PUBLIC SUMMARY DOCUMENT
Product: Pregabalin, capsules, 25 mg, 75 mg, 150 mg and 300 mg, Lyrica®
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission sought an Authority Required (Streamlined) listing for:

1) Initiation and up-titration of treatment for neuropathic pain (75 mg);
2) Initiation of treatment for neuropathic pain in patients requiring a reduced dose due to renal impairment (25 mg);
3) Continuation of treatment in patients who have received a PBS prescription for initiation of treatment and have shown an adequate clinical response (all strengths); and
4) Continuation of treatment in patients who had shown clinical response to pregabalin prior to PBS listing (all strengths).

2. Background

This was the second consideration by the PBAC of an application to list pregabalin for neuropathic pain.

At the March 2011 meeting, the PBAC rejected a submission seeking to list pregabalin as an Authority Required (Streamlined) benefit for the initial and continuing treatment of neuropathic pain in patients who meet certain criteria because of uncertain cost effectiveness.

A copy of the Public Summary Document (PSD) from the March 2011 meeting is available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-pregabalin-march11

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

Capsule 25 mg (MQ: 56, Rpts: 0)

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

Authority required (STREAMLINED)
Initiation of treatment for neuropathic pain in patients requiring dosage reduction due to renal impairment.

Capsule 75 mg (MQ: 56, Rpts: 0)

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.

All strengths (MQ: 56, Rpts: 5)

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 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 (e.g. diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), HIV neuropathy).

Current therapies used to treat neuropathic pain include tricyclic antidepressants, gabapentin, pregabalin, other antiepileptics, opioid analgesics, selective serotonin re-uptake inhibitors (SSRIs) and selective noradrenaline re-uptake inhibitors (SNRIs) and various non-pharmacological treatments.

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

6. Comparator

The submission nominated amitriptyline as the main comparator, gabapentin as the secondary comparator and placebo as the comparator for patients who have exhausted all treatment options.

The PBAC had previously considered the clinical comparison against both an active comparator (amitriptyline) and placebo to be acceptable.

7. Clinical Trials

The basis of the re-submission was 74 randomised comparative trials: three head-to-head trials with pregabalin and amitriptyline arms in diabetic peripheral neuropathy (one new trial, Gribble LC et al. in press – also had a duloxetine arm), one head-to-head trial with pregabalin, amitriptyline, gabapentin and placebo arms in neuropathic cancer pain (new data, Mishra S et al. 2011), 26 trials comparing pregabalin with placebo (one new trial, Study 1107 in spinal cord injury), 12 trials comparing amitriptyline with non-active comparator, one trial comparing amitriptyline and gabapentin with non-active

comparator, 30 trials comparing gabapentin with non-active comparator/placebo (seven new trials) and one trial comparing gabapentin, morphine and gabapentin plus morphine.

Details of the trials published at the time of submission are in the table below.

Trial ID/First author	Protocol title/ Publication title	Publication citation
Gabapentin versus placebo in DPN		
210 Backonja 1998	Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. A randomized controlled trial.	*Journal of the American Medical Association,* 1998; 280(21): 1831-1836
Gorson 1999	Gabapentin in the treatment of painful diabetic neuropathy: A placebo controlled, double blind, crossover trial.	*Journal of Neurology Neurosurgery and Psychiatry*, 1999; 66(2): 251-252
Perez 2000	Gabapentin therapy for diabetic neuropathic pain.	*The American Journal of Medicine,* 2000; 108(8): 689
Simpson 2001	Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy.	*Journal of Clinical Neuromuscular Disease,* 2001; 3(2): 53-62
Gabapentin versus placebo in PHN		
211 Rowbotham 1998	Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial.	*JAMA: the Journal of the American Medical Association*, 1998; 280(21): 1837-1842
295 Rice 2001	Gabapentin in postherpetic neuralgia: A randomised, double blind, placebo controlled study.	*Pain,* 2001; 94: 215-224
Backonja 2011	Efficacy of gabapentin enacarbil vs placebo in patients with postherpetic neuralgia and a pharmacokinetic comparison with oral gabapentin.	*Pain Medicine,* 2011; 12:1098-1108
Gu 2009	A multicenter, randomized, double-blind, placebo-controlled, parallel design study on the efficacy and safety of gabapentin, an anticonvulsant drug in the treatment of postherpetic neuralgia. (*Abstract only in English)*	*Zhonghua Pifuke Zazhi [Chinese Journal of Dermatology],* 2009; 42(7): 451-454.
Irving 2009 Irving 2011	Efficacy and tolerability of gastric-retentive gabapentin for the treatment of postherpetic neuralgia: results of a double-blind, randomized, placebo-controlled clinical trial. Effect of study country on efficacy and adverse event profile of once-daily gabapentin extended-release (G-ER) for the treatment of postherpetic neuralgia (PHN). 30th Annual	*The Clinical Journal of Pain* 2009; 25(3): 185-192 *Journal of Pain,* 2011; 12 (4 suppl): page P68

