National PBM Drug Monograph

Pregabalin (Lyrica®) C-V

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VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Pregabalin is a gabapentin-like agent that has been approved in the U.S. for painful diabetic neuropathy (PDN), postherpetic neuralgia (PHN), and partial seizures (PS). The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating pregabalin for possible addition to the VA National Formulary; (2) evaluate whether pregabalin and gabapentin exhibit a class effect; (3) define the role of pregabalin in therapy; and (4) identify parameters for its rational use in the VA.

Mechanism of action

- Pregabalin binds to the alpha$_2$-delta (A2D) receptors of an auxiliary subunit associated with voltage-gated calcium channels in central nervous system tissues, and thereby inhibits influx of calcium and release of glutamate, norepinephrine, substance P, and other neurotransmitters.

Pharmacokinetics

- Absorption of pregabalin is rapid and bioavailability seems to be better (≥ 90%) than that of gabapentin (27% to 60%).
- Unlike gabapentin, pregabalin exhibits linear pharmacokinetics and has low intersubject pharmacokinetic variability.
- Like gabapentin, pregabalin is eliminated primarily via renal excretion and is nearly proportional to creatinine clearance.

Dosage and Administration

- Painful diabetic neuropathy: Administer pregabalin in 3 divided doses. Initiate at 150 mg daily; may increase to maximum of 300 mg daily. Starting therapy with lower and less frequent doses would be reasonable measures to improve tolerability and patient convenience.
- Postherpetic neuralgia and partial-onset seizures: Administer pregabalin in 2 or 3 divided doses. Initiate at 150 mg daily; may increase to maximum of 600 mg daily.

Summary of Efficacy and Safety Findings

Neuropathic pain

- Based on a meta-analysis of randomized trials evaluating the effects of pregabalin and gabapentin, each relative to placebo, pregabalin may be associated with a relatively high rate of withdrawals due to adverse events, and the evidence does not support that there are differences between the two agents in terms of responder rates in PDN and PHN.
- One trial showed that the onset of effect of pregabalin was as early as 2 days after initiation of fixed-dose pregabalin in the treatment of PHN.

- Daily doses of pregabalin 300 and 600 mg are efficacious in reducing pain, whereas the efficacy of 150 mg is inconsistent.
- The findings of long-term open-label extension studies do not suggest that loss of efficacy due to tolerance is a problem with long-term treatment.

Partial-onset seizures

- The evidence from 3 placebo-controlled randomized clinical trials (RCTs) showed that add-on pregabalin, dosed two or three times daily, is efficacious in reducing the frequency of PS and secondary generalized seizures in adults (weighing 50 to 135 kg) who are not adequately controlled on available antiepileptic drugs (AEDs) and are refractory to at least one AED.
- The number-needed-to-treat for benefit (NNTB) for at least 50% reduction in seizure frequency at the highest dose evaluated (600 mg daily) was 3 (95% CI: 2 to 4) as compared with an NNTB of 6 (3 to 20) for gabapentin at the highest dose evaluated (1800 mg daily).[86] The overlapping confidence intervals of this indirect comparison do not allow one to conclude that there is a difference between the two agents.
- Response to pregabalin is dose-dependent and the minimally effective dose is 150 mg daily. Thrice daily, but not twice daily, dosing of pregabalin (600 mg in divided doses) has been shown to significantly increase the number of patients who become *seizure-free.*

Adverse events

- Indirect comparisons of the rates of withdrawals due to adverse events suggest that pregabalin and gabapentin are not consistently dissimilar in terms of tolerability across different trials.
- Weight gain ≥ 7% above baseline had a placebo-corrected incidence of 6% on pregabalin across all trials and was not reported—but possibly not evaluated—for gabapentin.
- The most common adverse events leading to withdrawal, as well as overall, were dizziness and somnolence for either pregabalin or gabapentin.
- Dizziness, somnolence, weight gain ≥ 7% over baseline, edema / peripheral edema, ophthalmologic events, increased creatine kinase, and decreased platelet count are listed as precautions in the product information for pregabalin. None of these are listed as precautions for gabapentin.

Drug Abuse and Dependence

- Pregabalin is classified in the U.S. as a controlled substance schedule V. The overall rate of euphoria reported as an adverse event was 4% (range, 1% to 12%) in pregabalin-treated patients and 1% in placebo-treated patients in controlled clinical trials.

Evaluation of Pregabalin for Class Effect in Neuropathic Pain

- In indirect comparisons of pregabalin and gabapentin, the relative benefit increase for efficacy (numerical rating scale [NRS]-50) for both agents are similar and the relative risk increase for withdrawals due to adverse events for the two agents do not support a difference between the two agents. Overall, pregabalin and gabapentin have similar adverse event profiles. The main difference in their safety characteristics is the controlled substance (schedule V) classification of pregabalin because of its causal relationship with euphoria. Some experts feel that the controlled substance classification is of little clinical relevance and that there is a class effect between pregabalin and gabapentin.

Conclusions

Pregabalin is the second agent to be approved for neuropathic pain (PDN and PHN) and partial epilepsy in the A2D-receptor binding class of antiepileptic drugs. The advantages of pregabalin relative to gabapentin include greater potency (mg/kg), better oral bioavailability, linear pharmacokinetics, smaller intra- and intersubject pharmacokinetic variability, and shorter titration. To a certain extent, these pharmacologic and pharmacokinetic advantages may have translated into clinical advantages in that pregabalin showed somewhat more consistent efficacy across large, multicenter PDN trials and gained FDA approval for PDN, whereas gabapentin was less consistently efficacious and failed to receive FDA approval for this indication.In terms of NRS-50 and NRS-30 responder rates, pregabalin and gabapentin are similar in efficacy in neuropathic pain. Using seizure-free (SF)-50 responder rates in PS, pregabalin may be slightly more effective than gabapentin, but confidence intervals overlap.

Overall, the adverse event profiles of pregabalin and gabapentin are similar. The main exception to the similarity in safety characteristics is the controlled substance (schedule V) classification of pregabalin.

Based on indirect comparisons (which should be considered inconclusive), there may be other possible dissimilarities which could be clinically important in some individuals. Weight gain $\geq 7\%$ over baseline, adverse ophthalmologic events, euphoria, increased creatine kinase, decreased platelet count, and PR interval prolongation may be more likely to occur during pregabalin therapy, whereas gabapentin may be more likely to be associated with fatigue and diarrhea.

Pharmacoeconomic analyses suggest that generic gabapentin is more cost-effective than pregabalin, although pregabalin incremental cost-effectiveness ratios and quality-adjusted life-years (QALYs) are within the range of other medical interventions.

Recommendations

- Pregabalin should be made nonformulary with criteria.
- Since pregabalin is considered to have a class effect, it should be considered a treatment alternative in patients with PDN, PHN, or PS who have had a documented inadequate response, intolerance, hypersensitivity, or contraindication to gabapentin. It should be used with caution in patients with substance use disorder.
- There is no evidence to support combined therapy with pregabalin and gabapentin.
- Although there is considerable published evidence supporting its use for the treatment of generalized anxiety disorder; the PBM SHG recommends that clinicians await further FDA evaluation of pregabalin for this indication.
- Pregabalin should not be used for chronic low back pain, chronic pain due to hip osteoarthritis, and panic disorder, given preliminary evidence suggesting lack of efficacy in these conditions.

Introduction

Pregabalin is a gabapentin-like agent that has been approved in the U.S. for painful diabetic neuropathy (PDN), postherpetic neuralgia (PHN), and partial seizures (PS). Investigation into its potential application for a number of other indications is being pursued, and based on our literature searches, it has been evaluated in 10 neurologic, psychiatric, and pain conditions. According to the manufacturer (J. Yanchik, verbal communication, October 2005), the New Drug Application for pregabalin was the largest ever submitted to the Food and Drug Administration.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating pregabalin for possible addition to the VA National Formulary; (2) evaluate whether pregabalin and gabapentin exhibit a class effect; (3) define the role of pregabalin in therapy; and (4) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Mechanism of action

The exact mechanism of action of pregabalin is unclear. Pregabalin binds with high affinity to the alpha$_2$-delta (α2δ or A2D) receptors of an auxiliary subunit associated with voltage-gated calcium channels in central nervous system tissues, and is believed to thereby inhibit calcium influx at nerve terminals and decrease release of glutamate, norepinephrine, substance P, and other neurotransmitters. This recently discovered mechanism of action is likely responsible for pregabalin's (and gabapentin's) analgesic, antiseizure, and anxiolytic activities. Pregabalin is a substrate for the system L neutral amino acid transporter. Prolonged application of pregabalin to cultured neurons has also been shown to increase the density of gamma-aminobutyric acid (GABA) transporter protein and increase the rate of functional GABA transport. Electrophysiologic analysis using dorsal root ganglia neurones of neonatal rats showed that pregabalin can reversibly *enhance* (as opposed to inhibit) K^+-evoked Ca^{2+} transients, whereas this pharmacologic effect has not been observed with gabapentin.[1] In addition, pregabalin and gabapentin together were not additive in their modulatory effects on calcium channels. Therefore, the mechanism of pregabalin is similar to that of gabapentin; however, subtle differences have been demonstrated.

Pharmacokinetics

The pharmacokinetic characteristics of pregabalin are compared with those of gabapentin in Table 1.

Table 1 Comparative Pharmacokinetic Characteristics

Pharmacokinetic Property	Pregabalin	Gabapentin
Absorption–Time to Cmax (h)	1.5	1.5–4
Bioavailability	≥ 90%	27%–60%[†]
Effect of food on absorption	↓ rate, ↔ extent	14% ↑ in AUC and Cmax
Protein Binding	None	3%
Metabolism	Negligible	None
Elimination	Renal	Renal
Half-life (h)	6.3	5–7
Dose-Concentration Relationship	Proportional	Disproportionate

[†] Corresponding to 4800 to 900 mg/day; inversely proportional to dose

Absorption of pregabalin is rapid and bioavailability seems to be better (≥ 90%) than that of gabapentin (27% to 60%). Food does not affect absorption of either drug to a clinically relevant degree. Like gabapentin, pregabalin is eliminated primarily via renal excretion and is nearly

proportional to creatinine clearance. Pregabalin clearance is decreased in patients with renal impairment. Pregabalin exhibits linear pharmacokinetics; therefore, doubling the dose results in doubling of the pregabalin peak plasma concentration and exposure over the daily dosage range. Intersubject pharmacokinetic variability is low. These characteristics contrast with those of gabapentin, which tends to have a nonlinear dose-concentration properties and high intersubject variability. These differences are attributable to a higher affinity of pregabalin, relative to gabapentin, to an active L-type amino acid transport system in the upper small intestine.

Pharmacokinetic characteristics in special populations

As seen with gabapentin, the oral clearance of pregabalin decreases with age, consistent with age-related impairment in renal function. Hepatic impairment is not expected to alter pregabalin pharmacokinetics. Pharmacokinetic analyses have shown that gender, race, and menopausal status do not alter pregabalin pharmacokinetics.

FDA-approved Indication(s) and Off-label Uses

FDA-approved indications

- Management of neuropathic pain associated with diabetic peripheral neuropathy
- Management of postherpetic neuralgia
- Adjunctive therapy for adult patients with partial-onset seizures

Off-label uses under evaluation

- Treatment of generalized anxiety disorder in adults (reported in 5 published RCTs[2-6] The FDA issued a "non-approvable" letter for the initial review of pregabalin in generalized anxiety disorder in August 2004. According to the manufacturer (J. Yanchick, e-mail, 22 February 2006), there are an additional 3 unpublished trials, and 7 of the 8 trials showed pregabalin to be superior to placebo in the primary efficacy variable. Negotiations with the FDA continue for this indication. In January 2006, the European Medicines [Evaluation] Agency (EMEA) approved pregabalin for adult generalized anxiety disorder based on the U.S. new drug application data.
- Treatment of social anxiety disorder/social phobia (reported in 1 RCT[7])
- Reduction of pain associated with fibromyalgia syndrome (a large, fair-quality, 8-week multicenter double-blind placebo-controlled randomized trial [RCT] showed pregabalin 450 mg daily (in 3 divided daily doses), but not 300 or 150 mg daily, was efficacious in reducing pain scores[8].)
- Reduction of neuropathic pain associated with spinal cord injury (reported as meeting abstract only[9])
- Treatment of postoperative dental pain (reported in 1 RCT)[10]

Off-label uses not supported by current evidence

- Treatment of chronic low back pain: 2 large, adequately-powered placebo-controlled trials showed that pregabalin is ineffective for chronic low back pain (reported as meeting abstract only.[11])
- Treatment of chronic pain associated with osteoarthritis of the hip (reported as meeting abstract only[12]). A 12-week multicenter double-blind randomized controlled trial in 296 patients with osteoarthritis of the knee (81% of patients) or hip (19% of patients) failed to show a statistically significant difference between pregabalin (either 300 or 600 mg daily)

and placebo in the primary efficacy measure (weekly mean pain score) at study end point. Post hoc analyses showed some benefits at certain time points with pregabalin 600 mg daily; however, these results are only exploratory and need further evaluation.

– Treatment of panic disorder: one double-blind, randomized, placebo- and paroxetine-controlled trial (N = 354, Protocol 1008-091) failed to show significant efficacy of 10-week therapy with either pregabalin (600 mg daily) or paroxetine (40 mg daily) in the treatment of panic disorder; and 2 combined multicenter Phase III trials (Protocols 1008-093 and 1008-192), in which 271 patients entered an 8-week open-label run-in and 165 patients were randomized to a 26-week randomized, placebo-controlled double-blind maintenance phase, showed no significant efficacy of pregabalin (400 mg daily) in the treatment and relapse prevention of panic disorder with or without agoraphobia (available as nonconfidential unpublished trial summaries).{Pfizer Inc., 2004 #5834; Pfizer Inc., 2004 #5833}

Current VA National Formulary Alternatives

There are a number of formulary alternatives to pregabalin for its FDA-approved indications, including gabapentin and other antiepileptic drugs (Table 2). Pregabalin would be the most logical alternative for gabapentin because of their similar mechanisms of action and overlapping clinical indications.

Table 2 Formulary alternatives for FDA-approved indications of pregabalin

Pregabalin FDA-approved indication	Formulary Alternatives	Guidance / Restrictions
Painful diabetic neuropathy	Tricyclic antidepressant agents (TCAs)[13-15]	No
	Venlafaxine[16]	No
	Carbamazepine[13,14,17]	No
	Gabapentin[13-15,17-21]	Yes (National)
	Phenytoin[14,17]	No
	Valproate[22,23]	No
	Capsaicin 0.075% cream[14,24-26]	No
	Tramadol[14,27]	No
Postherpetic neuralgia	Tricyclic antidepressant agents (TCAs)[13,14,28]	No
	Gabapentin [13,14,17,28-30]	Yes (National)
	Capsaicin 0.075% cream[31,32]	No
	Opioids[33]	Yes (National)†
Partial-onset seizures, adjunctive therapy (adults)	Carbamazepine[34-36]	No
	Gabapentin [37-44]	No
	Lamotrigine[45-52]	Yes (VISN)
	Phenytoin[35,53]	No
	Valproate[34,54-57]	No
	Topiramate[58-72]	Yes (VISN)

† Criteria for use of oxycodone controlled-release

Dosage and Administration

Pregabalin is available in 8 strengths, as 25-, 50-, 75-, 100-, 150-, 200-, 225-, and 300-mg capsules.

