INTRODUCTION

Pregabalin (Lyrica, Parke-Davis/Pfizer) has been approved by the FDA for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN). It has also been approved as an adjunctive therapy for adults with partial onset of seizures.

DPN is a progressive disorder characterized by pain in the extremities, accompanied by a progressive decline in peripheral sensation, which may result in a complete loss of sensation in the affected area. Initial symptoms are often manifested as a tingling or burning sensation, with sudden fluctuations in intensity. It is estimated that 15% of patients with a long history of diabetes will develop DPN.

PHN is a common and lingering complication associated with herpes zoster infections, also known as shingles. PHN is defined as a persistent pain present for three months or longer despite resolution of the herpes zoster rash. PHN is often refractory to conventional pain treatments.

Partial seizures are localized to one area of the brain, but they may spread rapidly throughout the brain. Partial seizures are classified as simple or complex. Patients experiencing simple partial seizures do not lose consciousness, whereas patients with complex partial seizures do.

CHEMICAL AND PHYSICAL PROPERTIES

Pregabalin is a structural analogue to gamma-aminobutyric acid (GABA), and it is chemically described as 5-methylhexanoic acid. According to the manufacturer, this white to off-white crystalline solid is freely soluble in water and in basic and acidic aqueous solutions.

As a Schedule V controlled substance, it is available as 25-, 50-, 75-, 100-, 150, 200-, 225-, and 300-mg hard-shell capsules.

MECHANISM OF ACTION

The exact mechanism of pregabalin’s anticonvulsant and anti-nociceptive effect is unknown. Pregabalin binds to the alpha2-delta (α2-δ) subunit on voltage-gated calcium channels in the tissues of the central nervous system (CNS). In studies conducted in vitro, there is a reduction in the release of calcium-dependent neurotransmitters, possibly as a result of calcium-channel modulation. Despite pregabalin’s structural similarities to those of GABA, it does not elicit any effect on GABA receptors.

PHARMACOKINETICS

Table 1 shows the absorption and metabolism of pregabalin.

ADVERSE DRUG EFFECTS

In clinical trials, the most commonly reported adverse drug events (ADEs) were dizziness and somnolence. Peripheral edema was noted in two clinical trials. In a study by Arroyo, patients reported weight gain (see “Clinical Efficacy”). Rosenstock et al. noted that patients who developed peripheral edema did not experience worsening of pre-existing cardiovascular, renal, or hepatic conditions, and no patient discontinued treatment because of edema.

Participants in clinical trials reported the occurrence of euphoria, and in a study of recreational users of sedative/hypnotic drugs, pregabalin was reported as providing a “high,” similar to that experienced with diazepam (Valium, Roche).

INDICATIONS AND CONTRAINDICATIONS

Pregabalin is contraindicated in patients with a known hypersensitivity to the drug or any of its components.

Table 2 presents the indications and dosage for pregabalin.

Discontinuation of Medication

If pregabalin is to be discontinued, the dose should be tapered over a minimum of one week.
Drug Forecast

Special Populations

Elderly Patients. Before pregabalin therapy is initiated for elderly patients, clinicians should evaluate renal function because of the general decline of creatinine clearance (CrCl) that is observed with the progression of age.

Hepatically Impaired Patients. No dose adjustments are necessary for patients with hepatic impairment.

Renally Impaired Patients. According to the manufacturer, the dose of pregabalin should be reduced in patients with renal impairment. If the patient’s CrCl is between 30 and 60 ml/minute, the total daily dose of pregabalin should be reduced by 50%. If the CrCl is between 15 and 30 ml/minute, the total daily dose should be reduced by 75%. If the CrCl is below 15 ml/minute, the total daily dose should be reduced by 10 to 15%.

Pregnant and Lactating Women. Pregabalin is categorized as a Pregnancy Category C agent. No studies have been conducted with pregabalin in pregnant women or nursing mothers. It is unknown whether pregabalin is excreted in human milk. The potential risks and benefits of using pregabalin should be considered before it is prescribed during pregnancy or lactation.

