Executive Summary

Pregabalin (Lyrica by Pfizer) Formulary Review

Lyrica® (pregabalin) is a new prescription medication indicated for use in painful diabetic peripheral neuropathy (DPN), post-herpetic neuralgia, and as adjunct therapy for partial seizures. Off-label uses of pregabalin include generalized anxiety disorder (for which the FDA denied the application), fibromyalgia, and dental pain. This review will focus on the treatment of DPN.

Pregabalin is pharmacologically similar to gabapentin, another agent used in these indications. Pregabalin and gabapentin bind to the same receptor, and elicit the same response. Pregabalin is six times more potent than gabapentin.

Four randomized placebo-controlled studies demonstrated the efficacy of pregabalin in relieving painful diabetic peripheral neuropathy. Regimens of 300 mg daily (given bid or tid) achieved a greater than 50% reduction in pain in about 40-50% of patients, with a corresponding NNT=4-5.

Common side effects of pregabalin use include dizziness and somnolence. Weight gain and peripheral edema are also fairly common, especially when given with a thiazolidinedione, an agent commonly prescribed for diabetics.

In pregabalin trials of DPN, the Numbers Needed to Treat (NNTs) ranged from 4-5 to achieve a 50% reduction in pain over 5 to 12 weeks of treatment. The pregabalin NNTs are similar to those measured in trials of other agents treating DPN. In addition to clinical trials, the older agents have extensive treatment experience for the treatment of DPN and other neuropathic pain conditions. There are no trials available to determine the effectiveness of pregabalin in the long-term treatment of DPN.

Pregabalin (sold as the brand Lyrica®) is more expensive than the majority of other agents used to treat these disease states, such as amitriptyline, nortriptyline, gabapentin, carbamazepine, and phenytoin. The following table illustrates approximate costs for one patient to achieve a positive outcome using 300 mg daily.

<table>
<thead>
<tr>
<th>Disease State</th>
<th>NNT (average)</th>
<th>Duration</th>
<th>Cost ($)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPN</td>
<td>4</td>
<td>6-8 weeks</td>
<td>880-1180</td>
<td>50% reduction in pain score</td>
</tr>
</tbody>
</table>

Because there are no studies comparing pregabalin with existing agents, and pregabalin offers no clinically significant safety advantages to gabapentin, and the cost of pregabalin exceeds that of other agents, there is no compelling reason to add pregabalin to the formulary at this time for the treatment of DPN. Use should be limited for patients with DPN who have either failed a trial of formulary alternatives or have a contraindication.
Pregabalin (Lyrica by Pfizer) Formulary Review

Key Questions:
1. Is pregabalin more effective than current therapy in the treatment of diabetic peripheral neuropathy?
2. Is pregabalin safer than currently used agents such as gabapentin and TCAs?
3. Does pregabalin offer increased value compared with currently used agents?
4. Should pregabalin be added to the formulary?
5. Are there any restrictions that should be placed on pregabalin usage?

Indications
Pregabalin is approved by the FDA for the following indications:
- Painful Diabetic Peripheral Neuropathy (DPN)
- Post-Herpetic Neuralgia
- Adjunct therapy for Partial Seizures

This review will focus on the use of pregabalin for DPN.

Off-Label Uses
The FDA denied approval for the use of pregabalin in generalized anxiety disorder. Studies have been performed evaluating the use of pregabalin in social anxiety disorder, fibromyalgia, and dental pain.

Brief Overview of Diabetic Peripheral Neuropathy
Peripheral neuropathy is a common complication of diabetes mellitus estimated to affect 20-24% of patients with diabetes. Other estimates place the amount of patients suffering from painful diabetic neuropathy at more than 3 million. The exact cause of the neuropathy is unknown. Painful diabetic neuropathy often presents as burning or aching pain, with allodynia (super-sensitivity) also common. Pain generally starts at the distal ends of the limbs (fingers and toes) and progresses toward the torso. Diabetic neuropathy can lead to numbness in the limbs, ulcerations, and eventual amputation if not controlled.

Prevention involves strict glucose control. High cholesterol, tobacco use, hypertension, and excessive alcohol use accelerate progression of the disease. Control of these factors slows the onset and development of DPN.