Trial ID/First author	Protocol title/ Publication title	Publication citation
	Scientific Meeting of the American Pain Society Austin, TX United States.	
Rauck 2010	A randomized, placebo-controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with post-herpetic neuralgia.	*Neurology*, 2010; 74(Suppl2): A484. P05.228
Wallace 2010	Gabapentin extended-release tablets for the treatment of patients with postherpetic neuralgia. A randomized, double-blind, placebo-controlled, multicentre study.	*Clinical Drug Investigation,* 2010; 30(11):765-776.
Gabapentin versus active placebo in DPN and PHN		
Gilron 2005	Morphine, gabapentin, or their combination for neuropathic pain.	*New England Journal of Medicine*, 2005; 352(13): 1324-1334.
Gabapentin versus placebo in "Other" neuropathic pain		
306 Serpell 2002	Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial.	*Pain,* 2002; 99(3): 557-566
Argyriou 2006	Evaluation of Gabapentin in Patients With Chemotherapy-Induced Peripheral Neuropathy.	*Annals of Oncology* 2006; 17(Suppl 9):ix298-ix299
Bone 2002	Gabapentin in post amputation phantom limb pain: a randomized, double- blind, placebo-controlled, cross-over study.	*Regional Anaesthesia and Pain Medicine,* 2002; 27(5):481-486
Caraceni 2004	Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group.	*Journal of Clinical Oncology,* 2004; 22(14): 2909-2917
Gordh 2008	Gabapentin in traumatic nerve injury pain: A randomized, double-blind, placebo-controlled, cross-over, mufti-center study.	*Pain,* 2008; 138(2): 255-266
Hahn 2004	A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies.	*Journal of Neurology,* 2004; 251(10): 1260-1266
Hui 2011	Gabapentin for the treatment of carpal tunnel syndrome: a randomized controlled trial.	*European Journal of Neurology*, 2011; 18:726-730
Levendoglu 2004	Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury.	*Spine,* 2004; 29(7): 743-751
Nikolajsen 2006	A randomized study of the effects of gabapentin on postamputation pain.	*Anesthesiology*, 2003; 105: 1008-1015
Rao 2007	Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3).	*Cancer* 2007;110(9): 2110-2118

Trial ID/First author	Protocol title/ Publication title	Publication citation
Rintala 2007	Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury.	*Archives of Physical Medicine and Rehabilitation*, 2007; 88(12): 1547-1560
Smith 2005	Efficacy of gabapentin in treating chronic phantom limb and residual limb pain.	*Journal of Rehabilitation Research and Development*, 2005; 42(5): 645-654
Tai 2002	Gabapentin in the treatment of neuropathic pain after spinal cord injury: a prospective, randomized, double-blind, crossover trial.	*The Journal of Spinal Cord Medicine,* 2002; 25(2): 100-105.
van de Vusse 2004	Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1.	*BMC Neurology,* 2004; 4(epub): 13
Yelland 2009	N-of-1 randomized trials to assess the efficacy of gabapentin for chronic neuropathic pain.	*Pain Medicine,* 2009; 10(4): 754-761.
Yildirim 2003	The effectiveness of gabapentin in patients with chronic radiculopathy.	*The Pain Clinic,* 2003: 15(3): 213-218.
Gabapentin in combination "gabanoid" treatment		
Achar 2010	Comparative study of clinical efficacy with amitriptyline, pregabalin, and amitriptyline plus pregabalin combination in postherpetic neuralgia.	*Indian Journal of Dermatology, Venereology and Leprology* 2010, 76(1):63-5.
Gatti 2009	Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: Results of a multicenter Italian study.	*European Neurology* 2009; 61: 129–37
Zin 2010	Randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin.	*The Journal of Pain,* 2010; 11(5):462-71.

