Abstract

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

Pregabalin is thought to act by reducing the excessive release of several excitatory neurotransmitters by binding to the α2-δ protein subunit of voltage-gated calcium channels.

Oral pregabalin 150–600 mg/day, administered in two or three divided doses, was significantly more effective than placebo in relieving pain and improving pain-related sleep interference in four randomized, double-blind, multicentre studies of 4–13 weeks’ duration in patients with postherpetic neuralgia (PHN).

Pregabalin achieved a faster onset of pain relief than placebo. The median times to the onset of pain relief with fixed and flexible doses of pregabalin were 1.5 and 3.5 days compared with >4 weeks with placebo.

Pregabalin was generally well tolerated when titrated over 1 week to fixed dosages (maximum 600 mg/day) in clinical trials in mostly elderly PHN patients. Adverse events were usually mild to moderate in severity.
Herpes zoster (shingles) is caused by the re-activation of the varicella zoster virus lying dormant in the sensory spinal and cranial nerve ganglia following a primary infection (varicella chicken pox), usually in childhood. The main symptoms during the acute herpes zoster period are pain and the development of a characteristic vesicular dermatomal rash. Postherpetic neuralgia (PHN) is generally defined as pain that emerges subsequent to the resolution of the rash and persists for more than 3 months. The pain is often severe and can become physically and socially debilitating. The risk of developing PHN increases with advancing age, but data pertaining to the proportion of patients still experiencing pain 12 months after rash onset are conflicting. When pain associated with PHN was measured prospectively in the PINE (Prevention by epidural Injection of postherpetic Neuralgia in the Elderly) study in 598 patients aged >50 years, the proportion experiencing any pain after rash onset decreased from 92% to 16% in the first 6 months, and the proportion experiencing significant pain decreased from 73% in the acute phase to 8% at 3 months.

As with other forms of neuropathic pain, the management of PHN can be complex. It is further complicated by a lack of a definitive treatment algorithm specific to PHN. Recommended first-line pharmacological treatment includes tricyclic antidepressants (e.g. nortriptyline, desipramine), selective serotonin and norepinephrine reuptake inhibitors (e.g. duloxetine, venlafaxine), calcium channel α₂-δ ligands (gabapentin and pregabalin) and the topical lidocaine (lignocaine) patch. Controlled-release opioid analgesics and tramadol are generally recommended as second-line treatments. Because multiple mechanisms are thought to be involved in the cause of the neuropathic pain, combining agents with distinctly different mechanisms of action may increase efficacy.

Pregabalin (Lyrica®), the pharmacologically active S-enantiomer of 3-aminomethyl-5-methylhexanoic acid, was developed as a follow-up compound to gabapentin with the aim of improving efficacy and addressing the nonlinear pharmacokinetics associated with gabapentin. Pregabalin has demonstrated efficacy 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. This profile focuses on the efficacy and tolerability of oral pregabalin in the treatment of PHN. Medical literature on the use of pregabalin in patients with PHN was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

The pharmacological properties of pregabalin have been reviewed previously. This section summarizes the properties of pregabalin relevant to its use in patients with PHN.

- Pregabalin is associated with analgesic, anxiolytic and antiepileptic activity. In vitro, pregabalin selectively binds with high affinity to the α₂-δ protein, an auxiliary subunit of voltage-gated calcium channels, leading to a reduction of Ca²⁺ influx at presynaptic nerve endings. In a mutant mouse model of neuropathic pain, the analgesic effects of pregabalin were shown to be mediated through binding to the α₂-δ-1 subunit. As with gabapentin, pregabalin selectively binds with high affinity to the α₂-δ protein, an auxiliary subunit of voltage-gated calcium channels, leading to a reduction of Ca²⁺ influx at presynaptic nerve endings.

- In a mutant mouse model of neuropathic pain, the analgesic effects of pregabalin were shown to be mediated through binding to the α₂-δ-1 subunit.

- As with gabapentin, pregabalin is a structural analogue of the inhibitor neurotransmitter GABA, although neither compound interacts with GABAₐ, GABAₐ or benzodiazepine receptors, alters rat brain GABA levels or augments GABA responses in cultured neurons. However, with prolonged exposure to cultured neurons, pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport.