Treatment involves a variety of pharmaceutical agents. The Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain designated tricyclic anti-depressants (TCAs), gabapentin, opioids, tramadol, and the 5% lidocaine patch as first line agents. These agents were chosen because of positive results in multiple randomized controlled trials. Since publication, the SNRI duloxetine has been FDA approved for neuropathic pain. According to the Conference, choice between the first-line agents should take into account the cost of the agent, as well as the effects of side effects on the patient. They recommend caution in the use of TCAs in elderly patients due to anticholinergic side effects and adverse cardiac events. In addition, gabapentin, tramadol and opioids must be used cautiously in older patients due to side effects affecting cognitive and motor skills. Tramadol and opioids also carry a risk of dependence. Gabapentin and TCAs are considered to have a slower onset of pain relief, due to the need for titration of these drugs. The Conference does not make any statements concerning the relative efficacy between the first-line agents.

Clinical Pharmacology
Pregabalin is a structural analog of GABA, similar to gabapentin. It binds to the 2- protein, which is associated with voltage-gated calcium channels. Binding at this site reduces calcium influx at nerve terminals, and reduces the release of several neurotransmitters, including glutamate, norepinephrine, and substance P. This activity results in analgesic, anxiolytic, and anticonvulsant effects. Pregabalin is six times more potent than gabapentin in binding. Pregabalin does not show activity at GABA receptors, and it does not affect uptake or degradation of GABA.
### Pharmacokinetics (5,6)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregabalin</th>
<th>Gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Time to Peak</td>
<td>1 hour</td>
<td>1.5-4 hours</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>90%</td>
<td>60%</td>
</tr>
<tr>
<td>Absorption</td>
<td>Linear</td>
<td>Saturated (F=33% for 1200 mg q8hr)</td>
</tr>
<tr>
<td>T1/2</td>
<td>5-6.5 hrs</td>
<td>5-7 hrs</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Negligible</td>
<td>Negligible</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal (92-99%)</td>
<td>Renal (76-81%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fecal (10-23%)</td>
</tr>
<tr>
<td>Protein Bind</td>
<td>None</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>Food Effect</td>
<td>Time to peak prolonged, no change in AUC</td>
<td>Slight increase in AUC, Cmax</td>
</tr>
</tbody>
</table>

The main difference between pregabalin and gabapentin relating to pharmacokinetics is that pregabalin has linear absorption whereas gabapentin has saturable absorption, for which the clinical implications are uncertain.

### Clinical Efficacy

Four randomized, placebo-controlled studies were reviewed for evidence of efficacy in diabetic peripheral neuropathy.7-10 The studies enrolled adult patients with HbA1C<11% and a minimum of a 6-12 month history of symmetric peripheral pain in the distal extremities. There were approximately 80 patients per treatment group in the studies, and trials lasted from 5-12 weeks. Primary endpoints included mean pain score and the percentage of patients achieving a 50% reduction in pain. Pain score improvements >30% are considered clinically relevant. About 40-50% of patients in the pregabalin groups receiving ≥300 mg daily experienced a 50% reduction in pain. Mean pain scores decreased about 2-2.5 points on an 11 point scale. NNTs ranged from 4-5 to achieve a 50% reduction in pain over 8 to 15 weeks of treatment. Pregabalin has not been directly compared to gabapentin or TCAs. The pregabalin NNTs are similar to data from separate trials of these agents for treating DPN. In addition to clinical trials, the older agents have extensive treatment experience for the treatment of DPN and other neuropathic pain conditions. There are no trials to determine the effectiveness of pregabalin in the long-term treatment of DPN.

The FDA review panel faulted the Lesser and Rosenstock studies for using a flawed intent to treat policy in the statistical review. The studies each used a “Last Observation Carried Forward” (LOCF) method for analysis. Thus, when a patient discontinues the study, the last pain scores recorded are used as the final pain scores for that patient. This can overestimate efficacy, as a patient may experience pain relief, but be unable to continue taking the drug due to an adverse event. The FDA recommends a “Baseline Observation Carried Forward” (BOCF) method for patients discontinuing due to an adverse event. The FDA did perform statistical analysis of the data from the Lesser and Rosenstock trials and found efficacy for the pregabalin regimens of 300 mg or more daily.11 Pain score data and responder rate were similar to the values reported using the LOCF method. The Richter and Freynhagen studies also used the LOCF method, but were not included in the FDA review package.