Abbreviations: DPN, diabetic peripheral neuropathy; PHN, post-herpetic neuralgia

The table below summarises the additional trials with pregabalin and/or amitriptyline arms identified which were published (or about to be published) at the time of submission.

Trial ID / First author	Protocol title/ Publication title	Publication citation
Pregabalin and amitriptyline in DPN		
Gribble LC et al.	Poorer quality of sleep is associated with pain interference, reduced quality of life and lower cognitive status in patients with painful diabetic peripheral neuropathy.	*Diabetic Medicine*, 26 (Suppl 1): 44 (P17)
	A double-blind randomised study comparing the effects of pregabalin, duloxetine and amitriptyline on aspects of neuropathic pain, mood and sleep in diabetic subjects with painful neuropathy.	*Diabetologia*, 2010; 53(Suppl 1): S16 (26)
	Randomised, placebo-controlled comparison of	Manuscript (in press)

Trial ID / First author	Protocol title/ Publication title	Publication citation
	amitriptyline, duloxetine and pregabalin in patients with chronic diabetic peripheral neuropathic pain. Impact on pain, polysomnographic sleep, daytime functioning and quality of life.	
Pregabalin versus amitriptyline versus gabapentin in "Other" neuropathic pain		
Mishra S et al.	A comparative efficacy of amitriptyline, gabapentin and pregabalin in neuropathic cancer pain.	American Society of Anesthesiologists Annual Meeting, New Orleans (2009)
	A comparative efficacy of amitriptyline, gabapentin and pregabalin in neuropathic cancer pain.	*American Journal of Hospice & Palliative Medicine*, 2011; Epub ahead of print

Abbreviations: DPN, diabetic peripheral neuropathy; SCI, spinal cord injury

The re-submission presented multiple meta-analyses of the results of the pregabalin versus placebo trials, the amitriptyline versus non-active comparator trials, and the gabapentin versus placebo trials based on neuropathic pain type: diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN), and "other" neuropathic pain. These meta-analyses were stratified by doses and dosing regimens (fixed and flexible). The outcomes presented were mean change in pain score from baseline, responder rates (≥ 50% reduction in pain scores from baseline) and mean Patient Global Impression of Change (PGIC) score. New sub-group meta-analyses were presented for pregabalin versus placebo trials in "other" neuropathic pain: peripheral and central mechanisms of "other" neuropathic pain, and spinal cord injury.

8. Results of Trials

Diabetic peripheral neuropathy (DPN)

Head-to-head trials:

Two head-to-head trials were presented in the March 2011 submission. The following table summarises the key results from the additional head-to-head trial by Gribble (in press), where DPN patients were randomised to pregabalin, duloxetine and amitriptyline. Patients received 8 days of placebo run-in, followed by 14 days of the lower dose of the respective medications and then 14 days at the higher dose.

Results of the primary efficacy outcome of mean endpoint pain score (BPI) and secondary outcome of mean pain score (VAS) for Gribble (in press): completer analysis

Treatment	Baseline (Placebo)		2 weeks (lower dose)		4 weeks (higher dose)	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
BPI severity						
Pregabalin	24	3.1 (0.4)	21	**2.3* (0.4)**	19	2.4 (0.4)
Amitriptyline	27	3.5 (0.4)	24	**2.7* (0.4)**	23	2.6 (0.4)
Duloxetine	*23*	*3.4 (0.5)*	*23*	***2.5** (0.4)*	23	***2.2* (0.4)***
VAS (Secondary outcome)						
Pregabalin	24	16.8 (2.0)	21	**13.5* (2.1)**	19	13.2 (1.7)
Amitriptyline	27	29.6 (2.3)	24	**22.3** (2.1)**	23	23.6 (2.4)
Duloxetine	*23*	*23.3 (2.5)*	*23*	***16.3** (2.3)*	*23*	***13.2*** (2.2)***

Additional data in italics for duloxetine extracted from the publication for completeness.