- Pregabalin does not block sodium channels and, therefore, is not expected to affect cardiac action potential. Furthermore, the drug does not inhibit dopamine, serotonin or norepinephrine
• Pregabalin is inactive at opiate, serotonin and dopamine receptors, and does not alter cyclooxygenase enzyme activity.\textsuperscript{[16]}

• Pregabalin demonstrated antiallodynic and antihyperalgesic activities in various rodent models of neuropathic pain including mechanical allodynia induced by vincristine,\textsuperscript{[17]} streptozocin\textsuperscript{[18]} and nerve injury\textsuperscript{[19-21]} or surgery,\textsuperscript{[22]} and hyperalgesia induced by formalin,\textsuperscript{[23]} carrageenan,\textsuperscript{[23,24]} substance P,\textsuperscript{[25]} NMDA\textsuperscript{[25]} and thermal injury.\textsuperscript{[26,27]} In the models that compared pregabalin with gabapentin, pregabalin was effective at dosages 1.6- to 10-fold lower than those of gabapentin.\textsuperscript{[18,20,22-27]}

• In markedly inflamed rat spinal tissue, pregabalin and gabapentin modulated the release of the sensory neuropeptides, substance P and calcitonin gene-related peptide.\textsuperscript{[28]}

• Overall, pregabalin was not associated with impaired cognitive and psychomotor function in a randomized, double-blind, crossover study in healthy volunteers, as determined using a validated test battery.\textsuperscript{[29]} Reaction time, vigilance or serial memory scanning were not significantly impaired relative to placebo, but transient minor impairment of CNS arousal, divided attention and sedation, and moderately improved brake reaction time (all \(p<0.05\)), were recorded.

2. Pharmacokinetic Profile

The pharmacokinetics of orally administered pregabalin have been reviewed previously.\textsuperscript{[6,9]} This section summarizes data obtained from studies in healthy volunteers (data presented in an abstract),\textsuperscript{[30]} patients with PHN,\textsuperscript{[31]} and in otherwise healthy subjects with various degrees of renal function,\textsuperscript{[32]} supplemented with the manufacturer’s prescribing information.\textsuperscript{[16]} Mean pharmacokinetic parameters are reported throughout.

General Profile

• After oral administration, pregabalin is rapidly absorbed and displays linear pharmacokinetics.\textsuperscript{[16]} The oral bioavailability of pregabalin is \(\geq 90\%\) and is independent of the dose.\textsuperscript{[16]} Both the peak plasma concentration (C\textsubscript{\text{max}}) and the area under the plasma concentration-time curve (AUC) increased in proportion to the dose following single (25–300 mg) or multiple (75–900 mg/day) doses.\textsuperscript{[16]} Steady state is achieved within 24–48 hours following repeated pregabalin administration.\textsuperscript{[16]}

• After single-dose pregabalin (1–300 mg) administration in healthy volunteers, C\textsubscript{\text{max}} was achieved in a mean of 1.3 hours. Mean C\textsubscript{\text{max}} was 0.04–9.46 mg/L and mean AUC was 0.2–66.3 mg • h/L.\textsuperscript{[30,33]}

• Food delays the rate, but not the extent, of pregabalin absorption, decreasing C\textsubscript{\text{max}} by \(=25–30\%\), and increasing the time to C\textsubscript{\text{max}} to \(=3\) hours.\textsuperscript{[16]}

• Oral pregabalin does not bind to plasma proteins.\textsuperscript{[6,24]} The mean apparent volume of distribution is \(=0.5\) L/kg. In animal studies, pregabalin was shown to cross the blood-brain barrier.\textsuperscript{[16]}

• The metabolism of pregabalin is negligible, with most of the drug excreted unchanged in the urine.\textsuperscript{[16]} After a radiolabelled dose of oral pregabalin, \(=90\%\) was recovered in the urine and only 0.9% was accounted for by the major metabolite (the N-methylated derivative). The mean elimination half-life (\(t_{1/2}\)) was 6.3 hours, and mean renal clearance is estimated at 67.0–80.9 mL/min.