Pregabalin may be administered with or without food. The recommended initial dose is 150 mg daily in either 3 divided doses (50 mg 3 times daily) for painful diabetic neuropathy or in 2 or 3 divided doses (75 mg 2 times daily or 50 mg 3 times daily) for postherpetic neuralgia or partial onset seizures (Table 3). Lower initial doses may be necessary in elderly patients. For painful diabetic neuropathy, the manufacturer is evaluating initial doses given 2 times daily and cannot

recommend that dosing schedule at this time. However, it would be reasonable to start with twice daily dosing and increase to thrice daily dosing if pain breaks through on the less frequent dosing schedule.

The maximum recommended daily dose of pregabalin in painful diabetic neuropathy is 300 mg. A higher dose of 600 mg did not provide significantly greater benefit and was less tolerated. In postherpetic neuralgia and partial onset seizures, patients who have continued symptoms and tolerate 300 mg daily may have their daily doses increased to a maximum of 600 mg.

Table 3 Pregabalin dosage, normal renal function (CrCl ≥ 60 ml/min)

Dosing parameter	Painful diabetic neuropathy	Postherpetic neuralgia	Partial-onset seizures
Initial daily dose	50 mg 3 times daily (150 mg / d)	75 mg 2 times daily or 50 mg 3 times daily (150 mg / d)	75 mg 2 times daily or 50 mg 3 times daily (150 mg / d)
Interval before increasing initial dose to 300 mg / d	1 wk	1 wk	Base on individual response
Interval before making subsequent dosage increases	Not applicable	2 to 4 wk	Base on individual response
Maximum daily dose	300 mg / d	600 mg / d	600 mg / d

When pregabalin is discontinued, taper the dose gradually over a minimum of 1 week.

Patients with renal impairment

Since pregabalin is eliminated primarily by renal excretion, doses must be adjusted in patients who have renal impairment (CrCl < 60 ml/min) or undergo hemodialysis as shown in Table 4.

Table 4 Pregabalin dosage adjustment based on renal function

CrCl (ml/min)	Percentage of normal recommended daily dose	Total daily dose (mg/d)			No. of doses/day [†]
≥ 60	100%	150	300	600	2 or 3
30–60	50%	75	150	300	2 or 3
15–30	25%	25–50	75	150	1 or 2
< 15	12.5%	25	25–50	75	1
		Supplemental dose (mg) [‡]			
Hemodialysis	In addition to adjusted daily dose (for CrCl < 15)	25–50	50–75	100–150	Single dose

[†] Divide total daily dose by no. of doses/day to obtain mg/dose

[‡] In addition to adjusted daily dose (for CrCl < 15), give a supplemental dose as indicated after every 4-hour hemodialysis session

Pregabalin and gabapentin are compared in regards to their dosage and administration features in Table 5.

Table 5 Dosage and administration: comparison of pregabalin and gabapentin

	Pregabalin	Gabapentin
Administration in regards to food	With or without food	With or without food
Dosage formulation	Capsules	Tablets, scored (brand, generic) Capsules (generic)
Dosage range (mg/d)	150 to 300 / 600	300 to 3600
Dosage frequency (doses/d)	2 to 3, initiation and maintenance	1 to 2 during initiation 3 for maintenance
Dosing based on renal function	Yes	Yes

Pregabalin is available only as capsules, whereas gabapentin is available in both scored tablets and capsules. Pregabalin may be administered in 2 or 3 divided daily doses and has a more narrow dosage titration range, consisting of 2 to 3 dosage levels (150 to 300 / 600 mg daily). In contrast, gabapentin is generally given in 3 divided daily doses (except it may be started as a single daily dose then twice daily during initiation of therapy) and has multiple dosage titration levels in the range of 900 to 3600 mg daily.

Summary of Efficacy and Safety Findings

Efficacy and safety information were obtained from the manufacturer's AMCP dossier, published literature, and the scientific review of pregabalin by the European Medicines [Evaluation] Agency (EMEA). No information on pregabalin was found on the Web site of the National Institutes of Health and Clinical Excellence (NICE).

The published evidence consists of the results of 1 meta-analysis, 3 placebo-controlled trials in PDN, 3 in PHN, 1 in mixed neuropathic pain (PDN and PHN), and 4 placebo-controlled trials and 4 long-term open-label studies (discussed in a review article) in partial-onset seizures. There were no published head-to-head trials or prospective studies evaluating effectiveness in natural settings.

One additional, unpublished placebo-controlled trial in PDN was obtained from the EMEA scientific review. A poster presentation of a pooled analysis of results from PDN and PHN trials was available from the AMCP dossier. Unpublished, confidential trial results were made available for 1 active-control trial in PDN, 2 placebo-controlled trials in PHN, 2 open-label extension studies in PHN, and 2 open-label extension studies in mixed neuropathic pain (PDN and PHN).

All of the trials involved titration of pregabalin to fixed doses, except for two trials (one in mixed neuropathic pain and one in partial seizures [PS]) that included flexible dosing treatment arms.

For further details on the results of the clinical trials, refer to *Appendix: Clinical Trials* (page 33).

Neuropathic Pain

The total number of patients (N = 2244) evaluated in all of the randomized controlled trials (RCTs) evaluating pregabalin in neuropathic pain is the largest for any antineuralgic agent studied thus far. The population sizes in the individual RCTs are also among the largest of the RCTs conducted for any agent used to treat neuropathic pain.

Efficacy Outcome Measures

At least 30% reduction in pain on an 11-point numerical rating scale (NRS-30), which is considered to be a clinically relevant degree of pain reduction, corresponds to ratings of much improved or very much improved on the Patient Global Impression of Change (PGIC) scale.[73]

At least 50% reduction in pain on an 11-point numerical rating scale (NRS-50) corresponds to the highest degree of improvement, i.e., a PGIC rating of very much improved. Previous reports have used the NRS-50 as an indicator of clinically relevant pain reduction.

Pregabalin versus Gabapentin, indirect comparisons from meta-analysis

- Indirect comparisons of pregabalin and gabapentin, based on meta-analysis of randomized trials evaluating their effects relative to placebo, suggest that pregabalin may be associated with a relatively high rate of withdrawals due to adverse events, and the findings provide no evidence to support treatment differences in terms of responder rates in PDN and PHN[74] (also see Data Compilation Tables, page 17). The NNTB (95% CI) for pregabalin (overall dosage range, 150 to 600 mg) in these two neuropathic pain types

was 4.2 (3.4 to 5.4), and the NNTH (95% CI) was 11.7 (8.3 to 19.9). Across various types of neuropathic pain disorders (i.e., painful diabetic neuropathy, postherpetic neuralgia, phantom limb pain, spinal cord injury, HIV-related neuropathy, and mixed neuropathic pain types), different study designs, and different dosage regimens (overall daily dosage range, 900 to 3600 mg), the overall NNTB of gabapentin for at least 50% pain relief in the intent-to-treat analysis population (95% CI) was 5.1 (4.1 to 6.8) and the NNTH based on rates of withdrawal due to adverse events was 26.1 (14.1 to 170) (7 of 10 trials with data, N = 1241).

Table 6 Indirect comparison of pregabalin and gabapentin

Result	Outcome measure	Pregabalin 150–600 mg/d PDN, PHN	Gabapentin 900–3600 mg/d Various NPP
NNTB (95% CI)	NRS-50 responder rate	4.2 (3.4–5.4)	5.1 (4.1 to 6.8)
NNTH (95% CI)	WDAEs	11.7 (8.3–19.9)	26.1 (14.1 to 170)

Source: Finnerup (2005) [74]

NNTB, Number-needed-to-treat for benefit; NNTH, Number-needed-to-treat for harm; NPP, Neuropathic pain; PDN, Painful diabetic neuropathy; PHN, postherpetic neuralgia, WDAEs, Withdrawals due to adverse events

- Pregabalin has been more consistent than gabapentin in producing favorable results in PDN trials and achieved FDA approval for PDN, whereas gabapentin did not obtain approval for PDN (only one[18] of two large major efficacy trials of gabapentin in PDN showed a significant benefit whereas two major efficacy trials of pregabalin both showed superiority over placebo).
- One trial showed that the onset of effect (i.e., first statistically significant analgesic effect) of pregabalin was as early as 2 days after initiation of fixed-dose pregabalin (300 or 600 mg daily depending on creatinine clearance) in the treatment of PHN.[75] Studies involving gabapentin have not reported results by daily pain scores within the first week of therapy and therefore, it is unclear whether pregabalin has a faster onset than gabapentin. Among trials that presented weekly or monthly pain scores, the onset of effect seemed to be similar for pregabalin (1 week)[76-78] and gabapentin (1 to 2 weeks).[18,29,30] In a trial comparing fixed and flexible dosing regimens in patients with PDN or PHN, the onset of effect was 1 week for the fixed dose and 2 weeks for the titrated dose.[79]
- The indirect comparisons should be interpreted cautiously because they have not been confirmed by head-to-head trials (comparisons of pregabalin with other antiepileptic drugs [AEDs]).

Painful Diabetic Neuropathy

Pregabalin versus Placebo

- Results of 3 published RCTs and 1 unpublished RCT reviewed by the EMEA showed that pregabalin in doses of 300 and 600 mg daily are superior to placebo in reducing pain scores by a clinically relevant degree and in significantly improving sleep interference scores, patient and clinical global impressions of change, and certain domains of quality of life, whereas pregabalin 75 mg daily was shown to have no therapeutic benefit over placebo in patients with painful diabetic neuropathy. Additional unpublished data have shown the 150-mg dose to have some therapeutic effect[81]; however, results with this dose are inconsistent.

- Pregabalin 600 mg daily showed no additional benefit over 300 mg in PDN (1 trial).[77]
- Two[82,83] of four PDN trials and one[84] of five placebo-controlled trials did *not* exclude nonresponders to gabapentin ≥ 1200 mg daily and the remainder excluded such patients because of its similar mechanism of action to that of pregabalin. If response to gabapentin predicts response to pregabalin, this exclusion may have favored finding beneficial results with pregabalin.

Postherpetic neuralgia

Placebo-controlled trials

- Pregabalin in fixed doses of 150 to 600 mg daily decrease postherpetic neuralgia pain (3 trials,[75,76,84] beginning as early as 2 days after start of treatment.[75] (See Appendix Table 3.)
- Placebo-corrected NRS-50 responder rates show a dose-response relationship, ranging from 16% to 18% for pregabalin 150 mg, 18% to 19% for 300 mg, and 30% for serum creatinine–adjusted doses of 300/600 mg daily.

Mixed neuropathic pain (PDN or PHN)

Placebo-controlled trials

- One placebo-controlled RCT in patients with neuropathic pain showed that a statistically significant difference in analgesic effect, relative to placebo, was obtained at week 1 with a fixed dose of pregabalin (600 mg daily) and at week 2 with a flexible dosing regimen (no statistical analysis for the difference between the two pregabalin groups) (Appendix Table 5).[79]
- Both regimens of pregabalin were generally well-tolerated. The fixed-dose regimen, however, appeared to be less tolerated than the flexible dosing regimen.
- According to EMEA pooled analyses of all neuropathic pain trials (PDN and PHN), pregabalin was shown to be efficacious in PDN (polyneuropathy) and PHN (mononeuropathy) at fixed doses up to 300 and 600 mg daily. The mean difference in pain score between pregabalin and placebo ranged from –0.18 to –1.57 for 300 mg daily and –0.64 to –2.02 for 600 mg daily.[82] Lower doses are either inconsistently efficacious (150 mg daily) or not efficacious (75 mg daily).
- An NRS-50 response is achieved by 16% to 46% of patients at doses of 300 mg daily, and 32% to 50% of patients at doses equivalent to 600 mg daily.[82] Improvements in sleep interference, patient and clinical global impression of change, and other secondary outcome measures generally supported the primary efficacy measures. Quality of life and effects on mood were inconsistent, with the exception of improvement in bodily pain.

Meta-analysis

- According to the EMEA scientific discussion on pregabalin, a meta-analysis of all 9 completed fixed-dose neuropathic pain (PDN and PHN) trials (excluding the amitriptyline-controlled trial and ineffective 75-mg dose arms), showed that pregabalin produces a substantial treatment effect (difference, 0.28 to 0.47 depending on dose group) that is larger in PHN than PDN trials.
- The difference between twice daily and thrice daily dosing regimens in placebo-corrected treatment effect size is substantial—but of uncertain clinical relevance—for only the 300-mg dose.

Long-term noncomparative studies

- Preliminary, unpublished results of a combined analysis of 4 unpublished long-term (2-year) open-label extension studies (PDN and PHN) showed that the efficacy of flexibly dosed pregabalin was durable, producing consistent pain control for up to 2 years (abstract).[85]
- The adverse event profile of pregabalin was similar to that in short-term trials.
- According to the EMEA scientific review, the findings of long-term open-label extension studies did not definitively show durability of efficacy because of their design and number of dropouts. In a retrospective cohort analysis of 4 extension studies involving patients who had benefited from pregabalin treatment, pain scores remained stable.[82]
- Altogether, the data do not suggest that loss of efficacy due to tolerance is a problem with long-term treatment.

Partial-onset seizures

Placebo-controlled trials

- The evidence from 3 placebo-controlled RCTs showed that add-on pregabalin, dosed two or three times daily, is efficacious in reducing the frequency of PS and secondary generalized seizures in adults (weighing 50 to 135 kg) who are not adequately controlled on available AEDs and are refractory to at least one AED (Table 17, Table 18, Appendix Table 8).
- The NNTB for at least 50% reduction in seizure frequency at the highest dose evaluated (600 mg daily) was 3 (95% CI: 2 to 4). This is slightly better than the NNTB of 6 (3 to 20) for gabapentin at the highest dose evaluated (1800 mg daily)[86]; however, the overlapping confidence intervals of this indirect comparison do not allow one to conclude that there is a difference between the two agents.
- Thrice daily, but not twice daily, dosing of pregabalin (600 mg in divided doses) has been shown to significantly increase the number of patients who become *seizure-free*, particularly for the last 28-day period (2 of 4 trials).[87,88]
- Response to pregabalin is dose-dependent and the minimally effective dose is 150 mg daily. A mixed-effects model analyzing data from the three partial epilepsy trials estimated that a dose-response relationship occurs in 75% of patients with refractory PS, and that a dose of 186 mg daily is associated with a 50% reduction in seizure frequency from baseline.[89]
- The early evidence from short-term (12-week) trials using mostly fixed-dosed regimens suggests that the drug is well-tolerated overall, and lower doses (150 and 300 mg daily) are better tolerated than the highest dose (600 mg daily).
- The percentages of patients discontinuing due to adverse events seemed to be larger on the highest dose of pregabalin, 600 mg daily as compared with lower doses when doses were started with titration[88] and without titration.[90] Dizziness and somnolence were the most frequently reported treatment-emergent adverse events.[88,90]

Adverse events

Pooled analysis, pregabalin versus placebo

A pooled analysis in the EMEA scientific discussion of pregabalin showed a number of adverse events that occurred at significantly higher rates on pregabalin than placebo (Table 7).

