PUBLIC SUMMARY DOCUMENT
Product: Pregabalin, capsule, 25 mg, 75 mg, 150 mg and 300 mg, Lyrica®
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an Authority Required (STREAMLINED) listing for the initial and continuing treatment of neuropathic pain in patients who meet certain criteria.

2. Background

This drug had not previously been considered by the PBAC for this indication.

3. Registration Status

Pregabalin was TGA registered on 13 April 2005 for the treatment of neuropathic pain in adults and as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

4. Listing Requested and PBAC's View

Note: Pregabalin is not subsidised for fibromyalgia or acute pain or chronic pain of non-neuropathic origin.

Authority Required (STREAMLINED)
Initiation and up-titration of treatment for neuropathic pain.

Authority Required (STREAMLINED)
Continuation of treatment in patients who have received a PBS prescription for initiation of treatment and have shown an adequate clinical response.

Continuation of treatment in patients who had shown an adequate clinical response to pregabalin prior to PBS-listing.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Neuropathic pain refers to a specific pain syndrome characterised by pain and sensory abnormalities in body parts that have lost their normal peripheral innervation or sensory representation in the central nervous system. There are many types of neuropathic pain, with classification based on the underlying condition eg. diabetic peripheral neuropathy, postherpetic neuralgia, human immunodeficiency virus (HIV) neuropathy.

Current therapies used to treat neuropathic pain include tricyclic antidepressants, gabapentin, carbamazepine, other antiepileptics, simple analgesics, opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin re-uptake inhibitors (SSRIs), selective noradrenaline re-uptake inhibitors (SNRIs), and complementary medicines. Patients cycle between treatments, switching and adding other neuropathic pain agents. Non-pharmacological treatments may also be useful in reducing and managing the pain.

The submission proposed that pregabalin would provide an additional PBS-subsidised option for the treatment of neuropathic pain.

6. Comparator

The submission nominated amitriptyline as the main comparator; carbamazepine, gabapentin and opioid analgesics are secondary comparators.

The PBAC considered the clinical comparison against both an active comparator (as represented by the sponsor's nominated main active comparator, amitriptyline) and placebo to be reasonable.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials & Results of Trials

The clinical trials were presented by type of neuropathic pain - diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN) and other.

DIABETIC PERIPHERAL NEUROPATHY (DPN)

Pregabalin versus amitriptyline:
The submission presented two trials (Trial 040 and Bansal 2009) which compared amitriptyline and pregabalin. Trial 040 also included a placebo arm and no difference was shown between pregabalin and placebo in change in mean endpoint pain score, proportion of responders or mean Patient Global Impression of Change (PGIC). Amitriptyline was statistically significantly better than placebo on all three measures. Both active treatments showed quality of life improvements (SF-36) compared to placebo.

Bansal 2009 was a crossover study showing no differences between pregabalin and amitriptyline on pain scores, responder rates or PGIC.

Pregabalin versus placebo:
The submission identified 12 additional trials comparing pregabalin to placebo, as well as trial 040. The submission performed stratified meta-analyses by dose of pregabalin. There were no statistically significant differences between pregabalin 75 mg, 150 mg/day and placebo in changes in pain scores. Pregabalin ≥ 300 mg/day was more effective than placebo (change in pain scores, responder rates, PGIC scores).

Amitriptyline versus placebo:
The submission identified two additional cross-over trials comparing amitriptyline with non-active comparator. Only one eligible trial was identified for indirect comparisons (Trial 040). There were statistically significantly larger reductions in pain scores, more responders and improved PGIC scores in amitriptyline users compared to placebo.

Indirect comparison pregabalin vs amitriptyline (placebo common comparator):
The submission also presented meta-analyses of the results of 13 trials comparing pregabalin with placebo at differing dosages and based on mean changes in pain scores, responder analyses (≥ 50% reduction in pain scores) and Patient Global Impression of Change (PGIC). The results of the placebo-controlled trials were used in indirect analyses, comparing pooled estimates from the pregabalin trials with the amitriptyline arm of Trial 040. There were no statistically significant differences between pregabalin and amitriptyline 75 mg/day for any

dose of pregabalin. Amitriptyline 75 mg/day was associated with larger numerical reductions in pain scores than pregabalin for all doses less than pregabalin 600 mg/day. Similarly, there were no statistically significant differences in responder rates or mean PGIC scores between pregabalin and amitriptyline. Numerically the estimates favoured amitriptyline. There were substantial placebo response rates in the trials for DPN.