• Pregabalin oral clearance is directly proportional to creatinine clearance (CL\textsubscript{CR}).\textsuperscript{[32]} In patients with varying degrees of renal impairment (including 12 undergoing haemodialysis), pregabalin exposure increased with decreasing renal function and was highly cleared by haemodialysis.\textsuperscript{[32]} Accordingly, mean \(t_{1/2}\) was prolonged and mean AUC from 0 to \(\infty\) was increased. Therefore, dosage reductions of pregabalin are necessary in patients with impaired renal function and in those undergoing haemodialysis.\textsuperscript{[16]}

• Consistent with age-related changes in renal function, pregabalin clearance is reduced in the elderly, and dosage reductions, based on CL\textsubscript{CR}, may be necessary.\textsuperscript{[16]}

• In an 8-week, randomized, double-blind, placebo-controlled trial in 173 patients with PHN,\textsuperscript{[31]} dosage adjustment stratified according to CL\textsubscript{CR} (patients with a CL\textsubscript{CR} >60 mL/min received pregabalin 200 mg three times daily, and patients with a CL\textsubscript{CR} of >30 to \(\leq 60\) mL/min received pregabalin 100 mg...
three times daily) resulted in similar plasma pregabalin concentrations in the two groups. Across all patients, the pregabalin volume of distribution and clearance ranged from 29.8–34.2 L and 42.7–52.2 mL/min, respectively.\textsuperscript{[31]}

Potential Drug Interactions

- Pregabalin is not associated with any pharmacokinetic drug interactions.\textsuperscript{[16]} Because the drug does not undergo hepatic metabolism and does not induce or inhibit cytochrome P450 (CYP) enzymes \textit{in vitro}, interactions with CYP1A2 or CYP3A4 substrates are not expected.

- In drug interaction studies in healthy volunteers and various patient populations, the concomitant administration of pregabalin with lorazepam, oxycodone, alcohol, antihyperglycaemics (glibenclamide [glyburide], insulin and metformin), furosemide (frusemide) and numerous anticonvulsants did not significantly affect the pharmacokinetics of pregabalin.\textsuperscript{[16]} The pharmacokinetics of oral contraceptives (norethisterone [norethindrone] and ethinylestradiol), lorazepam, oxycodone, alcohol and numerous anticonvulsants were not affected when coadministered with pregabalin.\textsuperscript{[16]}

3. Therapeutic Trials

This section focuses on the efficacy of pregabalin in the treatment of PHN reported in four randomized, double-blind, placebo-controlled, multicentre studies of 4–13 weeks’ duration.\textsuperscript{[31,34–36]} A brief discussion of the long-term efficacy of the drug, as reported in a noncomparative, open-label, 15-month extension study of patients with refractory neuropathic pain (44% had PHN and the remainder had DPN), is also included.\textsuperscript{[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 they had completed at least four daily pain diaries and had a minimum mean daily score of ≥24 on an 11-point numerical pain rating scale\textsuperscript{[38]} (0 = no pain to 10 = worst possible pain) during the baseline week preceding randomization, and they had pain equivalent to ≥40 mm on the 100 mm visual analogue scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) at baseline and randomization visits.\textsuperscript{[31,34–36]}

Exclusion criteria included CL\textsubscript{CR} ≤30\textsuperscript{[31,34,35]} or <60\textsuperscript{[36]} mL/min and prior neurolytic or neurosurgical therapy for PHN. All trials enrolled mostly elderly patients (mean age =67–73 years).\textsuperscript{[31,34–36]} and the mean duration of PHN ranged from approximately 30\textsuperscript{[36]} to 40.7\textsuperscript{[35]} months. In the open-label extension study in refractory patients, the mean age was 68 years and the mean duration of PHN was 7.4 years.\textsuperscript{[37]}

In the double-blind studies, the primary efficacy parameter was the endpoint weekly (i.e. averaged over the preceding 7 days) mean pain score\textsuperscript{[31,34,35]} or time to onset of pain relief,\textsuperscript{[36]} as determined by an 11-point numerical rating scale\textsuperscript{[38]} from patients’ daily pain diaries. 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).\textsuperscript{[31,34–36]}

Secondary efficacy measures included: SF-MPQ VAS;\textsuperscript{[31,34,37]} daily sleep interference score (averaged over the preceding 7 days on an 11-point numerical rating scale: 0 = no interference to 10 = complete interference);\textsuperscript{[31,34–36]} Medical Outcomes Study (MOS) sleep problem index;\textsuperscript{[31]} and Patient Global Impression of Change (PGIC).\textsuperscript{[31,34,36]} Another secondary efficacy parameter, health-related quality of life (HR-QOL), was assessed using the self-administered SF-36 Health Survey.\textsuperscript{[31,34]}

Pregabalin dosages of 150, 300 and 600 mg/day were administered in two\textsuperscript{[35]} or three\textsuperscript{[31,34]} divided doses. One study\textsuperscript{[36]} compared twice-daily fixed (pregabalin 300 mg/day) or flexible (pregabalin 150–600 mg/day) dosages with placebo. Dosage adjustments in the flexible-dose group were based on the patient’s clinical response and tolerability.\textsuperscript{[36]} Patients assigned to the 600 mg/day dosage groups received pregabalin 600 mg/day only if their CL\textsubscript{CR} was >60 mL/min; those with a CL\textsubscript{CR} of >30 to ≤60 mL/min received a clinically equivalent dosage of pregabalin 300 mg/day.\textsuperscript{[31,35]} In fixed dosage
groups, pregabalin was titrated to the final fixed dosage over 1 week. In the long-term study, patients received flexible dosages of pregabalin 150–600 mg/day three times daily for periods of 3 months, followed by a 3- to 28-day 'drug holiday', for a total of 15 months' treatment (i.e. five treatment cycles). Results of efficacy analyses performed on the intent-to-treat population, defined as all patients who received at least one dose of study medication (n = 368, n = 236, n = 172, n = 269, and n = 81), are presented.

- Pregabalin 150–600 mg/day was superior to placebo in relieving pain associated with PHN, and results suggest a dose-dependent effect. In the three studies that primarily assessed endpoint least squares (LS) mean pain scores, results were as follows: 5.26, 5.07 and 4.35 with pregabalin 150, 300 and 600 mg/day twice daily (all p<0.01 vs placebo [6.14]); 5.14 and 4.76 with pregabalin 150 and 300 mg/day three times daily (p≤0.0002 vs placebo [6.33]); and 3.60 with pregabalin 600 mg/day three times daily (p=0.0001 vs placebo [5.29]). Baseline LS mean pain scores were =6–7 across all treatment groups in each of the three studies.

- Significant improvements compared with placebo in weekly LS mean pain scores were seen at week 1 in all three studies and were sustained throughout 8–13 weeks' treatment (p<0.01). Pregabalin achieved an earlier onset of pain relief than placebo. The median times to the onset of pain relief were 1.5 days with fixed-dose pregabalin and 3.5 days with flexible-dose pregabalin. Because only 31% of patients receiving placebo met the criteria for pain relief during the 4-week study, the median time to onset of pain relief in the placebo group was considered to be >4 weeks (p<0.0001 for fixed- and flexible-dose pregabalin groups vs placebo). The difference in the time to onset of pain relief between the twice-daily fixed- and flexible-dose pregabalin treatment groups was not significant. At the time of onset of pain relief, the median dosages in the fixed- and flexible-dose groups were pregabalin 300 and 150 mg/day, respectively.

- Responder rates for patients achieving ≥50% and ≥30% reductions in pain from baseline to endpoint across all four trials are shown in figure 1. The difference between twice-daily pregabalin fixed- and flexible-dosing regimens did not reach statistical significance.

- Pregabalin 150–600 mg/day had a beneficial effect on sleep interference in all four trials. The endpoint LS mean sleep interference scores were significantly reduced with both two (p<0.001) and three times daily (p≤0.0003) dosage regimens compared with placebo. Weekly LS mean sleep interference scores were significantly improved by the end of the first week of treatment with both two and three times daily regimens (p<0.01 for all comparisons). At study endpoint, there were also significant improvements on the MOS sleep problem index with pregabalin 600 mg/day in three divided doses versus placebo (p=0.0001).

- In other secondary analyses, 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), with sustained improvement at study end (p≤0.006 vs placebo). Similarly, after 4 weeks' treatment, patients receiving twice-daily fixed- (300 mg/day) or flexible-dosages (pregabalin 150–600 mg/day) had significantly greater improvements on the SF-MPQ than those receiving placebo (p<0.001 for both).

- On the PGIC scale, patients receiving pregabalin 300 or 600 mg/day in three divided doses were more likely to experience improvement than those receiving placebo (p≤0.002). Similarly, in the studies using twice-daily pregabalin, global improvement was reported in significantly more patients receiving pregabalin 150 (p<0.05) or 600 mg/day (p<0.01) than those receiving placebo, and patients receiving fixed or flexible dosages of pregabalin were significantly more likely to rate themselves as being minimally, much or very much improved at endpoint than those receiving placebo (levels of significance not reported).
Fig. 1. Efficacy of pregabalin (PRB) in the treatment of postherpetic neuralgia (PHN). The proportion of responders experiencing ≥50% or ≥30% reduction in pain from baseline to endpoint, based on endpoint change in weekly mean pain score among patients with PHN receiving PRB fixed dosages of 150, 300 or 600 mg/day, or a flexible dosage of 150–600 mg/day, or placebo (PL), administered in two (bid) or three (tid) divided doses, for 4–13 weeks in four double-blind, multicentre trials: van Seventer et al. (n = 368), Sabatowski et al. (n = 236), Dworkin et al. (n = 172) and Stacey et al. (n = 269). * p < 0.01, ** p < 0.001, *** p < 0.0001 vs corresponding PL.

- VAS allodynia scores were improved significantly more in patients receiving twice-daily fixed- (300 mg/day) or flexible-dosages (pregabalin 150–600 mg/day) than in patients receiving placebo. Respective mean changes in scores at endpoint (week 4) were −20.8 mm (p < 0.01) and −26.2 mm (p < 0.0001) versus −11.8 mm. The difference between pregabalin groups and the placebo group was significant at each evaluation from week 1.

- Pregabalin three times daily was associated with an improvement in some measures of HRQOL. While differences between pregabalin and placebo treatment groups in some domains, including physical, social and emotional functioning, did not reach significance in either study, significantly (p < 0.05) greater improvement on the SF-36 was reported for body pain with pregabalin dosages of 300 or 600 mg/day, mental health (pregabalin 150 or 300 mg/day), vitality (pregabalin 300 mg/day) and general health perception (pregabalin 600 mg/day).

- Long-term (15 months) treatment with pregabalin was associated with sustained pain relief in patients with refractory neuropathic pain (including PHN and DPN). In a post hoc analysis, mean SF-MPQ VAS scores were similar and were improved by 34% from baseline during five pregabalin (150–600 mg/day in three divided doses) treatment cycles of 3 months. During each ‘drug holiday’, mean pain scores increased to baseline levels. Mean improvement in the SF-MPQ score was −23.2 in PHN patients and −25.4 in DPN patients.

4. Tolerability

The tolerability profile of pregabalin is based on data from well designed clinical trials in patients with PHN who received pregabalin 150–600 mg/day administered in two or three divided doses for 4–13 weeks (section 3).

- Pregabalin (maximum 600 mg/day) was generally well tolerated in clinical trials, which enrolled mostly elderly PHN patients. The most
frequently occurring adverse events included dizziness, somnolence, peripheral oedema, headache, dry mouth, ataxia and weight gain, which were usually mild to moderate in intensity.\textsuperscript{31,34-36} The most common treatment-emergent adverse events in the largest clinical trial (n = 368) are illustrated in figure 2.\textsuperscript{33}

- Discontinuation rates due to adverse events generally appeared to be dose dependent. In the studies administering pregabalin three times daily, discontinuation rates were 11\% and 16\% with pregabalin 150 and 300 mg/day versus 10\% with placebo,\textsuperscript{34} and 32\% with pregabalin 600 mg/day versus 5\% with placebo.\textsuperscript{31} In the studies administering pregabalin twice daily, the discontinuation rate for all patients receiving pregabalin 150, 300 or 600 mg/day was 13.5\% versus 4.3\% with placebo in one study,\textsuperscript{33} and in the other study, it was 18.2\% with fixed-dose pregabalin (300 mg/day) and 4.4\% with flexible-dose pregabalin (150–600 mg/day) versus 4.4\% with placebo.\textsuperscript{34} In one study administering pregabalin 600 mg/day in three divided doses, somnolence (11.2\%) was cited as the most common reason for discontinuing the drug.\textsuperscript{31}

- Clinically significant changes in laboratory variables (e.g. haematology, blood chemistry, urinalysis and ECG), or in visual, physical and neurological examinations were not associated with exposure to pregabalin 150–600 mg/day.\textsuperscript{31,34}

5. Pharmacoeconomic Considerations

Modelled pharmacoeconomic analyses have compared the cost effectiveness of pregabalin with gabapentin,\textsuperscript{39,40} desipramine,\textsuperscript{41} lidocaine 5\% plaster\textsuperscript{42} or various sequential management strategies for PHN.\textsuperscript{43} Analyses were based on randomized, controlled clinical trials (but none were based on head-to-head trials) in predominantly elderly patients with PHN. Two studies also included patients with DPN.\textsuperscript{39,40} Analyses included direct costs and were from the perspective of a healthcare payer over a time horizon of 3 or 6 months,\textsuperscript{39-42} except for one analysis\textsuperscript{43} that evaluated direct and indirect costs (discounted at 3\% per year) from a societal perspective over a lifetime horizon. All studies compared the cost per quality-adjusted life-year (QALY) gained.

As with all modelled analyses, these comparisons are subject to a number of limitations, with the potential for input data to differ from real-life situations. However, the following analyses were generally well conducted, included appropriate parameters and the model design was justified.
• Pregabalin (150–600 mg/day) was cost effective relative to gabapentin (900–3600 mg/day) with regard to the cost per QALY gained in two analyses modelled over 3 months; one from a Canadian perspective with a 2004 year of costing and one from a Spanish perspective with a 2006 year of costing. Pregabalin was estimated to achieve a mean of 9 (PHN patients only) and 8 (PHN and DPN patients) additional days with no or mild pain, and to provide an additional 0.0086 and 0.1186 QALYs compared with gabapentin. In the incremental cost-effectiveness ratio (ICER) analyses, pregabalin was dominant (i.e. less expensive and more effective) to gabapentin per QALY gained in Canada and the ICER in Spain was €20 535 per QALY gained relative to generic gabapentin.

• Desipramine (100 mg/day) was dominant relative to pregabalin (450 mg/day) or gabapentin (1800 mg/day), with regard to the cost per QALY gained, in the treatment of older patients with PHN in whom tricyclic antidepressants are not contraindicated (i.e. those without coronary artery disease) in a US analysis using a 2006 year of costing and modelled over 3 months. Gabapentin was the least cost effective, with an ICER of $US216 000 per QALY gained relative to pregabalin.

• Lidocaine 5% plaster was cost effective relative to pregabalin (300 or 600 mg/day) or gabapentin (1800 mg/day) with regard to the cost per QALY gained from a German perspective using a 2007 year of costing and modelled over 6 months. The ICER per QALY gained for lidocaine plaster was €3453 relative to gabapentin and €766 relative to pregabalin 300 mg/day. Lidocaine plaster dominated pregabalin 600 mg/day.

• In an analysis comparing the cost effectiveness of suggested treatment algorithms for PHN from a societal perspective (2005 year of costing), in patients with coronary artery disease, sequences beginning with generic gabapentin were favoured with respect to cost per QALY gained, with pregabalin or an opioid preferred next. In patients with no evidence of coronary artery disease, first-line treatment with a tricyclic antidepressant achieved a cost-effective option with regard to cost per QALY gained relative to first-line treatment with gabapentin.

• Sensitivity analyses were performed in all evaluations and demonstrated that results were generally robust to changes in key parameters.

6. Dosage and Administration

The recommended oral pregabalin dosage for the treatment of PHN in adults ranges from 150 to 600 mg/day in two or three divided doses. Dosage should commence with 150 mg/day and gradually increase to 300 mg/day within the first week. Dosage should be further titrated in week 2, based on individual patient response and tolerability, to a maximum of pregabalin 600 mg/day. If treatment needs to be discontinued, the dosage should be reduced gradually.

In patients with renal impairment or in those receiving haemodialysis, pregabalin dosage adjustment should be individualized based on CLCR (see manufacturer’s prescribing information). The local prescribing information should be consulted for detailed information, including contraindications, special warnings and precautions.

7. Pregabalin: Current Status in Postherpetic Neuralgia

Four well designed studies have shown that pregabalin 150–600 mg/day, administered in two or three divided doses, is effective in reducing pain and sleep interference, and is generally well tolerated, in patients with PHN.

Pregabalin is approved for the treatment of patients with peripheral neuropathic pain, which includes PHN and DPN, and as adjunctive therapy for partial seizures in patients with epilepsy in several countries including the US and EU.

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