Table 7 Pooled analysis of adverse events (all trials)

Adverse event	Placebo-corrected incidence (PGB–PBO) N = 5232 PGB N = 2290 PBO
Any AE	13.6%
*Significantly different from PBO**	
Dizziness	20.4%
Somnolence	14.8%
Dry mouth	5.7%
Weight gain	4.8%
Amblyopia	4.4%
Peripheral edema	4.2%
Thinking abnormal	4.0%
Ataxia	3.6%
Incoordination	3.4%
Euphoria	3.4%
Constipation	2.5%
Confusion	2.2%
Asthenia	2.1%
Amnesia	1.9%
Diplopia	1.6%
Increased appetite	1.5%
Accidental injury	1.3%
Tremor	1.1%
Flatulence	1.1%

Source: EMEA Scientific Discussion of Pregabalin[82]

* $p < 0.05$ for odds ratio or Fisher's Exact test

Euphoria, one of the adverse events that occurred at a significantly higher rate on pregabalin than placebo, was inconsistently reported as a common adverse event with pregabalin and has not been reported as a common adverse event with gabapentin. The FDA's evaluation of pregabalin's potential for drug dependence and abuse led to classification of pregabalin as a schedule V drug (similar to benzodiazepines). The EMEA did not categorize pregabalin as a controlled substance.

Indirect comparisons of pregabalin and gabapentin

Considering differences in study populations, rates of dosage titration, and use of co-medications across trials, indirect comparisons of the rates of withdrawals due to adverse events suggest that pregabalin and gabapentin are not consistently dissimilar in terms of tolerability across different trials when categorized by diagnostic indication. The types of common adverse events are also not consistently dissimilar, with the exception of weight gain, which had placebo-corrected incidences that were at least twice as high in pregabalin PDN, PHN, and PS trials than in corresponding gabapentin trials (Table 8).

Table 8 Placebo-corrected incidences of adverse events by diagnosis

	Placebo-corrected Incidence (Drug–Placebo)					
	Pregabalin			Gabapentin		
Adverse event	**PDN**	**PHN**	**PS**[†]	**PDN**	**PHN**	**PS**[†]
SAEs	NR	NR	NR	NR	NR	NR
WDAEs	**5%**	7%	**9%**	2.1%	7%	0%
Common TEAEs[‡]						
Dizziness	16.0%	17%	**21%**	18.9%*	20.5%	10.2%
Somnolence	9%	11%	11%	16.4%*	16.1%	10.6%
Peripheral edema	**7%**	8%	**3%**	NR	6.1%	1.2%
Ataxia	**2%**	4%	11%	NR	3.3%	6.9%
Fatigue	NR	NR	NR	NR	NR	**6.0%**
Headache	NR	**2%**	NR	**7.0%**	0.2%	NR
Diarrhea	NR	NR	NR	**2.1%**	**2.6%**	NR
Weight gain/increase	**4%**	**4%**	**11%**	NR	1.8%	1.3%

Sources: Product information for pregabalin[91] and gabapentin,[86] and Backonja (1998)[18]

Total number of patients by diagnosis was not reported.

* $p \leq 0.004$, gabapentin vs. placebo

† Add-on therapy in patients with partial-onset seizures; for pregabalin, patients were adults and for gabapentin, patients were > 12 years old.

‡ Incidence ≥ 10% in any treatment group and numerically higher in all drug than in placebo group for either pregabalin or gabapentin, for any indication

NR, Not reported (not a common or most frequently reported adverse event, as defined in the study); PDN, Painful diabetic neuropathy; PHN, Postherpetic neuralgia; PS, Partial seizures; TEAE, Treatment-emergent adverse event

Bolded figures indicate placebo-corrected incidences that were at least twice as high on the drug with the bolded value than on the other drug, or reported as a common adverse event on the drug with the bolded value but not the other, for respective diagnostic indications

Weight gain ≥ 7% above baseline had a placebo-corrected incidence of 6% on pregabalin across all trials and was not reported for gabapentin; however, it is possible that weight gain ≥ 7% was not a measured outcome in gabapentin trials.

The most common adverse events leading to withdrawal were dizziness and somnolence for either pregabalin or gabapentin, and this was a consistent finding across different diagnostic indications (Table 9).

Table 9 Types of adverse events

	Pregabalin			Gabapentin		
Adverse event	**PDN**	**PHN**	**PS**[†]	**PDN**	**PHN**	**PS**[†]
Most common WDAEs[†]	Dizziness Somnolence	Dizziness Somnolence	Dizziness Somnolence Ataxia	Dizziness	Dizziness Somnolence Nausea	Dizziness Somnolence Nausea/Vomiting Fatigue Ataxia

Sources: Product information for pregabalin[91] and gabapentin,[86] and Backonja (1998)[18]

NR, Not reported; SAE, Serious adverse event; WDAE, Adverse event leading to withdrawal; WDSAE, Serious adverse event leading to withdrawal

† Add-on therapy in patients with partial-onset seizures; for pregabalin trials, patients were adults and for gabapentin trials, patients were > 12 years old.

† Definitions of most common adverse events leading to withdrawal for PHN and PS differed between pregabalin and gabapentin. For pregabalin PDN, PHN, and PS, and gabapentin PDN, the definition used here was ≥ 2% on drug and < 1% on placebo. For gabapentin PHN and PS, the adverse events listed as the "most common" adverse events leading to withdrawal were used.

Contraindications

Hypersensitivity to pregabalin or any of its components

Warnings

Withdrawal of antiepileptic drugs. If pregabalin is to be discontinued, gradually taper the dose over a minimum of 1 week to prevent increased seizure frequency in patients with seizure disorders.

Tumorigenic potential. An unexpectedly high incidence of hemangiosarcoma was observed in two strains of mice in preclinical *in vivo* lifetime carcinogenicity studies. The clinical significance of the increased risk of vascular tumors in mice is unknown. In clinical studies, new tumors or worsening of pre-existing tumors was reported in 57 patients during 6,396 patient-years of exposure to pregabalin in patients > 12 years old. The effect of pregabalin on the incidence of tumors cannot be determined in the absence of a comparator cohort.

The warnings listed in the product information for pregabalin and gabapentin are summarized in Table 10. Pregabalin lacks the warning of sudden and unexplained death in patients with epilepsy, which is listed for gabapentin.

Table 10 Warnings: comparison of pregabalin and gabapentin

Warning	Pregabalin	Gabapentin
Withdrawal of antiepileptic drugs	Gradually taper dose over a minimum of 1 week	Do not abruptly discontinue treatment
Tumorigenic potential	Hemangiosarcoma (mice)	Pancreatic acinar adenocarcinoma (male rats)
Sudden and unexplained death in patients with epilepsy	Not listed as a Warning	It is unknown whether the incidence is or is not affected by treatment

Sources: Pregabalin product information[91]; gabapentin product information.[86]

Precautions

Dizziness, somnolence, weight gain ≥ 7% over baseline, edema / peripheral edema, ophthalmologic events, increased creatine kinase, and decreased platelet count are listed as precautions in the product information for pregabalin. None of these are listed as precautions for gabapentin, although some of them were reported as adverse events in clinical trials with gabapentin (Table 11).

Table 11 Precautions for pregabalin: indirect comparison with gabapentin

	Placebo-corrected Incidence (Drug–Placebo)		
	Pregabalin	Gabapentin	
Precautions for Pregabalin	**All CCTs**	**PHN**	**PS**[†]
Caused by pregabalin			
Dizziness	20%	20.5%	10.2%
Somnolence	14%	16.1%	10.6%
Weight gain ≥ 7% over baseline	6%	NR	NR
Peripheral edema	4%	6.1%	0.8%
Associated with pregabalin			
Blurred vision / Amblyopia	4%	1.8%	3.1%
Reduced visual acuity	2%	NR	NR
Visual field changes	1%	NR	NR
Funduscopic changes	0%	NR	NR
Increased creatine kinase (≥ 3 times ULN)	1%	NR	NR
Decreased platelet count[‡]	1%	NR	NR
PR interval prolongation	PNR	NR	NR

Sources: Product information for pregabalin[91] and gabapentin,[86]
CCT, Controlled clinical trials; NR, Not reported; PHN, Postherpetic neuralgia; PNR, Percentages (incidences on pregabalin vs. placebo) not reported; PS, Partial seizures
† Add-on therapy in patients > 12 years old with partial-onset seizures

‡ Potentially clinically significant decreases (20% below baseline and < 150 x 10^3/µl

The following ophthalmologic events, not listed in Table 11, have also occurred with gabapentin (placebo-corrected incidence): conjunctivitis (1.2%) and diplopia (1.2%) in PHN trials, and diplopia (4.0%) in add-on PS trials.

Caused by pregabalin

Dizziness and Somnolence. In clinical trials, dizziness and somnolence occurred in 29% and 22%, respectively, of pregabalin-treated patients versus 9% and 8%, respectively, of placebo-treated patients and were the adverse events that most frequently led to withdrawal (4% each). Dizziness and somnolence began shortly after the start of therapy, and in short-term trials, persisted until the last dose in 31% and 46% of patients, respectively. Higher doses of pregabalin were more likely to be associated with these adverse events.

Weight Gain. In clinical trials up to 13 weeks long, 8% of pregabalin-treated patients as compared with 2% of placebo-treated patients experienced weight gain of 7% or more over baseline weight, and 0.2% withdrew from the trials because of this adverse event. Weight gain was related to dose and duration of pregabalin therapy. The clinical implications of pregabalin-associated weight gain, such as the long-term risks of cardiovascular effects and development or worsening of diabetes mellitus, are unknown. No adverse effects on blood pressure and glycemic control (i.e., HgA1c) were observed during short-term clinical trials.

Edema and Peripheral Edema. Edema, primarily reported as peripheral edema, occurred in 6% of pregabalin-treated patients and 2% of placebo-treated patients. A small percentage (0.6%) of pregabalin patients and no placebo patients withdrew because of this adverse event. Peripheral edema occurred in patients without clinically significant cardiac or peripheral vascular disease, and had no apparent association with cardiovascular complications or laboratory changes suggestive of renal or hepatic dysfunction. Patients taking both pregabalin and a thiazolidinedione antidiabetic agent had higher frequencies of weight gain and peripheral edema compared with patients taking either drug alone. Thiazolidinediones have been associated with weight gain and / or fluid retention that potentially led to or exacerbated heart failure. Providers should use caution when administering pregabalin to patients who are taking thiazolidinediones or who have congestive heart failure (New York Heart Association Class III or IV cardiac status).

Associated with Pregabalin

Ophthalmologic Effects. Vision-related events, primarily blurred vision, occurred in a higher percentage of patients treated with pregabalin (6%) than with placebo (2%). In the majority of cases, symptoms resolved with continued dosing. Reduced visual acuity occurred in 7% of pregabalin-treated patients and 5% of placebo-treated patients. Visual field changes and funduscopic changes occurred in 13% and 2%, respectively, on pregabalin versus 12% and 2% on placebo.

Increased Creatine Kinase. Increases in creatine kinase at least three times the upper limit of normal were seen in 2% of pregabalin patients and 1% of placebo patients. The mean excursions in creatine kinase (from baseline to maximum value) were 60 U/l for pregabalin and 28 U/l for placebo. In all controlled trials, across different patient populations, 3 patients on pregabalin developed rhabdomyolysis. A causal relationship is unclear because the patients had confounding risk factors. Patients should be advised to report unexplained muscle pain, tenderness, or weakness, particularly if present with malaise or fever. If myopathy is diagnosed or suspected, or if marked increases in creatine kinase levels occur, pregabalin treatment should be discontinued.

Decreased Platelet Count. In all controlled trials, 3% of pregabalin patients and 2% of placebo patients developed potentially clinically significant decreases in platelets (i.e., 20% below

baseline value and < 150 x $10^3/\mu l$). Increases in bleeding-related adverse events were not observed during pregabalin treatment in randomized controlled trials.

PR Interval Prolongation. Small increases in PR interval (mean, 3 to 6 msec at pregabalin ≥ 300 mg daily) were observed without higher risks of PR increases ≥ 25% from baseline, PR interval > 200 msec, or second- or third-degree AV block. No predictors of PR interval prolongation were identified in limited subgroup analyses.

Special populations

Fertility. The mean difference between placebo- and pregabalin-treated men in mean percentage of sperm with normal motility was < 4% in a 3-month double-blind, placebo-controlled trial (N = 46 healthy males). The mean change from baseline in either group did not exceed 2%.

Pregnancy and Lactation. Reproductive toxicity has been observed in animals exposed to pregabalin. No well-designed studies have evaluated pregabalin in pregnant women. Pregabalin should not be used during pregnancy unless the potential benefits outweigh the risks. Women of childbearing potential should always use effective contraception during pregabalin treatment. It is not known whether pregabalin is excreted in breast milk of humans.

Geriatric Use. No overall differences in safety and efficacy were seen between older (≥ 65 years) and younger patients in controlled clinical studies of pregabalin in neuropathic pain and epilepsy. However, older individuals may be more sensitive to certain drugs and have renal impairment. The dose of pregabalin should be adjusted in elderly patients according to their renal function.

Pregabalin and gabapentin differ in their secretion into breast milk of lactating women and effects in elderly patients (Table 12).

Table 12 Special population precautions: comparison of pregabalin and gabapentin

Special Population	Pregabalin	Gabapentin
Pregnancy	Category C	Category C
Lactation	Secretion in human milk is unknown	Secreted in human milk
Elderly	No overall differences in effects between patients ≥ 65 y and younger patients	↑ effect in patients ≥ 75 y old vs. younger patients

Sources: Product information for pregabalin[91] and gabapentin,[86]

Drug Abuse and Dependence

Controlled Substance Schedule V. Pregabalin (450 mg, single dose) produced subjective effects rated as "good drug effect," "high," and "liking" in a study of 15 recreational users of sedative / hypnotic drugs, including alcohol. These effects were similar to those produced by diazepam (30 mg, single dose).

The overall rate of euphoria reported as an adverse event was 4% (range, 1% to 12%) in pregabalin-treated patients and 1% in placebo-treated patients in controlled clinical trials (N = 5500). Some patients developed symptoms suggestive of withdrawal effects due to physiologic dependence (including insomnia, nausea, headache, or diarrhea) after abrupt or rapid discontinuation of pregabalin. Providers should evaluate patients for a history of drug abuse and monitor them for signs and symptoms of pregabalin misuse or abuse.

In comparison, gabapentin was not evaluated for drug abuse and dependence potential in human studies, and is not recognized as a drug associated with substance use disorder.

Postmarketing Adverse Events

The following adverse events have been reported in case reports:

Asterixis (negative myoclonus) leading to recurrent falls.[92] In clinical trials, myoclonus was reported in at least 2% of patients with partial epilepsy treated with pregabalin 600 mg/day and at a rate ≥ 2% higher than that in both the placebo and pregabalin 150 mg/day group. Asterixis with falls have also been reported with gabapentin.[93]

Pregabalin withdrawal–related delirium / encephalopathy with focal vasogenic cerebral edema.[94]

Look-alike / Sound-alike (LA / SA) Error Risk Potential

A search of the Web sites for the Institute of Safe Medication Practices (http://www.ismp.org/) and the United States Pharmacopeia (http://www.usp.org/) found no reports of look-alike/sound-alike medication name confusion involving pregabalin or Lyrica to date.

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name *pregabalin*: Pregnyl, Prevalite, progesterone, Prograf, proguanil

LA/SA for trade name *Lyrica*: Lysine, Lymerix, , Lutera, Luride

Drug Interactions

Drug-Drug Interactions

Pregabalin is associated with a limited number of pharmacodynamic drug interactions. Like gabapentin, pregabalin is primarily eliminated by the kidney and is not highly protein bound. Pregabalin is not expected to cause pharmacokinetic drug interactions due to altered drug metabolism or protein binding.

Table 13 Drug interactions involving pregabalin

Object Drug	Potential effects
Pharmacodynamic interaction	
Oxycodone Lorazepam Ethanol	Additive effects on cognitive and gross motor function
Pharmacokinetic interaction	
Carbamazepine Lamotrigine Phenobarbital Phenytoin Topiramate Valproate	No clinically significant effects on object drug expected

Source: Product information for pregabalin.[91] This list of drug interactions is not all-inclusive. Consult appropriate references for further information.

Drug-Lab Interactions

None reported.

Data Compilation Tables

Effect size by diagnosis

Measures of effect size for pregabalin are shown for FDA-approved indications in Table 14 to Table 18.

PDN and PHN. The number-needed-to-treat for benefit (NNTB) based on NRS-50 ranged from 3 to 6 across neuropathic pain trials. In 4 trials, there were no significant differences between any dose of pregabalin (75 to 600 mg daily) and placebo in the rate of withdrawals due to adverse events. However, maximal doses (equivalent of 600 mg daily) were associated with a significant treatment difference in 7 trials, and the number-needed-to-treat for harm (NNTH) was relatively small, ranging from 4 to 11 across trials. This finding suggests that there may be a relatively narrow benefit-to-risk (of intolerance) ratio at the highest dose.

Partial seizures. The NNTB for at least 50% reduction in seizure frequency (SF-50) varied from 3 to 6 across fixed-dose trials, depending on pregabalin dose. Using flexible dosing, the NNTB for SF-50 was 5 (95% CI: 3 to 10). The number-needed-to-treat for harm (NNTH) based on the rate of withdrawals due to adverse events were not significant for lower fixed doses (50 and 150 mg) and was low, relative to the NNTB, at the highest evaluated dose (600 mg), ranging from 4 to 8 across trials. The relatively low NNTHs probably reflect the use of fixed dose regimens, since one trial showed that flexible dosing was better tolerated.[95]

Table 14 Painful Diabetic Neuropathy

	Lesser (2004)[77] T.I.D. Fixed dosing, 5 wk				Rosenstock (2004)[78] T.I.D. Fixed dosing, 8 wk		Richter (2005)[83] T.I.D. Fixed dosing, 6 wk			Study 149 (EMEA 2004)[82] B.I.D. Fixed dosing, 12 wk			
	Pregabalin (mg / d)			PBO	Pregabalin (mg / d)	PBO	Pregabalin (mg / d)		PBO	Pregabalin (mg / d)			PBO
	600	300	75	—	300	—	600	150	—	300/600	300	150	—
Efficacy measure: NRS-50													
Responder Rate	48%	41%	25%	18%	40%	14.5%	39%	19%	15%	46%	33%	34%	30%
NNTB (95% CL)	3 (2, 6)	4 (2, 7)	NSD	—	4 (3, 9)	—	4 (3, 8)	NSD	—	6 (3, 50)	NSD	NSD	—
Efficacy measure: NRS-30													
Responder Rate	65%	62%	37%	33%	50%	35%	NR	NR	NR	NR	NR	NR	—
NNTB (95% CL)	3 (2, 5)	3 (2, 7)	NSD	—	NSD (p = 0.08)	—	—	—	—	—	—	—	—
Safety measure: WDAEs													
Event rate	12.2%	3.7%	2.7%	3.1%	10.5%	2.9%	8.5%	2.5%	4.7%	12.9%	11.1%	5.0%	3.1%
NNTH (95% CL)	NSD (p = 0.068)	NSD	NSD	—	NSD	—	NSD	NSD	—	10 (6, 42)	NSD (p = 0.057)	NSD	—

Table 15 Postherpetic Neuralgia

	Sabatowski (2004)[76] T.I.D. Fixed dosing, 8 wk			Dworkin (2003)[75] T.I.D. Fixed dosing, 8 wk		Van Seventer (2006)[84] B.I.D. Fixed dosing, 13 wk			
	Pregabalin (mg / d)		PBO	Pregabalin (mg / d)	PBO	Pregabalin (mg / d)			PBO
	300 N = 76	150 N = 81	— N = 81	300 / 600	—	300 / 600 N = 90	300 N = 98	150 N = 87	— N = 93
Efficacy measure: NRS-50									
Responder Rate	28%	26%	10%	50%	20%	37.5%	26.5%	26.4%	7.5%
NNTB (95% CI)	6 (3, 17)	6 (4, 22)	—	3 (2, 6)	—	3 (2, 5)	5 (3, 11)	5 (3, 12)	—
Efficacy measure: NRS-30									
Responder Rate	50%	37%	19%	63%	25%	52%	41%	39%	18%
NNTB (95% CL)	3 (2, 6)	5 (3, 20)	—	3 (2, 4)	—	3 (2, 5)	4 (3, 10)	5 (3, 13)	—
Safety measure: WDAEs									
Event rate	15.8%	11.1%	9.9%	31.5%	4.8%	21.1%	15.3%	8.0%	5.4%
NNTH (95% CL)	NSD	NSD	—	4 (3, 6)	—	6 (4, 16)	10 (5, 67)	NSD	—

dd, Divided doses

Table 16 Mixed neuropathic pain (PDN and PHN)

	Freynhagen (2005)[79]		
	B.I.D. Flexible vs. Fixed dosing, 12 wk		
	PGB_{Flex} N = 141	PGB600 N = 132	PBO N = 65
Efficacy Measure: NRS-50			
Responder Rate (%)	48.2	52.3	24.2
NNTB (95% CI)	4.2 (2.7, 9.5)	3.6 (2.4, 6.9)	—
Efficacy Measure: NRS-30			
Responder Rate (%)	59.0	66.4	37.1
NNTB (95% CL)	4.6 (2.7, 13.6)	3.4 (2.3, 6.8)	—
Safety Measure: WDAEs			
Event rate (%)	17.0	25.0	7.7
NNTH (95% CL)	NSD	6 (4, 13)	—

Table 17 Partial-onset Seizures (Fixed Doses)

	Beydoun (2005)[87] Study 1008-009			Arroyo (2004)[88] and Miller (2003){Miller, 2003 #119 Study 1008-011			French (2003) [90]				
	B.I.D. vs. T.I.D. Fixed dosing, 12 wk			T.I.D. Fixed dosing, 12 wk			B.I.D. Fixed dosing without titration, 12 wk				
	Pregabalin (mg/d)		PBO	Pregabalin (mg/d)		PBO	Pregabalin (mg/d)				PBO
	600 (t.i.d.) N = 111	600 (b.i.d.) N = 103	— N = 98	600 N = 92	150 N = 99	— N = 96	600 N = 89	300 N = 90	150 N = 86	50 N = 88	— N = 100
Efficacy Measure: RRatio											
Difference (mean)	–36.7	–29.0	—	–32.3	–12.4	—	–33	–24	–17	–2	—
95% CI	–46.4, –27.0	–38.9, –19.0	—	–40.6, –24.0	–20.5, –4.3	—	NR	NR	NR	NR	—
p-value vs. PBO	< 0.001	< 0.001	—	≤ 0.0001	0.0007	—	≤0.0001	≤0.0001	≤0.0001	≤0.0001	
p-value vs PGB	—	—		≤ 0.0001	—	—	—	—	—	—	—
Efficacy Measure: SR–50											
Responder Rate	49%	43%	9%	43.5%	14.1%	6.2%	51%	40%	31%	15%	14%
NNTB (95% CI)	3 (2–4)	3 (2–4)	—	3 (2–4)	NSD	—	3 (2–4)	4 (3–7)	6 (3–18)	NSD	—
p-value vs PGB				≤0.001	—	—					
Efficacy Measure: Seizure-free during last 28 d											
Responder Rate	15%	NR	3%	12%	7%	1%	NR	NR	NR	NR	—
NNTB (95% CL)	NSD	—	—	0.002	0.065	—	—	—	—	—	—
Safety Measure: WDAEs											
Event rate	19%	26%	7%	18.5%	10.1%	6.2%	23.6%	14.4%	1.2%	6.8%	5%
NNTH (95% CL)	8 (5, 34)	5 (3, 11)	—	8 (5, 34)	NSD	—	5 (4, 11)	11 (6, 100)	NSD	NSD	—

Table 18 Partial-onset Seizures (Flexible Dosing)

	Elger (2005)[95]		
	B.I.D. Fixed vs. Flexible dosing, 12 wk		
	Pregabalin (mg/d)		PBO
	600	150–600	—
	N = 137	N = 131	N = 73
Efficacy Measure: RRatio			
Difference vs. PBO (mean)	–27.0	–15.8	—
95% CI	–38.5, –15.6	–27.4, –4.3	—
p-value vs. PBO	0.0001	–0.0091	—
Difference vs. PGB150–600 (mean)	–11.2	—	—
p-value vs. PGB150–600	0.0337	—	—
Efficacy Measure: SR–50			
Responder Rate	45%	31%	11%
NNTB (95% CI)	3 (2, 4)	5 (3, 10)	—
p-value vs PBO	0.001	0.001	—
p-value vs. PGB150–600	0.016	—	—
Efficacy Measure: Seizure-free during last 28 d			
Responder Rate	12.4%	12.2%	8.2%
NNTB (95% CL)	NSD	NSD	—
Safety Measure: WDAEs			
Event rate	33.0%	12.0%	7.0%
NNTH (95% CL)	4 (3, 6)	NSD	—

SF-50, 50% reduction in seizure frequency

Evaluation of Pregabalin for Class Effect in Neuropathic Pain

Efficacy and tolerability results of fair-quality, parallel-group trials were pooled to explore whether pregabalin and gabapentin exhibit a class effect in neuropathic pain,[96] which is expected to be the most common indication for both drugs. Trials that used a flexible dosing approach were preferred in order to approximate actual dosing practices. A single trial that involved a flexible dosing treatment arm was available for pregabalin. This trial compared flexible dosing with fixed dosing in patients with either PDN or PHN.[79] The results of two trials evaluating gabapentin were pooled to create a case mix somewhat similar to that of the pregabalin trial; one used flexible dosing in PDN,[18] and the other involved forced dosage titration to fixed doses in PHN.[29]

The relative benefit increase for achieving NRS-50 was similar in direction and magnitude for the two agents (Table 19). For withdrawals due to adverse events, the relative risk increase was 1.21 for pregabalin and 0.47 for gabapentin; however, the 95% confidence intervals overlapped. These preliminary findings do not support exclusion of a class effect. The primary difference between pregabalin and gabapentin, at least in terms of safety, is the controlled substance classification of pregabalin.. Some experts feel that the controlled substance classification is of little clinical relevance and that there is a class effect between pregabalin and gabapentin.

Table 19 Fair-quality flexible and fixed dosing trials (PDN, PHN)

	Pregabalin 150–600 mg/d	Gabapentin Up to 3600 mg/d
No. of RCTs	**1**	**2**
Responder Rate (NRS-50)		
Drug, n/N (%)	68/141 (48.2)	94/197 (47.7)
Placebo, n/N (%)	16/65 (24.2)	39/197 (19.8)
RBI (95% CL)	0.99 (0.25, 2.16)	1.41 (0.76, 2.31)
NNTB (95% CL)	4 (3, 9)	3.6 (3, 6)
WDAEs		
Drug (n/N)	24/141 (17.0)	28/197 (14.2)
Placebo (n/N)	5/65 ((7.7)	19/197 (9.6)
RRI (95% CL)	**1.21 (–0.12, 4.52)**	**0.47 (–0.15, 1.55)**
NNTH (95% CL)	NSD	NSD

References: Pregabalin—Freynhagen (2004)[79]; Gabapentin—Backonja (1998)[18], Rowbotham (1998)[29]

NNTB, Number-needed-to-treat for benefit; NNTH, Number-needed-to-treat for harm; NRS-50, At least 50% reduction in pain on an 11-point Numerical Rating Scale; RBI, Relative benefit increase; RRI, Relative Risk Increase; WDAE, Withdrawals due to adverse events

Pharmacoeconomic Analysis

At initial and maximum doses, pregabalin seems to be more costly than gabapentin when the measured outcome is percentage of patients achieving a minimal clinically important difference in pain (NRS-30, at least 30% reduction in pain score on an 11-point numerical rating scale) for PDN and PHN (see Table 20), and percentage of patients achieving SF-50 for PS. Responder rates at doses greater than 1800 mg daily were not available for gabapentin in PS. At the maximal *evaluated* doses, pregabalin (600 mg daily) is 3 times more costly as gabapentin (1800 mg daily); however, these may not be comparable doses in PS since gabapentin doses as high as 3600 mg daily have been used.

Table 20 Cost-effectiveness profile

Drug	Dose (mg/d)	Cost / Patient		NNTB (time period)			Yearly Cost / Responder		
		Per Day	Per Year	PDN	PHN	PS	PDN	PHN	PS
Pregabalin cap	150–600	$2.82	$1029	3 (5 wk)	3–6 (8 wk)	3–6 (12 wk)			
				1 (1 y)	1 (1 y)	1–2 (1 y)	$1029	$1029	$1029–$2058
Gabapentin tab	600–1800	$0.36–$0.95	$131–$347	NR[†]	4[‡] (7 wk)	7–9 (12 wk)[§]			
				—	1 (1 y)	2 (1 y)	NC	$131–$347	$262–$654

Lowest FSS acquisition costs as of 13 April 2006

NNTB, Number-needed-to-treat for benefit. For PDN and PHN, NNTB was calculated using at least 30% reduction in pain on an 11-point numerical rating scale. For PS, at least 50% reduction in seizure frequency was used. NNTBs extrapolated to 1 year assumes that the relative treatment benefit remains constant over time.

PDN, Painful diabetic neuropathy; PHN, Postherpetic neuropathy; PS, Partial seizures

† Using an NNTB of 4, calculated on the basis of NNTB from at least moderate improvement on CGIC of 4 (94% CI: 2–8) over 8 weeks (NNTB of 1 over 1 y), the yearly cost per responder would be $197–$690 for gabapentin in PDN, assuming that the relative benefit remains constant over time. (Note: NNTB was 2 (95% CI: 2–4) on PGIC.)[18]

‡ From Comments to Rice (2001)[97]; gabapentin 1800 and 2400 mg/d.

§ From Neurontin Product Information (2005).[86]

VA-oriented incremental cost-effectiveness ratio model for neuropathic pain

Pfizer developed a customizable cost-effectiveness model using techniques of dynamic simulation to estimate, over time, the effects of flexibly dosed pregabalin and other treatments (particularly, gabapentin) on daily pain experience and medical costs in patients with moderate or severe pain due to PDN or PHN.[98] In the dynamic simulation process, hypothetical patients are randomly assigned an average pretreatment pain score based on the distribution of patient-level mean pain scores observed in Freynhagn, et al. (2005; protocol 1008-155).[79] Efficacy data for gabapentin were based on results of protocols 945-210 and 945-211.[18,29] Each of the 1000 patients in the hypothetical cohort are stepped through the model, one at a time, yielding expected values for all outcomes for each patient and summaries of these outcomes for the entire cohort. The primary outcome measure in the model is "a day with no or mild pain." Efficacy rates reflected 12 weeks of treatment with pregabalin (mean daily dose 375 mg; range, 150 to 600 mg) and 8 weeks of treatment with gabapentin (mean daily dose, 2400 mg; range, 900 to 3600 mg).