DRUG INTERACTIONS

Because pregabalin is neither metabolized nor bound to plasma protein, it demonstrates a very low incidence of drug–drug interactions. According to the manufacturer, pregabalin may increase the impairment of cognitive and gross motor function caused by opiates and may potentiate CNS side effects of benzodiazepines and ethanol.

CLINICAL EFFICACY

Dworkin et al.2
(Post-herpetic Neuralgia)

A multicenter, parallel-group, double-blind, placebo-controlled, randomized trial consisted of two phases: a one-week baseline phase and an eight-week double-blind phase. Patients with PHN who completed the eight-week study or who withdrew early were given the option to enter an open-label extension of the study; 173 patients with PHN were enrolled, with 89 patients receiving pregabalin and 84 controls receiving placebo. The primary endpoint was pain reduction, as recorded by the patients. Secondary endpoints integrated additional pain ratings, sleep interference, quality of life, mood, and patient and clinician ratings of global improvement. Patients in the active-treatment arm with a CrCl of 60 ml/minute or greater received pregabalin 600 mg/day; patients with a CrCl of between 30 and 60 ml/minute were given 300 mg/day.

Inclusion criteria were as follows:

- Men and women of any race who were at least 18 years of age were eligible for enrollment in the study.
- Patients had to be free of serious or unstable medical conditions.
- Pain had to have been present for three or more months after healing of the herpes zoster rash.
- Patients needed a minimum pain score of 40 mm on the 100-mm Visual Analogue Scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ).
- Patients needed a minimum mean daily pain rating of 4 on an 11-point numerical pain rating scale.

Exclusion criteria were as follows:

- pain that was so severe that it might have confounded assessment or self-evaluation of pain as a result of PHN
- a history of previous neurolytic or neurosurgical therapy for PHN
- previous unsuccessful therapy for PHN with gabapentin (Neurontin, Pfizer) at dosages of 1,200 mg/day or higher
- pregnancy or lactation
- abnormal laboratory findings: a baseline CrCl of 30 ml/minute or less, a white blood cell count of below 2,500/mm³, a neutrophil count of below 1,500/mm³, or a platelet count of below 100 x 10³/mm³
- participation in any other clinical trial of an investigational drug within 30 days before screening

Patients who had been using gabapentin were required to stop using it at least seven days before starting the study medication. Use of the following medications was prohibited during the study: benzodiazepines, skeletal muscle relaxants, oral steroids, local and topical agents for relief of PHN, and anticonvulsants. If patients were stabilized on their current dose for at least 30 days, they were permitted to use narcotic and non-narcotic analgesics, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and antidepressants.

More patients in the pregabalin arm (34.8%) withdrew from the study, compared with those receiving placebo (11.9%). The primary reason for discontinuation in the pregabalin arm was intolerability to an adverse effect, particularly somnolence. Lack of efficacy was the primary reason for discontinuation in the placebo arm.

Pregabalin demonstrated superior pain relief throughout all eight weeks of

### Table 2 Indications and Dosage for Pregabalin

<table>
<thead>
<tr>
<th>Indication</th>
<th>Starting Dose</th>
<th>Titration</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain associated with diabetic peripheral neuropathy</td>
<td>50 mg orally three times daily</td>
<td>After one week of therapy, increase to 300 mg daily.</td>
<td>300 mg</td>
</tr>
<tr>
<td>Postherpetic neuralgia and adjunctive therapy for partial-onset seizures (epilepsy)</td>
<td>75 mg orally twice daily</td>
<td>After one week of therapy, increase to 300 mg daily.</td>
<td>600 mg</td>
</tr>
</tbody>
</table>

Adapted from prescribing information for pregabalin (Lyrica). Pfizer. August 2005.
treatment. The pregabalin patients demonstrated statistically significant reductions in pain, as compared with the placebo arm \((P = .0001)\). In addition, statistically significant differences were detected in several secondary outcomes.