Abbreviations: BPI, Brief Pain Inventory; PBO, placebo baseline; SE, standard error; VAS, visual analogue scale
Treatment vs PBO baseline, * P < 0.05, ** P < 0.01, *** P < 0.001 and **** P < 0.0001

For the pregabalin, amitriptyline and duloxetine arms, the mean pain scores during the first 14 days of low dose treatment were statistically significantly lower than the mean pain scores during the baseline placebo run-in period. The statistically significant differences compared to baseline at 14 days with lower doses were not maintained at 28 days after up-titration to higher doses for pregabalin and amitriptyline, but was maintained for the duloxetine arm.

Results for placebo controlled trials, and the indirect comparison of pregabalin versus amitriptyline have been previously reported in the March 2011 PSD.

Indirect comparison pregabalin vs gabapentin (placebo common comparator):
The re-submission presented indirect comparisons between data from the meta-analyses for the 13 pregabalin sponsored trials stratified by doses; and data from 2 gabapentin trials and the pooled estimates from 3 gabapentin trials stratified by doses, using placebo as the common comparator.

The PBAC noted that pregabalin and gabapentin appeared to have similar treatment effects in terms of the mean change in pain score from baseline for comparable fixed doses (pregabalin 600 mg/day versus gabapentin 3,600 mg/day). For the flexible dosing arm, pregabalin (150-600 mg/day) appeared to have a similar effect to gabapentin (900-2,400 mg/day). However, unlike pregabalin, gabapentin was not titrated to the maximum recommended dose of 3,600 mg/day in the flexible dosing trial. The PBAC considered there were uncertainties in the indirect comparisons due to variability in the placebo response, statistically significant heterogeneity across trials in some of the meta-analyses, and the short duration of the fixed/maintenance doses of the trials.

Post-herpetic neuralgia (PHN)

Placebo-controlled trials:
No additional pregabalin versus placebo trial or amitriptyline versus non-active comparator trial was identified. *Results have been previously reported in the March 2011 PSD.* The re-submission identified one additional gabapentin versus placebo trial, two additional gabapentin enacarbil versus placebo trials and two additional gabapentin extended-release versus placebo trials. Pregabalin, amitriptyline, and gabapentin appeared to be superior to placebo in PHN.

Indirect comparison pregabalin vs amitriptyline (placebo common comparator):
As with the March 2011 submission, no indirect comparisons were presented.

Indirect comparison pregabalin vs gabapentin (placebo common comparator):
The re-submission presented indirect comparisons between pregabalin and gabapentin using meta-analyses for 9 pregabalin trials stratified by dosing; and data from 3 gabapentin trials across the differing dosing arms.

Only one gabapentin trial informed the gabapentin fixed dose arms (1,800 mg/day and 2,400 mg/day). Pregabalin 300 mg/day and 600 mg/day produced comparable reductions

in pain scores as gabapentin 1,800 mg/day and 2,400 mg/day. However, there was no comparison of fixed maximum doses of pregabalin and gabapentin (600 mg/day and 3,600 mg/day respectively) presented. For the flexible dosing comparisons pregabalin 150-600 mg/day vs gabapentin 900-2400 mg/day and pregabalin 150-600 mg/day vs gabapentin 900-3,600 mg/day, the point estimates numerically favoured gabapentin, although differences were not statistically significant.

The re-submission claimed that pregabalin and gabapentin have similar treatment effects in PHN based on mean change in pain scores from baseline, response rates and mean Patient Global Impression of Change (PGIC) scores. Overall, the PBAC considered that the data were difficult to interpret as the conclusions were based on indirect comparisons where there was considerable variability in placebo responses, substantial heterogeneity across the trials and few comparisons of pregabalin and gabapentin at the maximum doses (600 mg/day and 3,600 mg/day respectively).

"Other" neuropathic pain

Head-to-head trials:
One new head-to-head trial in neuropathic cancer pain was presented by the re-submission (Mishra S et al. 2011). In this trial, immediate release morphine was given orally for rescue analgesia irrespective of the neuropathic symptoms if the patient had a visual analogue score (VAS) score greater than 3. The results of the trial are summarised in the table below.

Results of the primary efficacy outcome of mean endpoint pain score for Mishra et al. (2011) based on VAS

Treatment	Baseline pain score		Endpoint pain score (4 weeks)		Between group comparisons
	n	Mean (SD)	n	Mean (SD)	
Amitriptyline	30	7.77 (1.0)	NR	3.23 (0.70)	Significant lower mean pain score in pregabalin group compared amitriptyline (p=0.003), gabapentin (p=0.042), and placebo (p=0.024)
Gabapentin	30	7.50 (1.1)	NR	3.07 (0.80)	
Pregabalin	30	7.77 (0.81)	NR	2.50 (0.70)	
Placebo	30	7.47 (1.0)	NR	3.40 (0.66)	

Abbreviation: NR, not reported; SD, standard deviation; VAS, visual analogue scale

The endpoint mean pain score of the pregabalin 600 mg/day arm was statistically significantly lower than the mean pain score in the amitriptyline 100 mg/day arm (from week 3 onwards), gabapentin 1,800 mg/day (at week 4) and placebo (from week 3 onwards). Overall, the results suggested that amitriptyline, pregabalin and gabapentin in combination with morphine are effective for short-term treatment of neuropathic cancer pain (2 weeks maintenance dose); with the results being more favourable for pregabalin. However, the PBAC considered that interpretation of these data was limited by the dosing of gabapentin (1,800 mg/day, when the maximum recommended dose is 3,600 mg/day).

Placebo-controlled trials:
One new trial of pregabalin versus placebo was identified by the re-submission (Trial 1107 (unpublished) in spinal cord injury). The re-submission did not identify new amitriptyline versus placebo trials. Two new gabapentin versus placebo trials were identified.

There was some evidence that pregabalin is statistically significantly better than placebo in spinal cord injury, post-traumatic peripheral neuropathic pain and central neuropathic pain. Differences were not statistically significant for central post-stroke pain and HIV neuropathy. However, there were insufficient data for most of the individual pain conditions to draw conclusions about relative benefit of pregabalin in different settings.

The PBAC considered that the body of evidence for the comparisons of amitriptyline and gabapentin with placebo was generally of lower quality and was from smaller trials.

Pregabalin versus placebo updated meta-analyses:
The inclusion of Trial 1107 in the meta-analyses did not substantially affect the pooled results from the March 2011 submission, with statistically significantly larger reductions in mean pain score for pregabalin compared to placebo (mean difference -0.67; 95% CI -1.07, -0.28).

The re-submission presented new sub-group meta-analyses of unpublished Trials 125 and 1107 in spinal cord injury (pregabalin versus placebo). Pregabalin resulted in statistically significantly larger reductions in pain score compared to placebo for Trials 125, 1107 and the pooled results.

The re-submission presented subgroup meta-analyses of the "other" neuropathic pain conditions based on the peripheral mechanisms and central mechanisms for all outcomes. For "other" peripheral neuropathic pain, there were statistically significant differences favouring pregabalin over placebo for the mean change in pain score and mean PGIC meta-analyses, but not responder rates. Pregabalin was statistically significantly better than placebo in "other" central neuropathic pain conditions for all outcomes included in the meta-analyses.

Overall, the PBAC still had concerns over the re-submission's approach to meta-analysis trials from different pain conditions as "other" pain conditions given the variability between the trials in different clinical conditions. There was considerable heterogeneity between studies and variability in the magnitude of the placebo response.