POST-HERPETIC NEURALGIA (PHN):

Pregabalin versus placebo:
Nine trials were identified, and stratified meta-analyses by dose of pregabalin were conducted. There were no statistically significant differences between pregabalin 75 mg and placebo in changes in pain scores. Pregabalin ≥ 150 mg/day was more effective than placebo (change in pain scores, responder rates, PGIC scores). Placebo response appeared generally lower in these trials in PHN.

Amitriptyline versus placebo:
Four trials were identified, three crossover studies were excluded. There were statistically significantly larger reductions in pain scores (VAS) in amitriptyline users compared to placebo (Graff-Radford 2000).

"OTHER" NEUROPATHIC PAIN:

Pregabalin versus placebo:
The submission presented five RCTs of pregabalin versus placebo (spinal cord injury, central post-stroke pain, post-traumatic peripheral neuropathic pain, HIV neuropathy and central neuropathic pain).

Amitriptyline versus placebo:
Seven RCTs compared amitriptyline with non-active comparators (spinal cord injury, post-mastectomy, chemotherapy-induced neuropathic symptoms, HIV neuropathy, and amputation-related pain).

Indirect comparison pregabalin vs amitriptyline (placebo common comparator):
The submission pooled the results of four pregabalin versus placebo trials and two amitriptyline trials. The pooled results for pregabalin and amitriptyline trials in "other" neuropathic pain conditions and the individual trials for spinal cord injury were used in indirect comparisons. For 'other' neuropathic pain conditions, pregabalin 150-600 mg/day was numerically superior to amitriptyline 10-125 mg/day, but there were no statistically significant differences. However, for spinal cord injury there was a statistically significant difference favouring amitriptyline.

OTHER COMPARATOR THERAPIES

Carbamazepine: The submission included one systematic review, two RCTs in diabetic peripheral neuropathy (DPN), and four RCTs in trigeminal neuralgia comparing carbamazepine versus placebo.

In DPN, two crossover trials were identified, no treatment comparisons were possible. A Cochrane review (Wiffen 2005) concluded carbamazepine provides better pain relief than placebo in several neuropathic pain conditions including DPN.

No trials were identified in PHN. A Cochrane review (Wiffen 2005) concluded that carbamazepine provides better pain relief than placebo in several neuropathic pain conditions including PHN.

Gabapentin: The submission included seven RCTs in DPN, three RCTs in post-herpetic neuralgia (PHN), one RCT in a mixed population (DPN and PHN), and 15 RCTs in "other" neuropathic pain conditions comparing gabapentin versus placebo.

Of the seven trials identified in DPN, two cross-over studies were excluded. The trial data suggested gabapentin 3600 mg/day is statistically significantly better than placebo in DPN.

Three trials were conducted in PHN, one trial was conducted in a mixed PHN/DPN population (this was excluded as it was a crossover trial). No meta-analysis was possible due to differences in doses of gabapentin used in the trials. The individual trial results suggested that gabapentin (starting dose 900 mg/day) is statistically significantly better than placebo in PHN.

In "other" neuropathic pain, no individual study showed significant improvements of pain intensity in the gabapentin vs placebo comparison. Only two studies were meta-analysed for other/mixed types of neuropathic pain, and no significant improvement was demonstrated in this comparison.

Opioids: The submission included six RCTs in DPN, three RCTs in PHN, one RCT in a mixed population (DPN and PHN), and ten RCTs in "other" neuropathic pain conditions comparing opioids with placebo/non-active comparator.

Of the six trials were conducted in DPN, one trial was in a mixed DPN/PHN population. Two crossover studies were excluded. There were no common outcomes or dosing regimens therefore no meta-analysis of trial results was possible. Tramadol and oxycodone CR were associated with statistically significantly larger reductions in pain scores than placebo. Tramadol was associated with larger proportions of treatment responders and more improved PGIC scores than placebo.

Three trials were conducted in PHN, one trial involved a mixed PHN/DPN population. Three crossover studies were excluded. A single parallel arm trial (Boureau 2003) showed tramadol 100-400 mg/day (mean 275.5 mg/day) statistically significantly superior to placebo in reductions in pain scores and was associated with significantly higher responder rates than placebo.

In other/mixed types of neuropathic pain, only one study (Arbaiza 2007) in neuropathic cancer pain has reported the primary meta-analysis outcome, the re-analysis result did not show a significant pain score change from baseline with opioid (Tramadol).

For PBAC's comments on these results, see Recommendation and Reasons.

8. Clinical Claim

The submission claimed pregabalin as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over amitriptyline, which the PBAC considered acceptable.

For PBAC's view, see Recommendation and Reasons.

9. Economic Analysis

A modelled economic evaluation was presented, comparing two scenarios: 'Current Options' representing current prescribing patterns of neuropathic pain drugs in Australia; and 'New Options' based on expected prescribing patterns if pregabalin were listed on the PBS for neuropathic pain. The model was a Markov model, over five years (10 six-monthly cycles).

Rather than moving patients between neuropathic pain health states, the model moved patients between neuropathic pain treatment options, or treatment states. Each scenario had five treatment states: anti-epileptic drugs (AED); tricyclic antidepressants (TCA); tricyclic antidepressants plus anti-epileptic drugs (TCA+AED); other drugs; and no drug treatment.

The treatment alternatives TCA, AED and TCA+AED were assumed to have the same efficacy.

Utilities, based on pain scores measured during the pregabalin trials were used to derive QALYs. The costs included in the model were drug costs only. The only difference between the three sub-models was in utilities. There were no differences in the costs, or transition probabilities. The utilities used in the model are the same for each arm of the model ('Current option' vs 'New option').

The transition probabilities for the 'current options' (pregabalin not on the PBS) scenario were based on data from the sponsor's Community Study. The Community Study is a longitudinal patient audit of GP- and specialist-treatment of neuropathic pain in Australia.

To derive transition probabilities in the 'new options' (pregabalin on the PBS) scenario, the transition probabilities in the 'current options' arm are adjusted by multiplication factors to reflect the expected increased use of pregabalin, decreased use of other neuropathic pain drugs, and decreased numbers of patients receiving no drug treatment.

Based on the economic evaluation by type of neuropathic pain, an incremental cost per QALY gained was calculated to be less than $15,000.

The results of the sensitivity analyses indicated that the model was most sensitive to assumptions regarding utilities; the inclusion of a placebo effect among subjects not taking drugs; and the assumed mean daily dose of drugs.

For PBAC's view, see Recommendation and Reasons.

10. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated to be more than $100 million in Year 5.

11. Recommendation and Reasons

The PBAC accepted that there is a high clinical need for effective treatments for neuropathic pain. Given the high unmet need, the requested restriction for a first-line 'streamlined' authority listing was considered appropriate. A listing that required failure of other treatments was not considered practical for administrative reasons.

The PBAC considered the clinical comparison against both an active comparator (as represented by the sponsor's nominated main active comparator, amitriptyline) and placebo to be reasonable. However, it was also considered probable that pregabalin would be used in combination with other therapies such as amitriptyline, in which case the comparator would be placebo, or other non-PBS listed anti-epileptic drugs, such as gabapentin.

There were a number of issues with the clinical comparison, although the PBAC acknowledged the claim in the submission that the head-to-head trial 040, which included amitriptyline as an active control, lacked the power to show superiority or non-inferiority of pregabalin versus amitriptyline. In addition, concern was raised that the results of the indirect comparisons may not be particularly informative as the exchangeability of the trials included in these analyses is uncertain due to the variability in the placebo responses and heterogeneity between the trials. However, the PBAC acknowledged the Pre-PBAC Response comments that the heterogeneity between the trials was accounted for by random-effects meta-analysis.

Further uncertainty arises because of the doses used, and the short duration of the fixed/maintenance doses, in the trials. Up to 100 mg per day of amitriptyline can be given, and therefore there may have been underdosing of amitriptyline in Trial 040 (75 mg per day) and Bansal 2009 (maximum of 50 mg per day). The maximal dose for pregabalin of 600 mg per day was used in these trials.

Nevertheless, the Committee concluded that despite the uncertainty about the comparative effectiveness, the claim that pregabalin is no worse than amitriptyline, was acceptable, despite the limitations in the data. The PBAC further noted that the submission made no claim of therapeutic superiority for pregabalin over any other anti-epileptic or tricyclic anti-depressant drug therapy for neuropathic pain.

The PBAC noted that the modelled economic evaluation compares two scenarios: 'Current Options' representing current prescribing patterns of neuropathic pain drugs in Australia; and 'New Options' based on expected prescribing patterns if pregabalin were listed on the PBS for neuropathic pain. Thus, the model is effectively a comparison of pregabalin with a range of alternatives, with the alternative strategy most widely being replaced being no drug therapy. The PBAC noted that the modelled economic evaluation adopted a broader approach to possible substitutions than generally promoted by the concept of a "main comparator" in the PBAC Guidelines and considered it not to be unreasonable under the circumstances, if substantial uptake beyond switching between currently available drug therapies is expected. However, the PBAC was concerned whether the model had addressed all possible alternative scenarios to the 'Current options' scenario, for example the option of using drugs in sequence because pregabalin would most likely be used early in the treatment sequence of neuropathic pain.

The PBAC noted that the economic evaluation is primarily driven by data from the Community Study and assumptions about the neuropathic pain market size and market-share changes if pregabalin is listed on the PBS. The Pre-PBAC Response argues that the

Community Study on which the transition probabilities were based, was a large, local and highly relevant study. However, the submission did not provide a comprehensive study report of the Study, but presented a large series of tables detailing the overall results of the total population. The PBAC expressed concern about the lack of transparency associated with presentation of the results of the Study. The limitations of the Community Study included the small number of patients informing the transition probabilities particularly in later cycles, the quality of information is subject to the adequacy of record keeping, the eligibility to be selected is uncertain, and inconsistencies in reporting of data. In addition, the submission acknowledged that it was not possible to validate the results of the Community Study with the GPRN and BEACH surveys commissioned by the sponsor due to different sampling and collection methods.

The approach of modelling a utility gain in patients who are not currently adequately treated was not convincingly supported, and PBAC noted that this utility gain was an important driver in the model due to the modelling effect of increasing the number of patients moving to adequate drug treatment from inadequate drug treatment. The submission also did not present the analyses of the individual patient data on utilities for verification. Durations of treatments in the Community Study are not known. Furthermore, the base case did not include placebo-adjusted responses.

The model assumes that all patients currently untreated and 38% of patients receiving ineffective 'other drugs', have utility equal to the baseline utility of patients in the reported clinical trials. This assumption is not supported by any evidence.

The PBAC also noted that there are inconsistencies in the mapping of changes in pain scores to changes in utilities, such that a larger reduction in pain score seen in DPN subjects (compared with PHN and other subjects) is associated with a lower utility gain. Although the Pre-PBAC Response argued that trial-based utility data were used in the model, the PBAC agreed with the ESC that the utility data were not convincing.

The PBAC thus considered that considerable uncertainty remained about both the transition probabilities derived from the Community Study and utilities used in the model.

Given the high prevalence of the condition, the uptake of pregabalin would likely be high, and possibly higher than that predicted in the submission.

The PBAC therefore rejected the submission because of uncertain cost effectiveness.

Recommendation:
Reject

12. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

13. Sponsor's Comment

Pfizer Australia acknowledges that the reimbursement of new treatments for neuropathic pain is difficult as there is inherent uncertainty in the available evidence and agrees that there is a high unmet need. Therefore, the company will continue to work with the PBAC to make Lyrica available for this population of patients.