Another observation is that the Lesser and Rosenstock studies excluded patients that had failed a previous trial of gabapentin for pain relief. Because gabapentin acts at the same receptor site as pregabalin, this exclusion may result in overestimating the overall efficacy of pregabalin when applied to the general population.
### Adverse Effects (5,6)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Pregabalin</th>
<th>Gabapentin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>23-29%</td>
<td>7-17%</td>
<td>5%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13-16%</td>
<td>19%</td>
<td>3%</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>9-12%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4-7%</td>
<td>n/a</td>
<td>2%</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>4-6%</td>
<td>reported</td>
<td>0%</td>
</tr>
</tbody>
</table>

Adverse effect data was taken from package inserts and post-marketing data, not from a head to head comparison of pregabalin and gabapentin. The majority of adverse effects were dose-dependant. Percentages shown were for the 300 mg to 600 mg per day range, which corresponds with clinical efficacy.

The majority of the adverse effects were qualified as mild to moderate, and dropout rates due to adverse effects ranged from 10-30%, with higher doses resulting in higher dropout rates.

### Allergies and Interactions

Pregabalin is not an inducer, inhibitor, or substrate of the CYP-450 system. There are no known drug-drug interactions involving pregabalin.

Concurrent use of pregabalin with a thiazolidinedione (rosiglitazone, pioglitazone) results in an increased risk of weight gain and peripheral edema.

### Warnings/Precautions/Contraindications

Withdrawal of Antiepileptic Drugs: As with all antiepileptic medications, abrupt withdrawal may result in increased seizure frequency. In addition, patients also experienced insomnia, nausea, headache, and diarrhea following abrupt withdrawal. Withdraw pregabalin over a course of at least 1 week.

Tumorigenic potential: Pregabalin trials in mice resulted in a high incidence of hemangiosarcoma. It is not known how this translates to a human population.

Dizziness/Somnolence: Patients need to be counseled concerning the risks of driving while taking pregabalin.

Ophthalmological Effects: There is an increased risk of blurred vision with pregabalin use.

Weight Gain and peripheral edema: There is an increased risk of weight gain and peripheral edema with pregabalin use. This risk was increased with concurrent use of a thiazolidinedione.

Other effects: CK elevation, ECG changes, Decreased Platelet count.

### Dosage and Administration

**Diabetic Peripheral Neuropathy:** Pregabalin can be given with or without food. Dosing should be initiated at 50 mg tid, and can be increased to 100 mg tid within one week. Doses above 300 mg/day are poorly tolerated, and have not been found to improve outcomes. Pregabalin is renally cleared so the following adjustments should be made in patients with renal failure:

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Total Pregabalin Daily Dose (mg/day)</th>
<th>Dose Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>150</td>
<td>BID or TID</td>
</tr>
<tr>
<td>30-60</td>
<td>75</td>
<td>BID or TID</td>
</tr>
<tr>
<td>15-30</td>
<td>75</td>
<td>QD or BID</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25</td>
<td>QD</td>
</tr>
<tr>
<td>Supplementary dose following hemodialysis</td>
<td>25-50 mg</td>
<td>50-75 mg</td>
</tr>
</tbody>
</table>

Supplementary dose following hemodialysis

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## Cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength/Quantity</th>
<th>AWP-15% or MAC*</th>
<th>Usual Daily Dose</th>
<th>Cost of 30 Day Supply ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyrica</td>
<td>100 mg capsule</td>
<td>1.75</td>
<td>100 mg tid</td>
<td>157.50</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>600 mg tablet</td>
<td>1.42</td>
<td>600 mg tid</td>
<td>129.60</td>
</tr>
<tr>
<td></td>
<td>800 mg tablet</td>
<td>1.65</td>
<td>800 mg tid</td>
<td>148.50</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>50 mg capsule</td>
<td>0.12</td>
<td>50 mg q hs</td>
<td>3.60</td>
</tr>
<tr>
<td>Tramadol</td>
<td>50 mg tablet</td>
<td>0.18</td>
<td>50 mg qid</td>
<td>21.60</td>
</tr>
</tbody>
</table>


The cost to get one response to treatment (50% reduction in pain scores) is $1180. This calculation is based on the clinical trial NNT of 4 for 2 months of treatment.