Indirect comparison pregabalin vs amitriptyline (placebo common comparator):
For the indirect comparisons of pregabalin 150-600 mg/day vs amitriptyline 10-125 mg/day flexible dosing arms, the point estimate numerically favoured pregabalin over amitriptyline for "other" neuropathic pain conditions and spinal cord injury. However, the differences were not statistically significant. This differed to the March 2011 submission's claim that for spinal cord injury there is evidence of pregabalin being superior to amitriptyline (mean difference reported in the March 2011 submission: -1.47; 95% CI -2.71, -0.23). The inclusion of Trial 1107 changed the conclusions – the results for the indirect comparison now showed no statistically significant difference between pregabalin and amitriptyline for the treatment of pain associated with spinal cord injury.

The re-submission acknowledged that the first indirect comparison in which all "other" neuropathic pain conditions (excluding DPN and PHN) were combined may have been problematic due to different pain indications, statistical heterogeneity across pregabalin trials, and possibly uneven placebo response amongst trials. The comparison for spinal

cord injury was claimed to be "more robust" despite some differences in trial characteristics (i.e. different baseline pain score and treatment duration - which was deemed less likely to be an issue by the re-submission). It remained difficult to conclude that exchangeability holds and that an indirect comparison of trial results was appropriate for both the overall "other" group and for spinal cord injury subgroup.

Indirect comparison pregabalin vs gabapentin (placebo common comparator):
The re-submission presented new indirect comparisons between data from the meta-analyses for the 6 pregabalin sponsored trials and data from 2 gabapentin trials (Caraceni, 2004; and 306 where 16% of patients have DPN or PHN), using placebo as the common comparator.

For the flexible dosing comparisons pregabalin 150-600 mg/day vs gabapentin 600-1,800 mg/day and pregabalin 150-600 mg/day vs gabapentin 900-2,400 mg/day, the point estimate numerically favoured pregabalin but the differences with gabapentin were not statistically significant. The first comparison of pregabalin 150-600 mg/day vs gabapentin 600-1,800 mg/day was uncertain, given the transformation of the data from the gabapentin trial by Caraceni 2004 and imputation of the standard deviations required to facilitate the comparisons. Interpretation of the second comparison of pregabalin 150-600 mg/day vs gabapentin 900-2,400 mg/day was limited by the lack of possible up titration of gabapentin to the maximum dose of 3,600 mg/day, whereas pregabalin could be up-titrated to the maximum dose. Additionally, there was statistically significant heterogeneity between trials, considerable variability in the magnitude of placebo response, and concerns regarding combining data for different types of neuropathic pain conditions. It was unclear whether the trials included in the indirect comparisons were comparable.

Overall, the PBAC agreed that the additional trials presented supported pregabalin being clinically no worse than gabapentin.

Combination "gabanoid" treatment:
The re-submission presented two pregabalin combination studies: Achar et al. (2010) comparing pregabalin, amitriptyline, and pregabalin plus amitriptyline; and Zin et al. (2010) comparing oxycodone plus pregabalin and placebo plus pregabalin. One potentially relevant pregabalin combination study (Gatti et al. 2009) comparing oxycodone CR plus pregabalin, oxycodone CR and pregabalin appeared to have been excluded. The re-submission also presented data from three gabapentin studies.

Statistically significantly more patients treated with pregabalin plus amitriptyline (73.3%) had a satisfactory improvement (defined as >75% improvement) than in the pregabalin monotherapy (53.3%) and the amitriptyline monotherapy (13.4%) groups in Achar et al. (2010). Gatti et al. (2009) found that combination oxycodone CR plus pregabalin and oxycodone CR monotherapy were more effective than pregabalin alone, but pregabalin patients had a lower baseline pain score. However, Zin et al. (2010) found that there were no statistically significant differences in the proportion of patients who achieved a ≥2 cm drop in pain score (VAS) and a pain score of <4 cm (VAS) between the oxycodone/pregabalin arm (69%) and the placebo/pregabalin arm (76%).