VHA PBM requested that gabapentin be used as the comparator drug, that different time frames (12 and 52 weeks) be used in scenarios, and that VHA costs be used for medication and neuropathic pain–related services. Default model parameters were used for probability of primary care and/or specialist visits and health-state utilities. In the context of the assumptions used for the impact model, the manufacturer states that there are no clinically relevant differences in the safety profiles of pregabalin and gabapentin, and the same assumption was made for other comparator drugs. Therefore, adverse events were not considered in the model. It was also assumed that treatment discontinuations due to adverse events or inefficacy occurred at the same frequencies across therapies.

The incremental cost per additional day with no or mild pain on pregabalin (150 to 600 mg daily, flexible dosing) relative to gabapentin (mean flexible dose, 2400 mg daily) in mixed neuropathic pain (PDN and PHN) ranged from –$182 to $670 over 52 weeks for drug costs only (and –$229 to $622 for all health care costs). The incremental cost per quality-adjusted life year (QALY) gained was $2711 (95% CI: $682 to $4328).

The manufacturer concluded that pregabalin provided more days of no or mild pain than gabapentin and that the incremental cost-effectiveness ratios (ICERs) and QALYs obtained in the analysis were within the range of other valued medical interventions, such as treatment of chronic

noncancer pain, use of proton pump inhibitors for gastroesophageal reflux disease, and treatment of major depression.

Limitations of this pharmacoeconomic analysis include omission of safety costs, efficacy rates that seem to be inconsistent with published rates, extrapolation of short-term efficacy rates to 52 weeks, and incomplete disclosure of calculations.

VA-oriented incremental cost-effectiveness ratio model for partial-onset seizures

A cost-effectiveness model using dynamic simulation was used to estimate the impact of add-on pregabalin, other selected add-on antiepileptic drug therapy, and no add-on therapy (i.e. standard therapy alone) on the frequency of seizure-free days in adults with partial epilepsy refractory to at least one antiepileptic agent. In the model, a hypothetical cohort of 1000 patients are randomly assigned a pretreatment monthly average number of seizure-days, based on the pooled distribution of mean seizure-days at baseline among patients who participated in two randomized controlled trials (protocols 1008-011 and 1008-034).[88,90] A predicted number of seizure-days is then randomly assigned to each month using a Poisson distribution with a mean equal to the pretreatment mean frequency of seizure-days and a variance equal to that mean. Seizure-day rates are permitted to vary randomly from patient to patient. The model allows adverse events and discontinuations due to adverse events or inefficacy. Each patient is randomly stepped through the model to yield expected values for all outcomes for each patient in the cohort. The model then calculates summary measures of the expected patient outcomes, including mean duration of study therapy, percentage of patients discontinuing therapy, mean number of seizure-free days (the primary outcome of interest), percentage of patients experiencing selected adverse events, and quality-adjusted life expectancy. Duration of therapy may be customized to one year (i.e., no treatment discontinuations) or less than one year (assuming withdrawal due to adverse events or inefficacy). The median reduction in seizure frequency was 36.7% for pregabalin 300 mg daily, 43.0% for pregabalin 600 mg daily, and 26.0% for gabapentin 1800 mg daily. Daily medication costs and costs of neurology clinic visits reflected current VA prices. Incremental cost-effectiveness of other antiepileptic drugs (lamotrigine, levetiracetam, oxcarbazepine, and topiramate) were also calculated but not discussed here.

The estimated incremental cost per additional day without seizures was $18 (95% CI: $16 to $21) for pregabalin and $11 ($8 to $17) for gabapentin. The cost per additional QALY gained was $29,533 (95% CI: $25,775 to $34,941) for pregabalin and $17,520 ($10,819 to $29,647) for gabapentin. When expected costs of care for adverse events per patient (including drug and specialist visits) are added to the model, the costs are $19 ($17 to $22) per additional day without seizures and $34,574 ($28,738 to $46,643) per QALY gained for pregabalin and $10 ($7 to $15) and $19,288 ($10,866 to $40,134), respectively, for gabapentin.

The manufacturer concluded that pregabalin provides a greater number of seizure-free days than other second-generation antiepileptic drugs; the ICERs and QALYs for pregabalin are within the range of other medical interventions; and that at a price of $2.70 per 1800-mg dose of gabapentin, the ICER for pregabalin is dominant.

Limitations of this model include questionable derivation of efficacy rates and incomplete disclosure of calculations.

Conclusions

Pregabalin is the second agent to be approved for neuropathic pain (PDN and PHN) and partial epilepsy in the A2D-receptor binding class of antiepileptic drugs. The advantages of pregabalin relative to gabapentin include greater potency (mg/kg), better oral bioavailability, linear pharmacokinetics, smaller intra- and intersubject pharmacokinetic variability, and shorter titration. To a certain extent, these pharmacologic and pharmacokinetic advantages may have

translated into clinical advantages in that pregabalin showed somewhat more consistent efficacy across large, multicenter PDN trials and gained FDA approval for PDN, whereas gabapentin was less consistently efficacious and failed to receive FDA approval for this indication.

In terms of NRS-50 and NRS-30 responder rates, pregabalin and gabapentin are similar in efficacy in neuropathic pain. Using SF-50 responder rates in PS, pregabalin may be slightly more effective than gabapentin, but confidence intervals overlap.

Overall, the adverse event profiles of pregabalin and gabapentin are similar. The main exception to the similarity in safety characteristics is the controlled substance (schedule V) classification of pregabalin.

Based on indirect comparisons (which should be considered inconclusive), there may be other possible dissimilarities which could be clinically important in some individuals. Weight gain ≥ 7% over baseline, adverse ophthalmologic events, euphoria, increased creatine kinase, decreased platelet count, and PR interval prolongation may be more likely to occur during pregabalin therapy, whereas gabapentin may be more likely to be associated with fatigue and diarrhea.

Pharmacoeconomic analyses suggest that generic gabapentin is more cost-effective than pregabalin, although pregabalin incremental cost-effectiveness ratios and QALYs are within the range of other medical interventions.

Recommendations

- Pregabalin should be made nonformulary with criteria.
- Since pregabalin is considered to have a class effect, it should be considered a treatment alternative in patients with PDN, PHN, or PS who have had a documented inadequate response, intolerance, hypersensitivity, or contraindication to gabapentin. It should be used with caution in patients with substance use disorder.
- There is no evidence to support combined therapy with pregabalin and gabapentin.
- Although there is considerable published evidence supporting its use for the treatment of generalized anxiety disorder; the PBM SHG recommends that clinicians await further FDA evaluation of pregabalin for this indication.
- Pregabalin should not be used for chronic low back pain, chronic pain due to hip osteoarthritis, and panic disorder, given preliminary evidence suggesting lack of efficacy in these conditions.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to October 2005) and the Cochrane Registry of Controlled Trials using the search terms *pregabalin* and *Lyrica*. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All systematic reviews and randomized controlled trials evaluating efficacy and safety, and observational studies evaluating durability of response and safety were included.

Abbreviations Used in Appendix Tables

AE, Adverse event

AED, Antiepileptic drug

BL, Baseline

CGIC-much, Clinical Global Impression of Change scale rating of at least "much improved"

CL, Confidence limits

DFH, Drug-free holiday

Diff, Difference (PGB – PBO)

EP, End point

EQ-5D, EuroQoL Health Utilities Index

LSM, Least squares mean

Δ, Mean change from baseline to end point, unless otherwise specified

†, Denotes calculated value

‡, p-values for both NRS-50 and -30

N, Number of patients enrolled; N_R and N_A not specified

N_A, Number of patients analyzed

ND, Not done

NNTB-50 or NNTB-30, Number-needed-to-treat for benefit based on number of patients achieving NRS-50 or NRS-30, respectively

N_R, Number of patients randomized

NRS-50 or NRS-30 denotes at least 50% or 30% improvement from baseline, respectively, on 11-point Numerical Rating Scale for pain

OCA, Observed case analysis

PEM, Primary efficacy measure

PGIC-imp, -much, or -min denotes Patient Global Impression of Change scale rating of "improvement" (not otherwise defined), at least "much improved" or at least "minimally improved," respectively

Responder Rate-50, percentage of patients who have at least a 50% reduction in 28-d seizure frequency compared with baseline

RRatio, Response ratio; reduction in partial seizure frequency; calculated as the difference in 28-d seizure frequencies at the end of the study period and the baseline period, divided by the sum of the endpoint and baseline seizure frequencies, and multiplied by 100

SAE, Serious adverse event

SFI, Seizure-free interval

TCAD, Tricyclic antidepressant

TR, Treatment-related

TRSAE, Treatment-related serious adverse event

ULN, Upper limit of normal

WDAE, Withdrawal due to adverse event

WDTRAE, Withdrawal due to treatment-related adverse event

WDLE, Withdrawal due to lack of efficacy

WDSAE, Withdrawal due to serious adverse event

Appendix Table 1 Painful Diabetic Neuropathy: active-control trials

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
No trials			

Appendix Table 2 Painful diabetic neuropathy: placebo-controlled trials

Citation Design, Quality

Lesser (2004)[77,80]
Study 029
MC DB PC PG RCT
ITT, LOCF
Total N_R = 338

Interventions
Pregabalin 75, 300, or 600 mg/d (in 3 divided doses) vs. Placebo for 5 wk
(75- and 300-mg doses started without titration; 600-mg dose was titrated over 1 wk, then fixed for 4 wk)
Allowed co-medications
Acetaminophen (up to 3 g/d); selective serotonin reuptake inhibitors (stable doses)

Fair quality
Results may be applicable to short-term treatment of compliant patients with stable diabetes but not necessarily those who have not responded to gabapentin ≥ 1200 mg / d.

Major Eligibility Criteria, Population Profile

Inclusion criteria: Age > / = 18 years; type 1 or 2 diabetes mellitus; distal symmetric sensorimotor polyneuropathy for 1 to 5 y; stable antidiabetic medication; completed at least 4 daily pain diaries during baseline phase; average baseline daily pain score >/= 4 (on 0 to 10 scale); score of >/= 40 mm on visual analog scale (VAS)

Exclusion criteria:
failed to respond to previous gabapentin >/= 1200 mg/d for PDN

Population Profile
Age, mean (range), y: 59.9 (26 to 85)
M / F: 202 / 135
Race, white / black / other, n (%): 318 (94.4) / 12 (3.6) / 7 (2.1)

Estimated CrCl, mean, ml / min: 98.1
Diabetes type, 1 / 2, n (%): 31 (9.2) / 306 (90.8)
Baseline pain score, mean (range): 6.4 (2.9 to 10.0)
Antidiabetic medication, Insulin / Oral, n (%): 142 (42.1) / 247 (73.3)

Efficacy Results

Average Daily Pain score (0–10 Numerical Rating Scale)

Average daily pain	PGB600 N = 81	PGB300 N = 81	PGB75 N = 77	PBO N = 97
EP LSM	3.60	3.80	4.91	5.06
Diff	–1.45	–1.26	–0.15	0
95% CL	–2.06, -0.85	–1.86, -0.65	–0.76, 0.45	—
p-value	.0001	.0001	NSD	—
Δ†	–2.60	–2.40	–1.79	–1.54

Onset of first statistically significant difference from placebo: 1 wk (pregabalin 300 and 600 mg / d).

Responder rates (% of patients) at 5 wk

Outcome	PGB600	PGB300	PGB75	PBO
NRS-50	48	41	~25	18
NRS-30	65	62	~37	33
p-value†‡	< .0001	< .0001	NSD	—
NNT-50†	3	4	NC	—
95% CL†	2, 6	2, 7		—
NNT-30†	3	3	NC	—
95% CL†	2, 5	2, 7		—

Sleep interference score, short-form McGill Pain Questionnaire, VAS score, Present Pain Intensity score, PGIC and CGIC "improvement," and SF-36 social function and bodily pain domains: for each outcome, the results showed statistically significant ($p < 0.05$) treatment benefit on pregabalin 300 and 600 but not 75 mg / d vs. placebo. POMS, tension-anxiety mood scale results showed a statistically significant ($p < 0.05$) treatment benefit on pregabalin 300 but not 600 or 75 mg / d vs. placebo.

Safety Results

Deaths and Other Serious Adverse Events: No deaths; 8 SAEs (4 on PGB600, 1 on PGB75, 3 on PBO)

Withdrawals (% of patients)

Withdrawals	PGB600 N = 82	PGB300 N = 81	PGB75 N = 77	PBO N = 97
Total	14.6	6.2	13.0	8.2
SDSAEs	0.0	0.0	0.0	1.0
WDAEs	12.2	3.7	2.7	3.1

Adverse events (% of patients)

Adverse event	PGB600 N = 82	PGB300 N = 81	PGB75 N = 77	PBO N = 97
≥ 1 AE	87	75	62	67
Reported in ≥10% of patients in any group				
Dizziness	39.0	27.2	7.8	5.2
Somnolence	26.8	23.5	3.9	4.1
Peripheral edema	13.4	7.4	3.9	2.1
Headache	9.8	8.6	6.5	10.3
Reported on PGB but not PBO				
Accidental injury	4.9	2.5	5.2	0.0
Euphoria	4.9	6.2	0.0	0.0

Other specific AEs reported in >/= 5% of patients in any pregabalin grou
ataxia, neuropathy, pain, amnesia, accidental injury, dry mouth, euphori
diarrhea, infection

