5.14 and 4.76 with pregabalin 150 and 300 mg/day three times daily ($p \leq 0.0002$ vs placebo [6.33]);[32] and 3.60 with pregabalin 600 mg/day three times daily ($p = 0.0001$ vs placebo [5.29]).[29] Baseline LS mean pain scores were between ≈6 and 7 for all treatment groups in all three studies.[29,32,33]

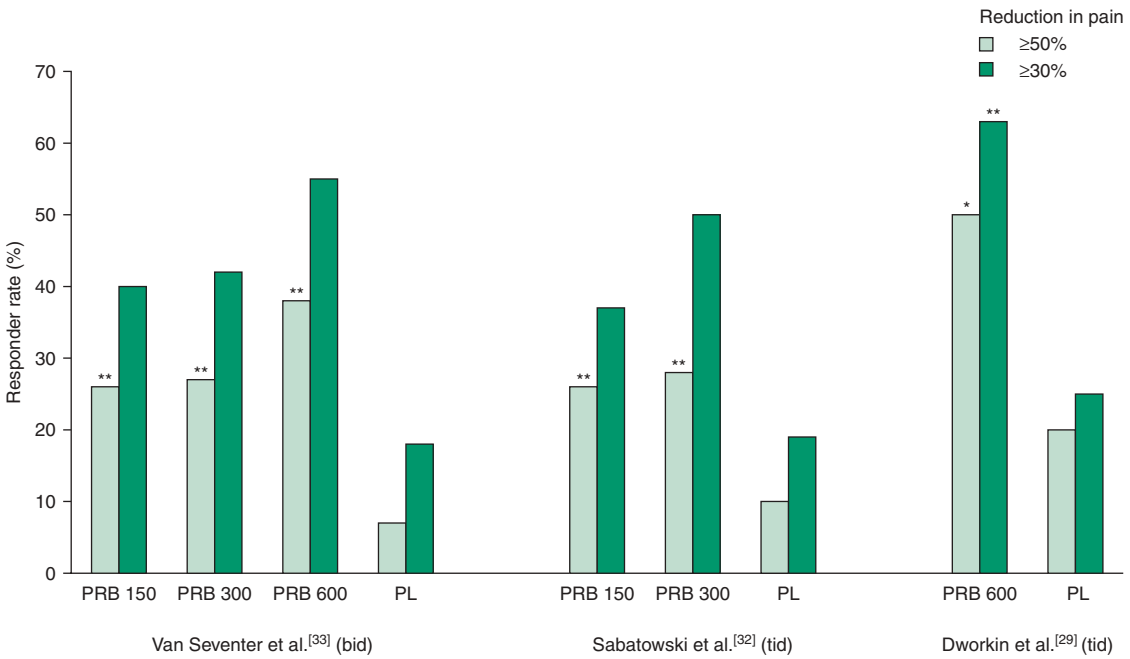

Fig. 1. Efficacy of pregabalin (PRB) in the treatment of postherpetic neuralgia (PHN). The proportion of responders (i.e. those experiencing ≥30% and ≥50% reductions in pain from baseline to endpoint, based on endpoint change in weekly mean pain score [primary endpoint]) among patients with PHN receiving PRB 150, 300 or 600 mg/day, or placebo (PL), administered twice daily (bid) or three times daily (tid), for 8–13 weeks in three double-blind, multicentre trials (n = 173–370).[29,32,33] As indicated, PRB dosage data are derived from one (bid)[33] or two (tid)[29,32] separate trials. Patients assigned to PRB 600 mg/day bid[33] or tid[29] dosage groups were stratified according to renal function: 600 mg/day was administered to those with a creatinine clearance (CL_{CR}) of >60 mL/min and a clinically equivalent dosage of 300 mg/day was administered to those with a CL_{CR} of >30 to ≤60 mL/min. Statistical comparisons of responder rates based on ≥30% reduction in pain with PRB 150–600 mg/day bid and PRB 150 and 300 mg/day tid versus corresponding PL not available. * $p \leq 0.05$ (actual value not provided), ** $p \leq 0.006$ vs corresponding PL.