The authors of this study concluded that pregabalin was safe and efficacious for patients with PHN.

### Rosenstock et al.5 (Diabetic Peripheral Neuropathy)

A multicenter, randomized, double-blind, placebo-controlled trial was conducted in two treatment phases: a one-week baseline phase and an eight-week, fixed-dose, double-blind phase. One hundred forty-six patients with DPN were enrolled: 76 received pregabalin, and 70 received placebo. The average age of the study participants was 60 years. Most of the enrolled patients had type-2 diabetes mellitus.

Patients were randomly assigned in a double-blind manner to receive a fixed dose of either pregabalin 300 mg/day or placebo.

**Inclusion criteria** were as follows:

- Patients had to be at least 18 years of age with type-1 or type-2 diabetes.
- Patients had to have symmetric painful symptoms in the distal extremities for one to five years before the study.
- Patients had to be generally free of serious or unstable medical conditions, including psychiatric illness.
- Patients needed minimum scores of at least 40 mm on the 100-mm VAS of the SF-MPQ.
- Patients needed minimum average daily pain scores of 4 on an 11-point numerical pain rating scale during the baseline period.
- Patients had to complete daily diaries during the week preceding randomization.

**Exclusion criteria** were as follows:

- A CrCl of 60 ml/minute or below, a baseline WBC count of below 2,500/mm\(^3\), a neutrophil count of below 1,500/mm\(^3\), or a platelet count of below 100 x 10\(^9\)/mm
- Pregnancy or lactation
- Conditions that could interfere with the evaluation of pain associated with DPN (i.e., amputations, except for the toes)
- A neurological condition not associated with diabetes and skin conditions that could affect sensation
- Previous failure to respond to gabapentin at doses of 1,200 mg/day or higher
- Participation in any other clinical trial of an investigational drug within 30 days before screening

Patients were prohibited from using benzodiazepines, skeletal muscle relaxants, capsaicin, narcotics, fatty acid supplements, evening primrose oil, myoinositol, chromium picolinate, anti-convulsants (if used for pain), tricyclic antidepressants, and centrally acting analgesics. However, they were permitted to use acetaminophen, aspirin (for cardiovascular health), and selective serotonin reuptake inhibitors (SSRIs), provided their dose had been stable for more than 30 days. The dosages of medications used to treat diabetes were to remain stable throughout the study.

The primary efficacy measure was the mean pain score, as recorded in patients’ daily diaries. This study used the same secondary endpoints and measures as in the Dworkin trial.2 Pregabalin at a dose of 300 mg/day demonstrated a statistically significant reduction in mean pain scores compared with placebo at the study’s endpoint \((P = .0001)\). Secondary outcomes were similar to those observed by Dworkin et al.2

One hundred twenty-seven patients completed the study (65 receiving pregabalin, 62 receiving placebo). More patients in the pregabalin arm (11%) than in the placebo arm (3%) discontinued treatment because of an ADE, but more patients in the placebo arm (4%) than in the pregabalin arm (1%) discontinued therapy because of a lack of efficacy.

The authors concluded that pregabalin was safe, effective, and well tolerated as a therapy for DPN.

### Arroyo et al.7 (Partial-Onset Seizures)

A 12-week, multicenter, double-blind, placebo-controlled, parallel-group trial by Arroyo et al. consisted of an eight-week baseline assessment period, followed by a 12-week treatment phase. Patients were randomly selected to receive either placebo or pregabalin 150 mg/day or 600 mg/day. An open-label extension was offered to patients who completed the 12-week treatment phase.

**Inclusion criteria** were as follows:

- Patients had to have at least 18 years of age or older (although two patients were 17 years of age)
- Body weight had to be between 50 and 135 kg.
- Patients had to have a diagnosis of partial seizures, as defined by the International League Against Epilepsy
- Treatment with at least one antiepileptic drug had to have failed
- Patients had to have experienced three or more partial seizures in the month prior to screening.
- Patients had to be taking one to three antiepileptic agents at tolerated and clinically relevant doses.
- Patients had to have had at least six partial seizures in the eight-week assessment period before randomization and could not be free of seizures for more than four weeks during this time.

**Exclusion criteria** were as follows:

- Absence seizures, Lennox–Gastaut syndrome, or status epilepticus within the last year
- Clinically relevant medical illness or abnormal electroencephalograms
- A significant psychiatric disorder (or recurrent major depression)
- Pregnancy or lactation
- A CrCl of 60 ml/minute or less
- The use of gabapentin unless it was discontinued at least one week before the baseline assessment period

Patients were required to maintain the dosage of their concurrent antiepileptic agents throughout the study. Patients were prohibited from using CNS-active medications, although currently prescribed antiepileptic drugs and anti-depressants for mild depression were allowed. Additional medications excluded from the study, because of the known safety problems or interactions with other antiepileptic drugs, were felbamate (Felbatol, Medpointe), vigabatrin (Sabril, Aventis/Ovation), macro-lides, astemizole (Hismanal, Janssen), terfenadine (Seldane, Hoechst Marion

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The primary outcome measure was the change from baseline in the frequency of seizures. The authors expressed the change as the “R-ratio.” Secondary outcome measures were the responder rate, the percentage of patients free of seizures, and the median percentage change in seizure frequency.

Of 288 patients randomly selected for treatment, one patient did not take at least one dose of the study medication. Approximately 50% of the patients enrolled took two concurrent antiepileptic drugs, and almost 30% took three concurrent antiseizure medications.

Carbamazepine (Tegretol, Novartis), lamotrigine (Lamictal, GlaxoSmithKline), and topiramate (Topamax, Ortho-McNeil) were the three most commonly used anticonvulsant drugs. Others used in the study included phenytoin (Dilantin, Pfizer), phenobarbital, valproate (e.g., Depakene, Abbott), and clobazam (Frisium, Hoechst).

Both treatment arms displayed a statistically significant reduction in the frequency of seizures, compared with placebo. The reduction in seizure frequency observed during the study was dose-related: with 150 mg/day, the R-ratio was –11.5; with 600 mg/day, it was –31.4; and with placebo, it was 0.9.

Patients receiving pregabalin 150 mg/day and 600 mg/day also experienced a reduction in seizure frequency from baseline measures (by 20.6% and 47.8%, respectively), whereas patients receiving placebo displayed an increase in seizure frequency (by 0.9%).

A significantly greater percentage of patients receiving pregabalin 600 mg/day (43.5%) were considered to be treatment responders (noted by a reduction of 50% or more in seizure frequency), compared with patients receiving pregabalin 150 mg/day and placebo ($P < .0001$). Median reductions in seizure frequency were 16.5% with pregabalin 150 mg/day and 42.6% with 600 mg/day. With placebo, seizure frequency increased by 1.3%.

The ADEs in this study were similar to those observed in the Dworkin and Rosenstock studies. The percentage of patients who withdrew from the study because of ADEs increased with the higher dose of pregabalin. Furthermore, the number of concurrent antiepileptic agents influenced both the type and tolerability of the ADEs reported.

**COST**

The average wholesale price (AWP) for 90 pregabalin capsules is $178.20. The AWP is the same for all strengths. Neurontin (gabapentin) 400-mg capsules are comparably priced, although gabapentin is also available as a generic product. No head-to-head studies comparing pregabalin and gabapentin have been conducted.

**CONCLUSION**

The advantages of pregabalin include a predictable pharmacokinetic and side-effect profile, few drug interactions, and a quick onset of action. Pregabalin is promising as a therapy for DPN and PHN and as an adjunctive therapy for patients with partial seizures.

Other studies are currently under way to evaluate pregabalin’s efficacy in other conditions ranging from sleep disturbances and fibromyalgia syndrome to Generalized Anxiety Disorder. Physicians and pharmacists should conduct a thorough assessment of a patient’s complaints of DPN, PHN, or partial seizures before prescribing this drug.

**REFERENCES**