Weight gain ≥7% (n): 1 on PGB300; 3 on PGB75; 3 on PBO

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Rosenstock (2004)[78,80] Study 131 MC DB PC PG RCT ITT, LOCF Total N_R = 146 *Interventions* Pregabalin 300 mg/d (in 3 divided doses) vs. Placebo for 8 wk (fixed-dose regimen without titration) *Allowed co-medications* Stable antidiabetic medications; acetaminophen up to 4 g/d; ASA up to 325 mg/d for MI or TIA prophylaxis; SSRIs at stable doses; drugs and supplements used for diabetic peripheral neuropathy; AEDs for pain; TCADs, centrally acting analgesics *Fair quality* *May apply to short-term treatment without dosage titration; may not apply to nonresponders to gabapentin ≥ 1200 mg/d.* Exclusion of gabapentin(≥ 1200 mg / d) nonresponders may bias results in favor of PGB.	Inclusion criteria: Age at least 18 y; type 1 or 2 diabetes mellitus; symmetrical painful symptoms in distal extremities for 1 to 5 y prior to study; symptoms attributable to sensorimotor diabetic peripheral neuropathy; score of at least 40 mm on 100-mm visual analog scale (VAS); completion of at least 4 daily diaries during the week preceding randomization; minimum average daily pain score of 4 on 11-point numerical rating scale (NRS) during baseline period; normal chest X-ray within prior 2 y; baseline hemoglobin A1c </= 11% Exclusion criteria: failed to respond to previous treatment with gabapentin ≥ 1200 mg/d for treatment of pain associated with diabetic neuropathy. *Population Profile* Pregabalin (N = 76) vs. Placebo (N = 70) Age, mean, y: 59.2 vs. 60.3 M / F: 55.3% / 44.7% vs. 57.1% / 42.9% Ethnicity, White / Black / Other: 84.2% / 7.9% / 7.9% vs. 91.4% / 4.3% / 4.3% Duration of diabetes, mean, y: 9.3 vs. 9.4	Average Daily Pain score (0–10 Numerical Rating Scale) Results for Average daily pain: PGB 300 N = 76 / PBO N = 70 EP LSM: 3.99 / 5.46 Diff: –1.47 / — 95% CL: –2.19, –0.75 p-value: .0001 Δ†: –2.5 / –0.8 p-value: NA Δ (BL to End of Wk 1): –2.2 / –0.4 p-value: 0.0001 CL, Confidence limits; LSM, Least squares mean; Δ, Change; †, Denotes calculated value Responder rates (% of patients) at 8 wk Outcome: PGB 300 / PBO NRS-50: 40.0 / 14.5 p-value: 0.001 NRS-30: 50.0 / 35.0 NNT-50†: 4 / — 95% CL†: 3, 9 / — NNT-30: NSD (p = 0.08) 95% CL†: — / — PGIC-imp: 67 / 39 p-value: 0.001 NNT-PGIC-imp: 4 / — 95% CL: 2, 8 / — Sleep interference score, SF-MPQ total score, VAS score, and PPI score, SF-36 bodily pain, POMS tension / anxiety and total mood disturbance: for each outcome measure (end point LSM), the results showed statistically significant ($p \leq 0.0364$) improvement on pregabalin 300 vs. placebo PGIC (see Responder Rates above) and CGIC improvement results also showed a statistically significant ($p \leq 0.004$) treatment benefit on pregabalin vs. placebo.	SAEs: None on pregabalin (not reported for PBO) Withdrawals (% of patients) Withdrawals: PGB 300 / PBO Total: 14.5 / 11.4 WDAEs: 10.5 / 2.9 AEs leading to withdrawal: somnolence, dizziness Adverse events reported in ≥ 10% of patients in the pregabalin group (% patients) Adverse event: PGB 300 / PBO Dizziness: 35.5 / 11.4 Somnolence: 19.7 / 2.9 Infection: 14.5 / 5.7 Peripheral edema: 10.5 / 1.4 Adverse events reported on pregabalin but not on placebo (% of patient Adverse event: PGB 300 / PBO Constipation: 5.3 / 0.0 Euphoria: 5.3 / 0.0 Hyperglycemia: 3.9 / 0.0 Adverse events considered to be related to study medication (pregabali placebo, n (%) of patients): 47 (62%) vs. 20 (29%)

Citation Design, Quality

Richter (2005)[80,83]
Study 1008-014
MC (29) DB PC PG RCT with open-label follow-on study
ITT, LOCF
Total N_R = 246

Interventions
Pregabalin 150 or 600 mg / d (in 3 divided doses) vs. Placebo for 6 wk (including 2 wk titration)
Allowed co-medications
ASA for MI prophylaxis and TIAs; APAP ≤ 3 g/d; stable doses of SSRIs

Fair quality
Results may be applicable to short-term treatment

Major Eligibility Criteria, Population Profile

Inclusion criteria: age ≥18 y; diabetic, distal, symmetric, sensorimotor polyneuropathy for 1-5 y with HgA1c ≤ 11%; SF-MPQ 100-mm VAS score ≥ 40 mm; completed at least 4 daily pain diaries; average score of ≥ 4 on daily Pain Rating Scale (0–10) over the 7 d prior to randomization

Exclusion criteria: previously treated with pregabalin; CrCl ≤ 60 ml/min; serious hepatic, respiratory, or hematologic illness; unstable CVD; symptomatic PVD; abnormal ECG or 2-min rhythm strip; neurologic disorders unrelated to diabetic neuropathy; clinically significant abnormalities on visual field and acuity tests (specific tests and requirements not delineated here); chronic hepatitis B or hepatitis B within previous 3 mo; HIV infection; use of analgesics other than ASA (≤ 325 mg/d for prophylaxis of MI and TIAs), acetaminophen, antidepressants other than SSRIs, AEDs, neuroleptics, or any concomitant medication that could alter effect of study treatment within the 14 or 30 d prior to start of study; other severe pain that could confound assessments; abuse of illicit drugs or alcohol within the last year

Population Profile
Age, mean, y: 57.0 y
Male/Female: 60.6% / 39.4%
White: 83.7%
Type I / II DM: 9% / 91%, ave. 9 y

Efficacy Results

Average Daily Pain score (0–10 Numerical Rating Scale)

Results for average daily pain	PGB600 N = 82	PGB150 N = 79	PBO N = 85
EP LSM	4.29	5.11	5.55
Diff	–0.44	–1.26	—
95% CL	NR	NR	NR
p-value	.0002	.1763	—
Δ†	–2.4	–1.5	–1.2
p-value	.0002	NR	NR

Responder rates (% of patients) at week 6

Outcome measure	PGB600	PGB300	PBO
NRS-50	39%	19%	15%
p-value	.002	.423	—
NNTB-50†	4	—	—
95% CL†	3, 8	—	—
PGIC-much	51.8%	NR	28.2%
p-value	.002	.235	—
CGIC-much	45.2%	NR	22.8%
p-value	.002	.708	—

NNTB-50, Number-needed-to-treat for benefit based on number of patients achieving NRS-50.
NRS-50, At least 50% improvement on 11-point Numerical Rating Scale (definition of responders)
PGIC-much, At least much improved on Patient Global Impression of Change scale
CGIC-much, At least much improved on Clinical Global Impression of Change scale

PGB600 but not PGB300 was superior to placebo in decreasing SF-MPQ end point scores (sensory, affective, VAS, PPI) (p = .0002) and sleep interference scores (p = 0.0004).

PGB600 and PGB300 were better than placebo in SF-36 QoL bodily pain domain (53.7 and 52.9 vs. 45.5, respectively; p = 0.01).
POMS scores: NSD

Safety Results

Deaths: None

Nonfatal Serious Adverse Events (n, %)

SAE	PGB600 N = 82	PGB150 N = 79	PBO N = 85
Total	5 (6.1)	1 (1.3)	2 (2.4)
WDSAE	1 (1.2)	0 (0.0)	0 (0.0)
Related to tx	0 (0.0)	0 (0.0)	0 (0.0)

WDSAE, Withdrawal due to serious adverse event

Withdrawals (n, % of patients)

Withdrawals	PGB600 N = 82	PGB150 N = 79	PBO N = 85
Total	10 (12.2)	4 (5.1)	13 (15.3)
WDAEs	7 (8.5)	2 (2.5)	4 (4.7)

Adverse events (n, % of patients)

Adverse event	PGB600 N = 82	PGB150 N = 79	PBO N = 85
≥1 AE	70 (85)	44 (56)	48 (57)

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Unpublished (EMEA 2004)[82] Study DPN-149 MC DB PC PG RCT mITT (received ≥ 1 dose and not withdrawn because of regulatory or ethics committee decisions) Total N_R = 396 *Interventions (mg/d, dosed b.i.d.):* Pregabalin 300/600 Pregabalin 300 Pregabalin 150 Placebo For 12 wk (1 + 11 wk) *Allowed co-medications:* APAP up to 3–4 g/d p.r.n.; others unknown *Quality not evaluable (insufficient information)* *External validity not evaluable*	*Population profile* Age (y, range of means), 47.6–59.5 Duration of DM (y, range of medians), 11–12.5 Type I DM (%, range), 14%–16% Type II DM (%, range), 84%–86%	Average Daily Pain score (0–10 Numerical Rating Scale) Results: EP LSM — PGB300/600 N = 98: 3.69; PGB300 N = 96: 4.48; PGB150 N = 96: 4.33; PBO N = 93: 4.66 Diff — PGB300/600: –0.97; PGB300: –0.18; PGB150: –0.33; PBO: — 95% CL — PGB300/600: –1.58, –0.36; PGB300: –0.79, 0.43; PGB150: –0.94, 0.28; PBO: — p-value — PGB300/600: 0.0054; PGB300: 0.558; PGB150: 0.558; PBO: — Δ† — PGB300/600: 2.91; PGB300: 1.92; PGB150: 1.87; PBO: 1.74 p-value — PGB300/600: NR; PGB300: NR; PGB150: NR; PBO: NR Responder rates (% of patients) at week 12 Outcome measure — PGB300/600 / PGB300 / PGB150 / PBO NRS-50 — 46 / 33 / 34 / 30 p-value — 0.04 / 0.74 / 0.74 / — NNTB-50† — 7 / NSD / NSD / — 95% CL† — 4, 50 / — / — / —	Deaths and Other Serious Adverse Events: NR Withdrawals (% of patients) Withdrawals — PGB300/600 N = 101 / PGB300 N = 99 / PGB150 N = 99 / PBO N = 97 Total — 23 / 20 / 17 / 18 WDAEs — 12.9 / 11.1 / 5.0 / 3.1 Adverse events (% of patients) Adverse event — PGB300/600 N = 101 / PGB300 N = 99 / PGB150 N = 99 / PBO N = 97 ≥ 1 AE *Reported in ≥10% of patients in any group* Dizziness Somnolence Peripheral edema Headache *Reported on PGB but not PBO* Accidental injury Euphoria Other specific AEs reported in >/= 5% of patients in any pregabalin gr

Appendix Table 3 Postherpetic neuralgia: placebo-controlled trials

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Dworkin (2003)[75] Study 1008-127, U.S. MC (29) DB PC PG RCT with optional open-label extension ITT, LOCF Total N_R = 173, N_A = 172 *Interventions* Pregabalin 300 or 600 mg/d (in 3 divided doses) depending on CrCl vs. Placebo for 8 wk including 1 wk titration *Allowed co-medications* If doses stable for 30 d prior to baseline and during study: narcotic and nonnarcotic analgesics; acetaminophen ≤ 4 g/d; NSAIDS, ASA, antidepressants (including. SSRIs). *Fair quality* *May apply to short-term treatment; may not apply to nonresponders to gabapentin ≥ 1200 mg/d*	Inclusion criteria: ≥ 18 y old; PHN, defined as pain present for > 3 mo after healing of HZ skin rash; pain at least 40 mm on 100-mm VAS of SF-MPQ; completed at least 4 daily pain diaries; mean daily pain rating of 4 on 11-point NRS; normal chest X-ray within previous 2 y Exclusion criteria: other severe pain that might confound assessments; previous neurolytic or neurosurgical therapy for PHN; failed gabapentin ≥ 1200 mg/d; baseline CrCl ≤ 30 ml/min; WBC < 2500/mm^3; PMN < 1500/mm^3; platelets < 100 x 10^3/mm^3 *Population profile:* Age, mean, y: 71.5 Male 46.8% White 94.8% Duration of PHN, mean, mo: 33.8 Low CrCl stratum (> 30, ≤ 60 ml/min), 31.8% Normal CrCl stratum (> 60 ml/min), 68.2%	Average Daily Pain score (0–10 Numerical Rating Scale) Average daily pain: PGB300/600 N = 88; PBO N = 84 EP LSM: 3.60; 5.29 Diff: –1.69; — 95% CL: –2.33, –1.05; — p-value: 0.0001; — Δ†: –2.7; –1.1 Onset of first statistically significant difference in scores: 2 wk for pain, 1 wk for sleep interference. Responder rates (% of patients) at 8 wk Outcome: PGB300/600; PBO NRS-50: 50.0%; 20.2% p-value: 0.001 NNT-50†: 3 95% CL†: (2, 6) NRS-30: ~67%; NR p-value: NC NNT-30†: NC 95% CL†: NC PGIC-Min.: 84%; 26% p-value: 0.001 CGIC-Min.: NR p-value: < 0.05 At study end point, PGB was better than PBO on SF-MPQ sensory, affective, and total pain scores (p < 0.005); SF-MPQ VAS pain and PPI pain scores; sleep interference scores beginning at wk 1 (p = 0.0001); Medical Outcomes Study (MOS) Sleep Scale sleep problem index; and SF-36 bodily pain and general health perception scales. Greater improvement was seen with PGB than PBO on the POMS depression-dejection scale but the difference did not reach the level of statistical significance (mean score, 6.70 vs. 8.47; p = 0.051).	Deaths: NR Nonfatal Serious Adverse Events (n, %) SAE: PGB300/600 N = 89; PBO N = 84 Total: NR; NR WDSAE: NR; NR TRSAE: 0 (0.0); NR Withdrawals (n, %) Withdrawals: PGB300/600; PBO Total: 31 (34.8); 10 (11.9) WDLE: 0 (0.0); 6 (7.1) WDAEs: 28 (31.5); 4 (4.8) p-value†: < 0.0001 NNTH (95% CL): 4 (3, 6) (11% of PGB patients withdrew because of somnolence.) Adverse events (n, %) Adverse event: PGB300/600 N = 89; PBO N = 84 ≥ 1 AE: 77 (87); 53 (63) *Reported in ≥ 10% in either group* Dizziness: 25 (28.1); 10 (11.9) Somnolence: 22 (24.7); 6 (7.1) Peripheral edema: 17 (19.1); 2 (2.4) Amblyopia: 10 (11.2); 1 (1.2) Dry mouth: 10 (11.2); 2 (2.4) *Reported on PGB but not PBO* Ataxia: 6 (6.7); 0 (0.0) Confusion: 6 (6.7); 0 (0.0) Speech disorder: 5 (5.6); 0 (0.0) Patients reporting maximum AE intensity of mild to moderate: 81% on PGB vs. 92% on PBO