- In the trial in which treatment was stratified according to renal function,[29] the significant difference in endpoint mean pain scores between pregabalin and placebo recipients persisted when patients in each of the two CL_{CR} subgroups were analysed separately (data not provided).

- Significant improvements in weekly mean pain scores compared with placebo were seen beginning at week 1 in all three studies and were sustained throughout 8–13 weeks' treatment ($p < 0.01$).[29,32,34]

- Of note, daily mean pain scores were significantly improved compared with placebo beginning on the first day of treatment in the titrated pregabalin 300 mg/day three times daily group ($p = 0.036$; initial dosage 75 mg/day), and beginning on the second day of treatment in the titrated pregabalin 150 mg/day three times daily ($p = 0.014$; initial dosage 75 mg/day) and 600 mg/day three times daily ($p = 0.004$; initial dosage 150 mg/day) groups.[36] Corresponding daily mean pain scores for the pregabalin 150–600 mg/day twice daily groups have not been reported.

- Responder rates based on ≥50% and ≥30% reductions in pain from baseline to endpoint across all three trials[29,32,33] are shown in figure 1.

- Pregabalin 150–600 mg/day had a beneficial effect on the secondary outcome measure of sleep interference. Compared with placebo, endpoint LS mean sleep interference scores were significantly reduced with both twice daily ($p < 0.001$[34]) and three times daily ($p \leq 0.0003$[29,32]) dosage regimens. Weekly mean sleep interference scores were significantly improved by the end of the first week of treatment with both twice daily (p-value not provid-

ed[34]) and three times daily ($p < 0.01$[29,32]) regimens. There were also significant improvements on the MOS sleep problem index versus placebo at study endpoint ($p < 0.003$ for all twice daily regimens;[34] $p = 0.0001$ for 600 mg/day three times daily[29]).

- With regard to other secondary efficacy measures, pregabalin 150–600 mg/day three times daily led to significantly lower SF-MPQ (VAS) scores by the end of the first week of treatment ($p < 0.01$ vs placebo[29]); this improvement was sustained at study endpoint ($p \leq 0.006$ vs placebo).[29,32] Pregabalin 300 or 600 mg/day three times daily was also superior to placebo on the PGIC ($p \leq 0.002$).[29,32] Corresponding SF-MPQ scores and PGIC assessments with pregabalin 150–600 mg/day twice daily regimens are not available.

- Pregabalin administered three times daily improved some measures of HRQoL, as assessed using the SF-36 Health Survey.[29,32] Significant ($p < 0.05$ vs placebo) improvements were reported for the following domains: mental health (with pregabalin dosages of 150 and 300 mg/day); vitality (300 mg/day); general health perception (600 mg/day); and bodily pain (300 and 600 mg/day).[29,32] Similarly, pregabalin administered twice daily improved measures of HRQoL, as assessed using the EQ-5D.[35] Significant ($p < 0.01$ vs placebo) improvements were reported for pain relief, EQ-5D utility score and VAS AUC with each pregabalin dosage (150, 300 and 600 mg/day).[35]

- Pregabalin 150–600 mg/day (dosage frequency not specified) appeared to be an effective long-term maintenance therapy based on an *ad hoc* analysis of a subset of 217 PHN or DPN patients (relative proportions not specified) who received the drug for ≥420 days in open-label extensions of randomised clinical trials.[37] Moreover, tolerance to flexible dosages of pregabalin (range 75–600 mg/day; dosage frequency not specified) did not develop based on another *ad hoc* analysis of all 517 PHN or DPN patients (relative proportions not specified) who received the drug for ≥420 days in open-label studies.[37]

4. Tolerability

The following preliminary tolerability profile of pregabalin is based on 779 patients with PHN who were evaluated for safety in three randomised, placebo-controlled trials of pregabalin 150–600 mg/day administered twice daily or three times daily for 5–8 weeks[29,32,33] (section 3).

- Pregabalin was generally well tolerated when force-titrated over 1 week to fixed dosages (maximum 600 mg/day) in the above-mentioned studies, which enrolled mostly elderly PHN patients[29,32,33] (section 3). Double-blind treatment completion rates appeared to be dose dependent; they were 88% and 79% with pregabalin 150 and 300 mg/day three times daily (vs 75% with placebo),[32] and 65% with pregabalin 600 mg/day three times daily (vs 88% with placebo).[29]

- The most frequently occurring adverse events included dizziness, somnolence, peripheral oedema, headache, dry mouth and diarrhoea. These (and other) adverse events were often[32] or mostly[29,33] mild to moderate in intensity.

- The three most common adverse events appeared to be dose dependent. The incidences of dizziness were 12% and 28% with pregabalin 150 and 300 mg/day three times daily (vs 15% with placebo), [32] and 28% with pregabalin 600 mg/day three times daily (vs 12% with placebo).[29] The incidences of somnolence were 15% and 24% with pregabalin 150 and 300 mg/day three times daily (vs 7% with placebo),[32] and 25% with pregabalin 600 mg/day three times daily (vs 7% with placebo).[29] The incidences of peripheral oedema were 3% and 13% with pregabalin 150 and 300 mg/day three times daily (vs 0% with placebo),[32] and 19% with pregabalin 600 mg/day three times daily (vs 2% with placebo).[29]

- The incidences of dizziness, somnolence and peripheral oedema with pregabalin dosages of 150–600 mg/day twice daily were 28.7%, 15.3% and 13.5%;[33] the respective incidences with placebo were 9.7%, 4.3% and 10.8%. Separate results for pregabalin 150, 300 and 600 mg/day twice daily dosages are unavailable.

- Discontinuation rates due to adverse events appeared to be dose dependent; they were 11% and

16% with pregabalin 150 and 300 mg/day three times daily (vs 10% with placebo),[32] and 32% with pregabalin 600 mg/day three times daily (vs 5% with placebo).[29] Somnolence (11.2%) was cited as the most common reason for discontinuing the drug in one study.[29]

- Exposure to pregabalin 150–600 mg/day was not associated with clinically significant changes in laboratory indices (e.g. haematology, blood chemistry, urinalysis and electrocardiogram), or in visual, physical and neurological examinations.[29,32]

5. Dosage and Administration

Based on EU approval (see below), the recommended pregabalin dosage range for the treatment of neuropathic pain, which includes DPN and PHN, is 150–600 mg/day administered in two or three divided doses (with or without food).[39] An initial dosage of 150 mg/day may be increased to 300 mg/day after 3–7 days, based on individual patient response and tolerability; if necessary, the dosage can be increased to 600 mg/day after an additional 7 days.[39] Pregabalin dosage adjustment should be considered in cases of renal impairment (section 2).[30]

6. Pregabalin: Current Status in Postherpetic Neuralgia

Three well designed studies have shown pregabalin 150–600 mg/day to be effective and generally well tolerated in reducing pain and sleep interference in patients with PHN when dosed 2 or 3 times daily.

In July 2004, pregabalin received EU approval for the treatment of peripheral neuropathic pain, which includes PHN and DPN, and as adjunctive therapy for partial seizures in patients with epilepsy.[40] In September 2004, the US manufacturer announced that pregabalin had received approvable letters from the US FDA for PHN, DPN and as adjunctive therapy in the treatment of partial seizures in adults.[6]

References

1. Kanazi GE, Johnson RW, Dworkin RH. Treatment of postherpetic neuralgia: an update. Drugs 2000 May; 59 (5): 1113-26
2. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003 Nov; 60 (11): 1524-34
3. Dubinsky RM, Kabbani H, El-Chami Z, et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004; 63: 959-65
4. Spruce MC, Potter J, Coppini DV. The pathogenesis and management of painful diabetic neuropathy: a review. Diabet Med 2003; 20 (2): 88-98
5. Huckle. Pregabalin (Pfizer). Curr Opin Investig Drugs 2004; 5 (1): 82-9
6. Pfizer Inc. Pfizer statement on regulatory status of Lyrica [online]. Available from URL: http://www.pfizer.com/are/news_releases/2004pr/mn_2004_0902.html [Accessed 2004 Sep 28]
7. Lauria-Horner BA, Pohl RB. Pregabalin: a new anxiolytic. Expert Opinon Investig Drugs 2003; 12 (4): 663-72
8. Bryans JS, Wustrow DJ. 3-Substituted GABA analogs with central nervous system activity: a review. Med Res Rev 1999; 19: 149-77
9. Nozaki-Taguchi N, Chaplan SR, Higuera ES, et al. Vincristine-induced allodynia in the rat. Pain 2001 Jul; 93 (1): 69-76
10. Field MJ, McCleary S, Hughes J, et al. Gabapentin and pregabalin, but not morphine and amitriptyline, block both static and dynamic components of mechanical allodynia induced by streptozocin in the rat. Pain 1999 Mar; 80 (1-2): 391-8
11. Field MJ, Bramwell S, Hughes J, et al. Detection of static and dynamic components of mechanical allodynia in rat models of neuropathic pain: are they signalled by distinct primary sensory neurones? Pain 1999 Nov; 83 (2): 303-11
12. Wallin J, Cui JG, Yakhnitsa V, et al. Gabapentin and pregabalin suppress tactile allodynia and potentiate spinal cord stimulation in a model of neuropathy. Eur J Pain 2002; 6 (4): 261-72
13. Chen SR, Xu Z, Pan HL. Stereospecific effect of pregabalin on ectopic afferent discharges and neuropathic pain induced by sciatic nerve ligation in rats. Anesthesiology 2001 Dec; 95 (6): 1473-9
14. Field MJ, Oles RJ, Lewis AS, et al. Gabapentin (neurontin) and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. Br J Pharmacol 1997 Aug; 121 (8): 1513-22
15. Hurley RW, Chatterjea D, Rose Feng M, et al. Gabapentin and pregabalin can interact synergistically with naproxen to produce antihyperalgesia. Anesthesiology 2002 Nov; 97 (5): 1263-73
16. Partridge BJ, Chaplan SR, Sakamoto E, et al. Characterisation of the effects of gabapentin and 3-isobutyl-gamma-aminobutyric acid on substance P-induced thermal hyperalgesia. Anesthesiology 1998 Jan; 88 (1): 196-205
17. Jun JH, Yaksh TL. The effect of intrathecal gabapentin and 3-isobutyl gamma-aminobutyric acid on the hyperalgesia observed after thermal injury in the rat. Anesth Analg 1998 Feb; 86 (2): 348-54
18. Jones DL, Sorkin LS. Systemic gabapentin and S(+)-3-isobutyl-gamma-aminobutyric acid block secondary hyperalgesia. Brain Res 1998 Nov 9; 810 (1-2): 93-9

19. Field MJ, Holloman EF, McCleary S, et al. Evaluation of gabapentin and S-(+)-3-isobutylgaba in a rat model of postoperative pain. J Pharmacol Exp Ther 1997 Sep; 282 (3): 1242-6

20. Bialer M, Johannessen SI, Kupferberg HJ, et al. Progress report on new antiepileptic drugs: a summary of the fifth Eilat conference (EILAT V). Epilepsy Res 2001; 43: 11-58

21. Fink K, Dooley DJ, Meder WP, et al. Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology 2002 Feb; 42 (2): 229-36