## Conclusions and Recommendations

1. **Is pregabalin more effective than current therapy in the treatment of diabetic peripheral neuropathy?**
   Pregabalin has been proven effective compared to placebo in clinical trials for the treatment of diabetic peripheral neuropathy. There are no trials available comparing pregabalin with current standard therapies. Since two of the four pregabalin trials excluded patients who failed previous gabapentin treatment and gabapentin and pregabalin have similar mechanisms of actions, patients who have already failed gabapentin are likely to be non-responders to pregabalin. A trial comparing pregabalin with gabapentin as well as with other available agents would be helpful to determine its place in therapy. At this time, pregabalin cannot be judged more effective than current therapy.

2. **Is pregabalin safer than currently used agents such as gabapentin and TCAs?**
   While pregabalin has not been directly compared with either of these agents, there is no compelling reason to believe that pregabalin will have a safer profile than gabapentin.

3. **Does pregabalin offer increased value compared with currently used agents?**
   Pregabalin has not been proven superior to currently used agents based on efficacy and safety and it has higher cost.

4. **Should pregabalin be added to the formulary?**
   As there are no trials showing pregabalin’s superiority to other agents, and other agents have a longer history of use, pregabalin should not be added to the formulary at this time. Pregabalin should require a prior authorization.

5. **Are there any restrictions that should be placed on pregabalin usage?**
   Yes prior authorization should be required. Criteria for authorization includes:
   a. Age 18 years or older **and**
   b. Diagnosis of DPN **and**
   c. Contraindication or previous trial and failure of at least two formulary agents, including gabapentin and a TCA, resulting in inadequate efficacy or discontinuation based on side effects **and**
   d. Any previous treatment with gabapentin should be discontinued prior to starting pregabalin.
   e. Apply a quantity limit of 300mg per day and approve for 3 months
   f. Follow-up documentation of effectiveness of treatment with at least a 50% reduction in pain before approving continued therapy.
### Inclusion Criteria
- M/F >18 yo
- DM Type 1 or 2
- Sym. Pain in Dist. Ext. for 1-5 yrs.
- ≥4 pain diaries completed during baseline week with average pain ≥4 on 11-point Likert scale

### Exclusions:
- Pregnant, lactating, HbA1C>11%, ClCr<60mL/min, failure of gabapentin >120 mg/day to treat pain, low WBC, PLT, neurologic disorders not related to DPN

Study also excluded use of pain meds except for APAP

<table>
<thead>
<tr>
<th>Patient Characteristics (St Dev.):</th>
<th>Avg Age = 60 yo (11.4)</th>
<th>56% Male</th>
<th>87.7% White</th>
<th>87% Type II DM</th>
<th>96% on anti-DM med</th>
<th>37% on insulin</th>
<th>80% on oral med</th>
<th>Mean Duration of DM = 9.4 y (10.3)</th>
</tr>
</thead>
</table>

### PLA Group had more Type I DM patients than the PGB groups, may influence internal validity if there is a difference in pain response between Type I and Type II patients.

### Abbreviations:
### Richter 29 center

**Inclusion Criteria**
- M/F ≥18 yo
- DM Type 1 or 2
- Sym. Pain in Dist. Ext. for 1-5 yrs.
- ≥4 pain diaries completed during baseline week with average pain ≥4 on 11-point Likert scale

**Exclusions:**
- pregnant, lactating,
- HbA1c >11%.,
- neurologic disorders not related to DPN,
- serious medical conditions

Study also excluded use of pain meds except for APAP

**Pt. Characteristics (St Dev.):**
- Avg Age = 57 yo
- 60% Male
- 84% White
- 91% Type II DM
- HbA1c = 8.2 (1.4)
- 94% on anti-DM med