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Sabatowski (2004)[76] Study 1008-045, Europe, Australia MC DB PC PG RCT with OL extension ITT, LOCF N_R = 238 *Interventions* Pregabalin 150 mg/d vs. Pregabalin 300 mg/d vs. Placebo (in 3 divided daily doses) for 8 wk, including 1-wk titration *Allowed co-medications* Stable regimens of APAP up to 3 g/d; NSAIDs; opioid or nonopioid analgesics; antidepressants *Prohibited medications* New analgesics; benzodiazepines and AEDs required 14-d washout *Fair quality* *May apply to short-term treatment; may not apply to nonresponders to gabapentin ≥ 1200 mg/d and patients with renal impairment (CrCl ≤ 30 ml/min) or other significant morbidities*	*Inclusion criteria:* pain present for more than 6 mo after healing of HZ rash; age ≥ 18 y; completed at least 4 daily pain diaries during 7-d baseline phase; average daily pain ≥ 4; score ≥ 40 mm on 100-mm VAS of SF-MPQ *Exclusion criteria:* active malignancy; clinically significant respiratory, hematologic, hepatic, or cardiovascular disease; failed PHN treatment with gabapentin ≥ 1200 mg/d; neurolytic or neurosurgical therapy for PHN; skin condition or severe non-PHN pain that might compromise assessments; CrCl ≤ 30 ml/min *Population profile (ranges across treatment groups):* Age, mean, y: 71.3–73.2 Male 41%–48% White, 98%–100% CrCl, mean, ml/min: 48.9–62.9 Duration of PHN, mean, mo: 40.7–44.8 Co-medications (% of patients): –Analgesics: 31%–46% –Antiinflammatories: 12%–21% –Antidepressants: 17%–22%	Average Daily Pain score (0–10 Numerical Rating Scale) PGB300 N = 76; PGB150 N = 81; PBO N = 81 EP LSM: 4.76; 5.14; 6.33 Diff: –1.57; –1.20; — 95% CL: –2.20, –0.95; –1.81, –0.58; — p-value: 0.001; 0.002; — Δ† : –2.2; –1.8; –0.3 Onset of first statistically significant treatment difference: 1 wk for both pain and sleep interference (PGB300, PGB150) Responder rates (% of patients) at week 8 Outcome measure: PGB300; PGB150; PBO NRS-50: 27.6; 25.9; 9.9 p-value: 0.006; 0.006; — NNTB-50†: 6; 6; — 95% CL†: 3, 17; 4, 22; — NRS-30: 50; 37; 19 p-value: NR; NR; — NNTB-30: 3; 5; — 95% CL: 2, 6; 3, 20; — PGIC-much: 38.2; 30.9; 13.5 p-value: 0.002; 0.064; — CGIC-much: NR; NR; NR p-value: NR; NR; NR Both PGB doses were significantly better than PBO (p ≤ 0.006) in MPQ VAS scores; sleep interference scores (as early as wk 1); SF-36 mental health domain. On the SF-36, PGB was better than PBO in mental health (PGB300, PGB150); bodily pain (PGB300), and vitality (PGB300). PGB150 was numerically better (p = 0.056) and PGB300 was statistically significantly better (p = 0.024) than PBO in the Zung Self-Rating Depression Scale index.	Deaths: 1 (MI on PBO) Other Serious Adverse Events: 1 on PGB300; 4 on PGB150, and 3 on PBO, including **ventricular extrasystoles** considered possibly or probably related to study medication (2 on PGB150, 1 on PBO) and **confusion** (1 on PGB150). Withdrawals (n, % of patients) Withdrawals: PGB300 N = 76; PGB150 N = 81; PBO N = 81 Total: 16 (21.1); 10 (12.3); 20 (24.7) WDAEs: 12 (15.8); 9 (11.1); 8 (9.9) WDLE: 1 (1.3); 0 (0.0); 7 (8.6) Adverse events (% of patients) PGB300; PGB150; PBO ≥1 AE: 83; NR; NR *Reported in ≥10% of patients in either PGB group* Dizziness: 28; 12; 15 Somnolence: 24; 15; 7 Peripheral edema: 13; 3; 0 Headache: 11; 11; 4 Dry mouth: 7; 11; 4 *Reported on PGB but not PBO* Peripheral edema: 13; 3; 0 Infection: 7; 3; 0 PGB300: Rated AEs mild (% of patients): 37% Rated AEs moderate (% of patients): 34% More patients in the PGB300 group experienced weight gain > 7% from baseline to termination (14% for PGB300 vs. 4% for PGB150 and 4% for PBO).

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Van Seventer (2006)[80,84] Study 1008-196 MC DB PC PG Phase III RCT with OL follow-on (study 1008-198) ITT, LOCF N_R = 370; N_{ITT} = 368 (stratified by center and CrCl) *Interventions* Pregabalin 150, 300, or 600 mg/d (based on CrCl; divided twice daily doses) vs. Placebo for 13 wk, including 1-wk titration CrCl 30–60 ml/min: max. randomized dose 300 mg/d CrCl > 60 ml/min: max. randomized dose 600 mg/d *Allowed co-medications:* NR	Inclusion criteria: *≥ 18 years old; pain for more than 3 mo after healing of HZ skin rash; SF-MPQ VAS score ≥ 40 mm; average daily pain score ≥ 4 over the 7 d prior to randomization; stable or normal chest X-ray within past 1 yr* Exclusion criteria: malignancy within past 2 y except basal cell carcinoma; neurolytic or neurosurgical therapy for PHN; CrCl ≤ 30 ml/min; WBC < 2500/mm^3; PMN < 1500/mm^3; platelets < 100 x 10^3/mm^3; clinically significant or unstable hepatic, respiratory, or hematologic illnesses; unstable cardiovascular disease; abnormal ECG; immunocompromised; history of chronic hepatitis B or C; hepatitis within past 3 mo; HIV infection; other severe pain that may interfere with assessments; skin condition within affected dermatome that could alter sensation; prohibited medications (long-acting benzodiazepines, AEDs) without appropriate washout; history of alcohol or illicit drug abuse within past 2 y; clinically significant or unstable medical or psychologic condition Population profile: ≥ 65 y old, 76%; White 99%; Males 46%; Normal CrCl (> 60 ml/min) 69%; low CrCl (30–60 ml/min) 32%	Average Daily Pain score (0–10 Numerical Rating Scale) PGB300/600 N = 90; PGB300 N = 98; PGB150 N = 87; PBO N = 93 EP LSM Diff: –1.47; –1.07; –0.88; — 95% CL p-value: 0.0003; 0.0016; 0.0077; — Δ[†] Onset of first statistically significant treatment difference: wk 1 Responder rates (% of patients) at week 13 Outcome measure / PGB300/600 / PGB300 / PGB150 / PBO NRS-50: 37.5; 26.5; 26.4; 7.5 p-value: 0.001; 0.001; 0.001; — NNTB-50[†]: 3; 5; 5; — 95% CL[†]: 2, 5; 3, 11; 3, 12; — PGIC-much: 36; 27; 23; 16 p-value: 0.003; NSD; 0.020; — CGIC-much: 38; 25; 25; 17 p-value: 0.003; NSD; NSD; — All PGB dosage levels were significantly better than PBO in sleep interference, in MOS sleep disturbance and overall sleep problems index; and in SF-MPQ except for PGB150 for VAS and PGB150 and PGB300 for PPI. Only PGB300/600 was significantly better than PBO on CGIC and only PGB300 was significantly better than PBO on PGIC. Only PGB300/600 was significantly better than PBO on any SF-36 domain (bodily pain); however, all PGB groups were significantly better than PBO on the EQ-5D Utility and VAS AUC. Allodynia and hyperalgesia (% of patients): NSD	Deaths: None Serious adverse events: 10 on PGB vs. 2 on PBO Serious adverse events considered related to treatments: Total 2 on PGB—1 on PGB300 / 600 (dizziness, face edema, myasthenia, peripheral edema, somnolence) and 1 on PGB300 (anaphylactoid reaction). A total of 126 / 368 (34%) were withdrawn during the double-blind phase, primarily because of lack of efficacy (57 patients, 16%) and adverse events (46 patients, 13%). Most frequent AEs leading to withdrawal: dizziness, somnolence, ataxia. Withdrawals (n) Withdrawals / PGB300/600 N = NR / PGB300 N = NR / PGB150 N = NR / PBO N = NR Total: NR; NR; NR; NR WDSAEs: 2; 1; 0; 0 WDTRAEs: 18; 15; 7; 4 WDLE: NR; NR; NR; NR Despite dosage differences based on renal function, more patients with CrCl 30–60 ml/min withdrew due to AEs than patients with CrCl > 60 ml/min (data not reported). Of the 368 patients who received study medication, 70% experience ≥ 1 AE. Most frequent AEs: dizziness, somnolence, and peripheral edema. Most AEs were mild or moderate in intensity.

Appendix Table 4 Postherpetic neuralgia: open-label studies

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
No studies			

Appendix Table 5 Mixed neuropathic pain (PDN and PHN): placebo-controlled trials

Citation Design,Quality

Freynhagen (2005)[79]
Study 1008-155, Europe
MC (60) DB PC PG Phase III RCT
mITT
Specifically measured weight changes and peripheral and nonperipheral edema
N_R = 338

Pregabalin flexible dose vs. fixed dose vs. Placebo for 12 wk (dd b.i.d.)
Flexible dose
(PGB_{Flex}) = escalating doses of 150, 300, 450, and 600 mg / d titrated at weekly intervals
Fixed dose
(PGB600) = 600 mg / d, starting with 300 mg / d for 1 wk then 600 mg / d for 11 wk

Fair quality
External validity: Possibly applicable to veteran population except experience in non-white populations is very limited. Flexible dosing schedule more closely reflects clinical practice than fixed dosing regimen.

Major Eligibility Criteria, Population Profile

Inclusion criteria: age ≥ 18 y; SF-MPQ VAS score ≥ 40 mm; average daily pain score ≥ 4 over the 7 d prior to randomization; for PAN patients, a diagnosis of type I or II DM, HgA1C ≤ 11%; diagnosis of painful, distal, symmetrical, sensorimotor polyneuropathy due to DM for at least 6 mo; for PHN patients, pain present for more than 3 mo after healing of HZ rash.

Exclusion criteria: clinically significant or unstable medical condition; malignancy within past 2 y except for basal cell carcinoma; anticipated need for surgery during study; previous pregabalin; abnormal ECG; CrCl < 60 ml / min; WBC < 2500 / mm^3; PMN < 1500 / mm^3; platelets < 100 x 10^3 / mm^3; abused illicit drugs or alcohol within past 2 y; use of prohibited medication without adequate washout; history of chronic hepatitis B or C; hepatitis B or C within past 3 mo; HIV infection; neurologic disorders other than PDN or other severe pain that may interfere with assessments; history of pernicious anemia; untreated hypothyroidism; skin conditions in the area of neuropathy that may alter sensation; amputations other than toes; past neurolytic or neurosurgical therapy for PHN

Population profile: Age, mean, y: 62.2; age < 65 y: 52.4%; Male 54.1; White 97.6%; PDN 73.7%; PHN 26.3%; CrCl, mean: 88.1 ml / min

Efficacy Results

Average Daily Pain score (0–10 Numerical Rating Scale)

Average daily pain	PGB_{Flex} N = 141	PGB600 N = 132	PBO N = 65
EP LSM	3.8	3.6	5.0
Diff (calc.)	1.2	1.4	—
95% CL	NR	NR	—
p-value	≤ 0.01	≤ 0.01	—
Δ†	–2.89	–3.09	–1.62
p-value	0.002	< 0.001	—

Onset of first statistically significant difference from placebo: wk 2 (PGB_{Flex}) vs. wk 1 (PGB600)

Responder rates (% of patients) at 5 wk

Outcome	PGB_{Flex}	PGB600	PBO
NRS-50	48.2	52.3	24.2
p-value	< 0.001	< 0.001	—
NRS-30	59.0	66.4	37.1
p-value	0.003	< 0.001	—
NNT-50†	4.2	3.6	—
95% CL†	2.7, 9.5	2.4, 6.9	—
NNT-30†	4.6	3.4	—
95% CL†	2.7, 13.6	2.3, 6.8	—
PGIC-much	52.0	53.6	30.5
p-value	< 0.01	< 0.01	—
CGIC-min	ND	ND	ND

All PGB
NNT-50: 3.8 (95% CI: 2.6–7.3; p < 0.001)
NNT-30: 3.9 (95% CI: 2.6–8.3; p < 0.001)

Safety Results

Deaths and Serious Adverse Events (% of patients)

	PGB_{Flex} N = 141	PGB600 N = 132	PBO N = 65
Death	0	2	0
TR Death	0	0	0
SAEs	0	2	0

Withdrawals (% of patients)

Withdrawals	PGB_{Flex}	PGB600	PBO
Total	34.8	37.9	46.2
WDAEs	17.0	25.0	7.7
WDSAEs	6.4	3.0	NR
WDLC	NR	NR	NR

Most frequent AEs leading to withdrawal: dizziness, nausea, vertigo, somnolence.

Adverse events (% of patients)

	PGB_{Flex} N = 141	PGB600 N = 132	PBO N = 65
≥ 1 AE	68.8	74.2	44.6
Associated AEs† (≥ 10% of patients in any group)			
Dizziness	19.1	28.8	4.6
Peripheral edema	15.6	7.6	3.1
Weight gain	12.1	13.6	3.1
Somnolence	10.6	12.9	0.0
Nausea	5.0	10.6	1.0
Reported on PGB but not PBO			
Somnolence	10.6	12.9	0.0
Asthenia	6.4	9.1	0.0
Facial/Periorbital edema	2.2	2.3	0.0
Generalized or abd. edema	0.7	0.8	0.0

† *Associated AEs—not defined*

Specific Weight Change Measures (Per protocol)

Weight Change	PGB_{Flex}	PGB600	PBO
≥7% Increase (% of patients)	13.9	7.0	NR
≥7% Decrease (% of patients)	0.7	0.8	NR
Mean Change (kg)	1.9	1.6	0.2

Citation Design,Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Freynhagen (2005)[79] Study 1008-155 (cont'd)		Secondary measures (p-values vs. PBO)	Number-needed-to-treat for harm for All PGB, most common AEs (≥ 10% of patients)

Outcome measure	PGB_{Flex}	PGB600
Sleep Interference	≤ 0.01	≤ 0.01
SF-MPQ		
Sensory	NSD	NSD
Affective	NSD	NSD
Total	NSD	NSD
VAS	< 0.001	< 0.001
PPI	0.014	0.012
SF-36		
Mental health	0.001	NSD
EQ-5D	NSD	NSD
Utility Index	NSD	NSD
VAS	0.005	NR

	NNTH
Dizziness	5.2
Peripheral edema	11.6
Weight gain	10.3
Somnolence	8.5
Nausea	16.2

Appendix Table 6 Neuropathic pain (PDN and PHN): open-label studies

Citation Design, Interventions *Quality rating* *External validity*	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
No studies			

Appendix Table 7 Neuropathic pain (PDN and PHN): pooled analyses

Citation Design, Interventions *Quality rating* *External validity*	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Freeman (2005, poster)[80,81] Pooled analysis of data from 6 DB PC RCTs of 5 to 12 weeks' duration. Patients had diagnoses of postherpetic neuralgia (PHN) (1 trial),[75] painful diabetic neuropathy (PDN) (2 published[77,78] and 2 unpublished trials, studies 1008-040 and 1008-149), or either PHN or PDN (1 trial).[79] N = 1346 (873 Pregabalin vs. 473 Placebo) *Interventions* Pregabalin 150, 300, 600 mg / d (in 2 or 3 divided doses) vs. Placebo for 5, 8, 9, or 12 wk (varied among trials) (Data on 75 mg / d, evaluated in one trial, was not presented in the AMCP dossier because it is considered to be nontherapeutic.) *Quality not assessable.*	*Eligibility criteria* Not reported *Population Profile:* Age, mean, y: 59; White, 92%; Male, 57%; Weight, 92 kg Baseline mean pain score (11-point NRS), 6.5	Average Daily Pain score (0–10 Numerical Rating Scale) PGB 600 N = 431; PGB 300 N = 266; PGB 150 N = 176; PBO N = 473 Endpoint LSM Δ (BL to EP)† : –2.35; –2.04; –1.48; –2.74 p-value: ≤ 0.007 vs. PBO Δ (BL to EP-Wk 1) p-value Responder rates (% of patients) Outcome / PGB 600 / PGB 300 / PGB 150 / PBO NRS-50: 46 / 39 / 27 / 22 p-value: < 0.001 / < 0.001 / NR / — NRS-30: 62 / 55 / 43 / 37 p-value: ≤ 0.04 / ≤ 0.04 / ≤0 .04 / ≤ 0.04 NNT-50† 95% CL† PGIC-imp p-value NNT-PGIC-imp 95% CL Sleep interference scores ($p < .0025$, all pregabalin groups vs. placebo) and health status on PGIC ($p < .001$, all pregabalin doses) were significantly improved.	Withdrawals due to adverse events and treatment-emergent adverse events Adverse event / All PGB / PBO Led to withdrawal: 10.7 / 4.2 *Most common TEAEs* Dizziness: 22.0 / 4.0 Somnolence: 12.1 / 2.3 *Other notable TEAEs* Peripheral edema: 10.0 / 2.3 Peripheral edema was not associated with cardiovascular complications or changes in renal or hepatic laboratory test values, and rarely led to treatment discontinuation.

Appendix Table 8 Partial-onset seizures: placebo-controlled trials (adjunctive therapy)

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Beydoun (2005)[87] Study 1008-009, Pfizer[80] MC (43) DB PC PG RCT, Phase III (adjunctive therapy) U.S., Canada mITT N_R = 313; N_A = 312 *Interventions* Pregabalin 200 mg t.i.d. vs. Pregabalin 300 mg b.i.d. vs. Placebo for 12 wk, including 1 wk titration; DB treatment started after an 8-wk baseline period *Allowed co-medications:* Stable dose of single antidepressant for mild depression *Fair quality:* *External validity:* *May be limited to patients with difficult-to-treat seizures*	*Inclusion Criteria:* ≥ *18* years old; 50 to 135 kg; epilepsy with partial seizures; EEG within past 2 y consistent with diagnosis of focal-onset epilepsy; at least 3 partial seizures during the month prior to screening; at least 6 partial seizures during the 8-wk baseline period with no 4-wk seizure-free periods; 1 to 3 AEDs dosed within therapeutic range; refractory to >1 AED at maximum tolerated dose; no progressive structural abnormality on CT scan or MRI within past 2 y *Exclusion Criteria:* Treatable cause of seizures; absence seizures; Lennox-Gastaut Syndrome; progressive neurologic or systemic disorders; WBC < 2500 / mm^3; PMN < 1500 / mm^3, platelets < 100 x 10^3 / mm^3; cardiovascular, hematologic, hepatic, or renal disease; status epilepticus within past 1 y; significant psychiatric disorder or recurrent severe depression within past 1 y; any concomitant medication that could alter medication response or seizure frequency; illicit drugs or alcohol abuse within past 1 y; received gabapentin unless discontinued at least 1 wk prior to baseline *Population Profile (N = 312):* Age (y, range of means) 38.4–39.6; Male 50%; White 85.3%; average duration of epilepsy 25.7 y; median seizure frequency 9.5 (PGB200 t.i.d.), 10 (PGB300 b.i.d.), and 11 (PBO).	Baseline difference: slightly higher incidence of generalized seizures in PGB b.i.d. group than PGB t.i.d. group (data NR). Disposition of Patients PGB200 t.i.d. N = 111 | PGB300 b.i.d. N = 103 | PBO N = 98 Completed study (%): 76.6 | 68.3 | 82.7 p-value: NR | NR | — **Selected Efficacy Outcomes** Outcome Measure | PGB200 t.i.d. N = 111 | PGB300 b.i.d. N = 103 | PBO N = 98 RRatio (mean): –36.1 | –28.4 | 0.6 p-value: ≤ 0.0001 | ≤ 0.0001 | — Responder rate-50 (%): 49 | 43 | 9 p-value: ≤ 0.001 | ≤ 0.001 | — Seizure-free during last 28-d (n): 15 | NR | 3 p-value: 0.012 | NSD | — 42-d (n): 7 | NR | 0 p-value: 0.015 | NSD 56-d (n): 6 | NR | 0 p-value: 0.031 | NSD | — Δ SFI, median (d): 218.3 | 142.3 | 26.2	**Adverse events (% of patients)** PGB200 t.i.d. N = 111 | PGB300 b.i.d. N = 103 | PBO N = 98 Deaths: 0.0 | 0.0 | 0.0 Nonfatal SAEs: 3.6 | 5.8 | 4.1 TR Nonfatal SAE: 0.0 | 1.0 | 0.0 WDSAE: 0.0 | 2.9 | 2.0 WDAE: NR | NR | NR ≥ 1 AE: 94.6 | 99.0 | 72.4 **Rated AEs mild or moderate (n): "majority"** **Associated AEs[†] (≥ 10% in any group) (% of patients)** PGB200 t.i.d. | PGB300 b.i.d. | PBO ≥ 1 AE: 2.7 | 4.8 | 3.1 Dizziness: 37.8 | 41.7 | 12.2 Somnolence: 23.4 | 30.1 | 12.2 Ataxia: 27.0 | 16.5 | 6.1 Weight gain: 15.3 | 20.4 | 2.0 Amblyopia: 17.1 | 9.7 | 4.1 Asthenia: 11.7 | 13.6 | 5.1 Diplopia: 13.5 | 9.7 | 4.1 Thinking abnormal: 10.8 | 8.7 | 1.0 [†] *Associated AEs, defined as those considered definitely, probably, or possibly related to study medication and events with inassessable association due to insufficient information*

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Arroyo (2004)[88] and Miller (2003)[89] Study 1008-011, Pfizer[80] MC (45) DB PC PG RCT, Phase III (adjunctive therapy) Europe, U.K., Australia, South Africa N_R = 288; N_A = 287 *Interventions (number of daily doses not reported):* Pregabalin 600 mg / d vs. Pregabalin 150 mg / d vs. Placebo for 12 wk, including a 1-wk titration period; DB treatment followed an 8-wk baseline period. *Quality:* Fair *External validity:* Limited to patients with refractory partial seizures; may not apply to veteran population	*Inclusion criteria*: Same as for Beydoun (2005) *Exclusion criteria*: Same as for Beydoun (2005) *Population profile (N = 287)*: Age, group mean 36.4–38.1 y; Male 50.5%; White 92.7%; Average duration of epilepsy 24.2 y	Baseline difference: The percentage of patients with a history of generalized seizures was higher in PGB600 (6.5%) and PGB150 (9.1%) groups vs. PBO group (3.1%). Disposition of Patients PGB600 N = 92 / PGB150 N = 99 / PBO N = 96 Completed study (%): 75.0 / 88.9 / 86.6 p-value: NR / NR / — **Selected Efficacy Outcomes** Outcome Measure (All partial seizures) / PGB600. N = 92 / PGB150 N = 99 / PBO N = 96 RRatio (mean): –31.4 / –11.5 / 0.9 p-value: ≤0.0001 / 0.0007 / — Diff in means: –32.3 / –12.4 / — 95% CL: –40.6, –24.0 / –20.5, –4.3 / — Responder rate-50 (%): 43.5 / 14.1 / 6.2 p-value vs. PBO: ≤0.001 / .087 / — p-value vs. PGB150: ≤0.001 / — / — Seizure-free during last 28-d (%): 12 / 7 / 1 p-value: 0.002 / 0.065 / — 42-d (%): NR / NR / NR p-value 56-d (%): NR / NR / NR p-value Δ SFI, median (d): 132.5 / 25.5 / 17.9 Analysis of treatment effects showed a linear PGB dose-response (p≤0.0001).	**Adverse events (% of patients)** PGB600 N = 92 / PGB150 N = 99 / PBO N = 96 Deaths: 0.0 / 0.0 / 0.0 Nonfatal SAEs: 3.3 / 4.0 / 5.2 TR Nonfatal SAE: 1.1 / 1.0 / 1.4 WDSAE: 2.2 / 1.0 / 1.0 WDAE: 18.5 / 10.1 / 6.2 WDIE: 1.1 / 0.0 / 5.2 ≥ 1 AE: 87.0 / 75.8 / 63.5 AEs rated mild or moderate: "most" Severe, associated AEs: 12 patients (4%) overall SAEs: hemiplegia (n = 1), maculopapular rash, amblyopia and dizziness Common WDAEs: dizziness, asthenia, ataxia Common AEs: somnolence, dizziness Other notable AEs: accidental injury, dose-related weight gain, myoclonus, peripheral edema

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
French (2003) [90] Study 1008-034, Pfizer[80] MC (76) DB PC PG RCT, Phase III (adjunctive therapy) mITT N_R = 455; N_A = 453 *Interventions (twice daily dosing):* Pregabalin 600 mg / d vs. 300 mg / d vs. 150 mg / d vs. 50 mg / d vs. Placebo for 12 wk, no titration period. DB treatment was started following an 8-wk baseline period. *Fair quality. External validity limited (relatively young mean age, mostly females, outpatients with refractory partial seizures)*	*Inclusion criteria:* Same as for Beydoun (2005), except that age and weight criteria were ≥ 12 y and ≥ 40 kg. *Exclusion criteria:* Same as for Beydoun (2005) *Population profile (N = 453): Male 48.1%, White 85.0%, average duration of epilepsy 25 y; Three concurrent AEDs 15.6% to 24.0% per treatment group*	**Disposition of patients** **Selected Efficacy Outcomes**	**Adverse events (% of patients)** **TEAEs (≥ 10% in Any Group)** **AEs rated mild or moderate: "most"**

Disposition of patients

Outcome Measure	PGB600. N = 89	PGB300 N = 90	PGB150 N = 86	PGB50 N = 88	PBO N = 100
Completed study (%)	68.5	78.9	92.0	88.6	87.0
p-value	NR	NR	NR	NR	—

Selected Efficacy Outcomes

Outcome Measure (All partial seizures)	PGB600. N = 89	PGB300 N = 90	PGB150 N = 86	PGB50 N = 88	PBO N = 100
RRatio (mean, PEM)	–37.4	–27.8	–20.5	–6.2	–3.8
p-value	≤0.0001	≤0.0001	≤0.0001	0.4232	—
Responder rate-50 (%)	51	40	31	15	14
p-value	≤0.001	≤0.001	≤0.006	0.840`	—
Seizure-free during last 28, 42, or 56 d	NR	NR	NR	NR	NR
p-value	—	—	—	—	—

Adverse events (% of patients)

	PGB600 N = 89	PGB300 N90	PGB150 N = 86	PGB50 N = 88	PBO N = 96
Death	0.0	0.0	0.0	0.0	0.0
Nonfatal SAE	4.5	3.3	2.3	3.4	4.0
TR Nonfatal SAE	1.1	0.0	0.0	0.0	1.0
WDSAE	2.2	1.1	0.0	0.0	0.0
≥ 1 AE	88.8	84.4	70.9	67.0	74.0
Severe AE	14.6	7.8	4.7	6.8	6.0

TEAEs (≥ 10% in Any Group)

	PGB600 N = 89	PGB300 N90	PGB150 N = 86	PGB50 N = 88	PBO N = 96
Dizziness	42.7	31.1	16.3	9.1	9.0
Somnolence	28.1	17.8	17.4	10.2	11.0
Accidental injury	12.4	11.1	5.8	14.8	5.0
Ataxia	14.6	10.0	10.5	3.4	3.0
Asthenia	10.1	12.2	8.1	5.7	8.0
Headache	5.6	5.6	9.3	6.8	13.0
Infection	3.4	5.6	9.3	9.1	10.0
Blurred vision	10.1	7.8	3.5	3.4	5.0
Tremor	11.2	6.7	3.5	3.4	3.0
Weight gain	12.4	6.7	2.3	1.1	0.0
Incoordination	10.1	3.3	2.3	2.3	1.0
Dry Mouth	10.1	2.2	1.2	2.3	1.0

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Elger (2005)[95] Study 1008-157, Pfizer[80] MC (53) DB PC PG RCT, Phase III (adjunctive therapy) N_R = 341; N_A = 341 *Interventions (divided doses b.i.d.):* Pregabalin 600 mg/d (fixed from day 1) vs. Pregabalin 150–600 mg/d (flexible dosing; started at 150 mg/d and titrated by 150 mg/d increments every 1–2 wk) vs. Placebo; total treatment duration 12 wk, including a 6-wk baseline period *Fair quality* *Limited generalizability to veterans with difficult-to-treat seizures*	*Inclusion criteria:* Similar to those for Beydoun (2005), except at least 4 (instead of 3) partial seizures had to occur within the 6-wk baseline period with no 4-wk seizure-free periods *Exclusion criteria:* Similar to those of Beydoun (2005) with the addition of the following: CrCl ≤ 60 ml/min; ALT, AST, bilirubin, urea, or creatinine values above twice the ULN; received treatment with CNS-active compounds except a single antidepressant and standard AEDs; received felbamate; received vigabatrin, unless discontinued at least 6 wk prior to screening and had no clinically significant findings on formal visual field examination; received Phenobarbital or primidone unless discontinued at least 30 d prior to screening Population profile: Male 49.9%; White 97.4%; Average duration of epilepsy 25.2 y; Percentage of patients taking 1, 2, and ≥3 AEDs, 23%, 50%, and 26%, respectively; Median baseline seizure frequency, 9 per 28 d.	**Disposition of patients** **Outcome Measure** — **PGB600. N = 137** — **PGB150–600 N = 131** — **PBO N = 73** Completed study (%) — 58 — 76 — 77 **Selected Efficacy Outcomes** **Outcome Measure (All partial seizures)** — **PGB600. N = 137** — **PGB150-600 N = 131** — **PBO N = 73** RRatio vs. PBO (diff in means, PEM) — –27.0 — –15.8 — — 95% CL — –38.5, –15.6 — –27.4, –4.3 — — p-value vs. PBO — 0.0001 — –0.0091 — — RRatio vs. PGB150–600 (mean) — –11.2 — — — — p-value vs. PGB150–600 — 0.0337 — — — — Responder rate-50 (%) — 45 — 31 — 11 p-value vs. PBO — 0.001 — 0.001 — — p-value vs. PGB150–600 — 0.016 — — — — Seizure-free during last 28 d (%) — 12.4 (NSD) — 12.2 (NSD) — 8.2 Seizure-free during 84-d tx period (%) — 5 (NSD) — 4 (NSD) — 2	**Adverse events (% of patients)** **PGB600 N = 137** — **PGB150–600 N = 131** — **PBO N = 73** Deaths — 0.0 — 0.0 — 0.0 Nonfatal SAEs — 4.0 — 5.0 — 1.0 TR Nonfatal SAE — NR — NR — NR WDSAE — NR — NR — NR WDAE† — 33.0 — 12.0 — 7.0 **WDAE, first wk** — **24.0*** — **3.0** — **0.0** ≥ 1 AE — 87.6 — 86.3 — 63.0 **"Severe" AE** — **23.0** — **10.0** — **4.0** **Weight gain ≥7%** — **19** — **16** — **3** **New or intensified neurological findings** — **28** — **16** — **9** † Patients on fixed PGB600 also withdrew due to AEs earlier than those on titrated PGB150–600 * p = 0.0001 for PGB600 vs. PGB150–600 and PBO AEs rated mild or moderate: "most" 5 Most Common TEAEs, occurred more commonly in PGB groups vs. PBO: dizziness, ataxia, weight gain, asthenia, somnolence TEAEs occurring more frequently in PGB600 than PGB150–600: dizziness, ataxia

Table 21 Partial seizures: long-term, open-label studies

Citation Design, Quality	Major Eligibility Criteria, Population Profile	Efficacy Results	Safety Results
Ryvlin (2005, review)[99] 4 long-term (2 y), OL studies		In long-term open-label trials, the efficacy of pregabalin was maintained with respect to 50% responder rates suggesting no obvious tolerance developing over 2 years. Seizure-free rates were 8.9% and 5.8% for the last 6 months and 1 year of pregabalin treatment, respectively.	Long-term open-label pregabalin treatment was well tolerated