22. Dooley DJ, Mieske CA, Borosky SA. Inhibition of K(+)-evoked glutamate release from rat neocortex and hippocampal slices by gabapentin. Neurosci Lett 2001 Feb; 280 (2): 107-10

23. Dooley DJ, Donovan CM, Meder WP, et al. Preferential action of gabapentin and pregabalin at P/Q-type voltage-sensitive calcium channels: inhibition of K+-evoked. Synapse 2002 Sep 1; 45 (3): 171-90

24. Taylor CP. Meeting report: the biology and pharmacology of calcium channel alpha2-delta proteins. Pfizer satellite symposium to the 2003 Society for Neuroscience Meeting. CNS Drug Rev 2004; 10 (2): 159-64

25. Fehrenbacher JC, Taylor CP, Vasko MR. Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. Pain 2003; 105: 133-44

26. Corrigan BW, Pool WF, Posvar EL, et al. Metabolic disposition of pregabalin in healthy volunteers [abstract no. PI-68]. Clin Pharmacol Ther 2001 Feb; 69: P18

27. Bockbrader HN, Hunt T, Strand J, et al. Pregabalin pharmacokinetics and safety in healthy volunteers: results from two phase 1 studies [abstract no. P06.051]. Neurology 2000 Apr 11; 54 Suppl. 3: 421

28. Busch JA, Strand JC, Posvar EL, et al. Pregabalin (CI-1008) single-dose pharmacokinetics and safety/tolerance in healthy subjects after oral administration of pregabalin solution or capsule doses [abstract no. 2.108]. Epilepsia 1998; 39 Suppl. 6: 58

29. Dworkin RH, Corbin AE, Young Jr JP, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003 Apr 22; 60 (8): 1274-83

30. Randinitis EJ, Posvar EL, Alvey CW, et al. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol 2003 Mar; 43 (3): 277-83

31. Bockbrader HN, Wesche D. Pharmacokinetic profile of pregabalin: results of a series of studies [abstract no. NR378]. 157th Annual Meeting of the American Psychiatric Association; 2004 May 1-6; New York, 140

32. Sabatowski R, Galvez R, Cherry DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with postherpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain 2004; 109: 26-35

33. Van Seventer R, Bladin C, Hoggart B, et al. Pregabalin dosed twice a day (BID) efficaciously and safely treats neuropathic pain associated with postherpetic neuralgia [abstract no. 800]. J Pain 2004; 5 Suppl. 1: 58

34. Van Seventer R, Bladin C, Hoggart B, et al. Pregabalin dosed BID is efficacious for improving sleep interference in patients suffering from postherpetic neuralgia: results of a large, randomized, placebo-controlled trial [abstract no. 806]. J Pain 2004; 5 Suppl. 1: 60

35. van Seventer R, Feister H, Young Jr JP, et al. pregabalin dosed twice daily improves health-related quality of life in patients with postherpetic neuralgia [abstract no. P1371]. 8th Congress of the European Federation of Neurological Sciences; 2004 Sep 4; Paris

36. Rowbotham M, Young J, Sharma U, et al. Pregabalin shows reduction in pain by day three of treatment. J Pain 2003 Mar; 4 Suppl. 1: 63

37. Portenoy R, Sharma U, Young J, et al. Pregabalin sustains its efficacy as long-term maintenance therapy for neuropathic pain associated with diabetic neuropathy and postherpetic neuralgia [abstract no. 599-P]. Diabetes 2004 Jun; 53 Suppl. 2: 142

38. Farrar JT, Young Jr JP, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001 Nov; 94 (2): 149-58

39. Data on file, Pfizer, 2004

40. Pfizer Inc. Pfizer receives approval to market Lyrica for neuropathic pain and add-on epilepsy in Europe [online]. Available from URL: http://www.pfizer.com/are/news_releases/2004pr/mn_2004_0706.html [Accessed 2004 Sep 28]

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