These studies were generally of low quality, and the use of pregabalin was unblinded. Overall, there was limited evidence to conclude that the addition of tricyclic

antidepressants (TCAs) or opioids to pregabalin results in a reduction in neuropathic pain and that combination therapy may enable the reduction in dosages of opioids or TCAs.

For PBAC's view, see Recommendation and Reasons.

The re-submission presented new toxicity data from the three new trials with pregabalin and/or amitriptyline arms, the new gabapentin trials, the updated Pregabalin European Summary of Product Characteristics and the latest Periodical Safety Update Report for pregabalin.

For pregabalin, the common adverse events (AEs) reported during the trials included dizziness, somnolence, peripheral oedema, headache, weight gain, dry mouth, amblyopia, asthenia, and thinking abnormal. For amitriptyline, commonly reported AEs included drowsiness/tiredness, dry mouth, dizziness, constipation, urinary difficulties/retention, palpitations, headaches and increased spasticity. The most commonly reported AEs across the pooled trial safety data based on the three indications included dizziness, somnolence, asthenia, headache, peripheral oedema, nausea, dry mouth, fatigue, malaise and confusion.

The adverse event profiles of combination "gabanoid" therapy appeared broadly consistent with the adverse event profile of the individual agents. Combination therapy was generally associated with more adverse events.

Overall, the data presented did not suggest that there are substantial differences in safety for pregabalin versus amitriptyline or gabapentin.

9. Clinical Claim

The re-submission described pregabalin as non-inferior in terms of comparative efficacy and non-inferior in terms of comparative safety to amitriptyline. The PBAC had previously 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 re-submission described pregabalin as non-inferior in terms of comparative efficacy and non-inferior in terms of comparative safety to gabapentin. This was accepted by the PBAC.

The re-submission described pregabalin as superior in terms of comparative efficacy and inferior in terms of comparative safety to placebo. This was accepted by the PBAC.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

An updated modelled economic evaluation was presented. The key differences in economic model compared to the previous model were that:

- Key inputs were based on a new sponsor-commissioned study, the 2011 Drug Audit (versus the 2010 Community Study in the previous submission);
- Trial based utilities adjusted for placebo-response from seven pregabalin trials were used, compared to non-placebo adjusted utilities obtained from mapping pain scores

to utility values;

- The model comprised of 5 treatment states: anti-epileptic drug (AED), TCA, other, 'no treatment – satisfied', and 'no treatment – not satisfied'. The AED+TCA treatment state in the previous model was combined with the AED treatment state, and the 'no treatment' state was split into two states: satisfied/not satisfied with pain control; and
- 19.7% of patients were assumed not to be represented by the 2011 Drug Audit, and these patients were not currently treated by default (included as a sub-population in the 'no treatment – not satisfied' state). This subpopulation was further divided into patients who were diagnosed and undiagnosed.

The economic model compared 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). The model moved patients between neuropathic pain treatment states. The costs included in the model were drug costs only. The model was evaluated for three sub-populations of neuropathic pain: DPN, PHN, and "other", as well as for the overall neuropathic pain population (the three sub-populations combined). The only difference between the three sub-models was in utilities.

Based on the assumptions used in the economic model, the incremental cost per QALY gained associated with listing pregabalin on the PBS for neuropathic pain was less than $15,000. Results of sensitivity analyses indicated that the model was most sensitive to the method of deriving the utilities, the cost of pregabalin, and the assumption that there were untreated patients who are not represented by the 2011 Drug Audit (19.7% of the model population).

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated per year was estimated in the resubmission to be greater than 200,000 in Year 5 at a net cost to the PBS of greater than $100 million in Year 5.

The Committee considered that the key issue was that the financial forecasts were underestimated and that there was huge potential for use outside the restriction (e.g. for fibromyalgia). See *Recommendation and Reasons*.

12. Recommendation and Reasons

The PBAC noted that the sponsor indicated agreement to restricting the listing of pregabalin to patients refractory to other therapies in its pre-PBAC response.

The PBAC noted that this submission included clinical data comparing pregabalin with amitriptyline and placebo, which had been previously considered and found acceptable comparators. In addition, the submission provided a comparison of data for pregabalin and gabapentin which had been requested by the PBAC.

The PBAC reiterated its acceptance of the clinical need for an alternative to current treatments for neuropathic pain. As with the previous submission, the PBAC accepted

that pregabalin is clinically superior over placebo and clinically no worse than amitriptyline. The additional clinical data provided did not change these views of the PBAC from its consideration of the previous submission.

An additional indirect comparison of gabapentin with pregabalin was presented in the submission. The PBAC agreed that the additional trials presented supported pregabalin being clinically no worse than gabapentin.

The PBAC noted that the clinical trial data is limited in some respects: no data in patients with head and neck pain, a group in whom there is likely to be considerable use of pregabalin, and limited data to assess comparative effectiveness for patients who have post-herpetic neuralgia and diabetic peripheral neuropathy. However, the Committee acknowledged the sponsor's argument that there is no basis to assume that patients with different types of neuropathic pain would respond differently to pregabalin treatment.

The PBAC noted that data to inform the comparison of pregabalin and placebo in patients for whom all other treatments have found not to be effective are limited. These data are crucial to the economic model and the extent of uncertainty in interpreting the trial results has substantial implications for the interpreting the modelled incremental effectiveness ratio.

The PBAC considered that the conceptual framework of the economic model is reasonable. The complexity of this framework with the resulting model structure and the many inputs are an attempt to reflect the various treatment pathways of patients with neuropathic pain. The PBAC noted the detailed clinician survey conducted to inform the inputs into the economic and financial analysis. The Committee considered that the survey method was satisfactory but noted that despite 26,979 GPs and specialists being approached, only 545 clinicians responded, of whom only two were pain specialists.

The PBAC noted two issues in the economic model that were important sources of uncertainty in the submission's calculated ICER: the derivation of the transition probabilities over the duration of the model from a cross-sectional subset of the survey responses and the lack of information from patients with head and neck pain to inform the estimates of utility gains. The PBAC acknowledged however that the model correctly adjusted the utility gains for placebo responses. The Pre-PBAC Response provided additional trial-based economic evaluations but the PBAC considered that these did not reflect sufficiently the issues of concern and additional sensitivity analyses would have been helpful.

The Committee considered that the key issue was that the financial forecasts were underestimated and that there was huge potential for use outside the restriction (e.g. for fibromyalgia). Also, even with the restriction, the estimates of numbers of patients likely to be prescribed pregabalin depend on prevalence of neuropathic pain in the Australian community, for which there are no precise estimates. The PBAC acknowledged the proposal for a risk-sharing arrangement to be developed to mitigate the risk of pregabalin being prescribed at higher doses than expected, as well as the risk of a higher number of patients than anticipated.

The PBAC considered there were uncertain inputs into a structurally complex economic

model coupled with forecasts for total costs that were likely to be underestimates. However, the PBAC accepted the clinical need for an alternative to current treatments for neuropathic pain.

The PBAC recommended the listing of pregabalin on the PBS as an Authority Required (Streamlined) benefit for the treatment of refractory neuropathic pain not controlled by other drugs on the basis of acceptable cost-effectiveness compared with placebo in patients dissatisfied with their current pain relief.

The PBAC agreed with the sponsor that pregabalin was superior to placebo and non-inferior to amitriptyline/gabapentin. The PBAC acknowledged the difficulty of modelling future use and future cost-effectiveness of pregabalin. The PBAC remained concerned about the potential for use beyond the estimates presented in the submission.

The PBAC considered that is was essential that the DUSC review usage 12 months after PBS listing.

The PBAC recommended that pregabalin is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements as continuing therapy only.

Recommendation:
PREGABALIN, capsules, 25 mg, 75 mg, 150 mg and 300 mg

Restriction:	Authority Required (STREAMLINED) Refractory neuropathic pain not controlled by other drugs. Note Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
Max quantity:	56
Repeats:	5

13. 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.

14. Sponsor's Comment

Pfizer welcomes the PBAC's decision and looks forward to working with the Department to achieve PBS listing for pregabalin for treatment of patients with neuropathic pain.