<table>
<thead>
<tr>
<th>Drug Regimens</th>
<th>n</th>
<th>Duration</th>
<th>End Points</th>
<th>Results (CI / p-value)</th>
<th>ARR</th>
<th>NNT/NH</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA</td>
<td>82</td>
<td>6 weeks (2 week titration period)</td>
<td>Mean Pain Score (avg. of last 7 daily diaries)</td>
<td>Mean Pain Score (Baseline/Conclusion) PLA (6.9/5.8)</td>
<td>p=0.1763</td>
<td>PLA 600mg/day (6.7/4.3)</td>
<td>p=0.0002</td>
</tr>
<tr>
<td>PGB 50 mg (150mg/day)</td>
<td>79</td>
<td>82</td>
<td>% Responders (Reduction of &gt;50% pain score to baseline)</td>
<td>PLA 14%</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGB 200 mg (600mg/day)</td>
<td></td>
<td></td>
<td></td>
<td>PGB 150mg/day 18% (non significant)</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGB 600mg/day</td>
<td></td>
<td></td>
<td></td>
<td>PGB 600mg/day 39% (p=0.002)</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SF-MPQ (VAS – Pain – Conclusion)**
- PLA 58.05
- PGB 150mg/day 53.27 (p=0.2058)
- PGB 600mg/day 43.38 (p=0.0002)

*estimates, as reported only in graphical form

**Other Secondary Results:**
- Both PGB groups significantly improved Sleep scores and the MOS-Sleep scale over PLA

**Study used doses greater than 300mg/day, the max as recommended by FDA.

### Freynhagen 60 center

**Inclusion Criteria**
- M/F ≥18 yo
- Diagnosis of DPN:
  - DM Type 1 or 2
  - Sym. Pain in Dist. Ext. for at least 6 months
- Or Diagnosis of PHN:
  - Pain worse than 40mm on the 100mm VAS of the SF-MPQ
- Pain worse than 40mm on the 100mm VAS of the SF-MPQ

**Exclusions:**
- pregnant, lactating,
- HbA1c >11%.,
- ClCr <60mL/min , unstable or clinically significant medical conditions

Study also excluded use of pain meds except for APAP

**Pt. Characteristics (St Dev.):**
- Avg Age = 57 yo
- 60% Male
- 84% White
- 91% Type II DM
- HbA1c = 8.2 (1.4)
- 94% on anti-DM med

<table>
<thead>
<tr>
<th>Drug Regimens</th>
<th>n</th>
<th>Duration</th>
<th>End Points</th>
<th>Results (CI / p-value)</th>
<th>ARR</th>
<th>NNT/NH</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA</td>
<td>65</td>
<td>12 weeks (1 week titration in 600mg/day group; weekly titration in flexible dose group)</td>
<td>Mean Pain Score (avg. of last 7 daily diaries)</td>
<td>Mean Pain Score (Baseline/Conclusion) PLA (6.9/4.7)</td>
<td>*estimates, as final values given only in graphical format</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGB Flex-dose</td>
<td>141</td>
<td>132</td>
<td>% Responders (Reduction of mean pain score to baseline)</td>
<td>PLA 4%</td>
<td>24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGB 300 mg bid (600mg/day)</td>
<td></td>
<td></td>
<td></td>
<td>PGB flexdose 73% (p=0.02)</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGB 600mg/day</td>
<td></td>
<td></td>
<td></td>
<td>PGB flexdose 73% (p=0.01)</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGB 600mg/day</td>
<td></td>
<td></td>
<td></td>
<td>PGB flexdose 73% (p=0.01)</td>
<td>22%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*estimates, as reported only in graphical form

**Withdrawal Rates Due to AE’s:**
- PLA 4.7%
- PGB 150mg/day 2.5%
- PGB 600mg/day 8.5%

**Other Secondary Results:**
- PGB 600mg/day showed significant improvement compared to PLA in Sleep scores, CGIC, and the SF-36 bodily pain component

**Study used doses greater than 300mg/day and bid dosing instead of tid as recommended by FDA.

**Abbreviations:**
References:


