

Pregabalin: 12 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

October 2014

Abstract

Purpose

To examine the utilisation of pregabalin for neuropathic pain in the twelve months after PBS listing (1 March 2013 to 28 February 2014). In recommending the listing of pregabalin at its March 2012 meeting, the PBAC was concerned about the potential for use beyond the estimates presented in the submission and considered that it was essential that the DUSC review usage 12 months after PBS listing.

Date of listing on PBS

1 March 2013.

Data Source / methodology

Data for pregabalin was extracted from the DUSC database from the date of listing on the PBS (1 March 2013) to the most current available data (March 2014).

Key Findings

- The total number of prescriptions of pregabalin supplied in the first 12 months of PBS listing of 1,389,678 was similar to predicted, however utilisation is yet to stabilise and the total number of prescriptions is increasing.
- There were 294,274 PBS/RPBS patients treated with PBS subsidised pregabalin in the first year of listing. This was higher than estimated, however it is unclear at this time point what proportion of patients are continuing on treatment with pregabalin, and for how long.
- The PBS/ RPBS expenditure in the first twelve months of listing was \$60.7 million.
- The most commonly supplied strength of pregabalin is 75 mg, accounting for approximately half of all prescriptions.

Purpose of analysis

To examine the utilisation of pregabalin for neuropathic pain in the twelve months after listing (1 March 2013 to 28 February 2014). In recommending the listing of pregabalin at its March 2012 meeting, the PBAC was concerned about the potential for use beyond the estimates presented in the submission and considered that it was essential that the DUSC review usage 12 months after PBS listing.

Background

Pharmacology

The mechanism of action of pregabalin has not been fully elucidated. It is used to treat neuropathic pain, which is pain caused by an abnormality of, or damage to, the nerves. Pregabalin is also used as an anticonvulsant.¹ In vitro studies show that pregabalin binds to an auxiliary subunit (alpha2-delta protein) of voltage-gated calcium channels in the central nervous system.²

Therapeutic Goods Administration (TGA) approved indications

Pregabalin is indicated for the treatment of neuropathic pain in adults. Pregabalin is also indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.²

Dosage and administration

Neuropathic pain: initiate at 150 mg per day, given as two divided doses. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day, given as two divided doses, after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval.

The dose should be reduced in renal impairment based on creatinine clearance.

The effectiveness of pregabalin in the treatment of neuropathic pain has not been assessed in controlled clinical trials for treatment periods longer than twelve weeks.²

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

¹ Lyrica (Pregabalin) Australian Consumer Medicine Information. Sydney: Pfizer Australia. February 2014. Available from <<https://www.ebs.tga.gov.au/>>. Accessed 17 July 2014.

² Lyrica (Pregabalin) Australian Approved Product Information. Sydney: Pfizer Australia. April 2014. Available from <<https://www.ebs.tga.gov.au/>>. Accessed 17 July 2014.

PBS listing details 1 July 2014

The PBS listing details for pregabalin as at 1 July 2014 are shown in Table 1.

Table 1: PBS listing of pregabalin

Item	Name, form & strength, pack size	Max. quant.	Repeats	DPMQ	Brand name and manufacturer
2348N	Pregabalin 25 mg capsule, 56	56	5	\$26.44	Lyrica®, Pfizer Australia Pty Ltd
2335X	Pregabalin 75 mg capsule, 56	56	5	\$49.11	Lyrica®, Pfizer Australia Pty Ltd
2355Y	Pregabalin 150 mg capsule, 56	56	5	\$70.63	Lyrica®, Pfizer Australia Pty Ltd
2363J	Pregabalin 300 mg capsule, 56	56	5	\$102.05	Lyrica®, Pfizer Australia Pty Ltd

Source: www.pbs.gov.au.

Restriction

Authority Required (Streamlined):
Neuropathic pain

Clinical criteria:

The condition must be refractory to treatment with 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.

Date of listing on PBS

1 March 2013.

Current PBS listing details are available from pbs.gov.au.

Relevant aspects of the PBAC consideration

In the submission to its March 2012 meeting, the PBAC 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 the prevalence of neuropathic pain in the Australian community, for which there are no precise estimates.

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 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 it was essential that the DUSC review usage 12 months after PBS listing.

For further details refer to the [Public Summary Document](#) from the March 2012 PBAC meeting.

Approach taken to estimate utilisation

The submission to the March 2011 PBAC meeting to list pregabalin for neuropathic pain was rejected due to uncertain cost effectiveness. The DUSC provided advice to the PBAC on the March 2011 submission.

The submissions (March 2011 and March 2012 resubmission) used an epidemiological approach. The submissions estimated the prevalence of chronic pain and subsequently the prevalence of chronic pain of neuropathic origin from the literature (3.7-3.8 % of the Australian population). The prevalence was then applied to the Australian Bureau of Statistics population projections to estimate patient numbers.

With reference to the literature, the submission assumed at least 60 % of eligible patients with neuropathic pain seek treatment for their condition. The submission predicted that the PBS listing of pregabalin was likely to increase the awareness and diagnosis of neuropathic pain and estimated the proportion of patients seeking treatment to be 62 % in the first year of listing, increasing to 70 % in year five.

Of the eligible patients seeking treatment for their neuropathic pain, the proportion estimated to receive a prescription medicine was 80 % to 90 % in the first five years of listing. Fifty percent of these patients were estimated to receive pregabalin in its first year of PBS listing, rising to 70 % in year 5. These estimations were based on an audit undertaken by the sponsor. Table 2 outlines the submission's estimated extent of use for the first five years of listing.

In estimating the number of packs of pregabalin, the submission estimated patterns of use including regular use, sporadic use, non-compliance, and discontinuation due to a lack of benefit or side effects based on the findings of the drug audit. The submission concluded that the mean total daily dose of pregabalin used in Australia in practice is 225 mg, based on the weighted average of the pregabalin doses used from all the data sources (the sponsor's drug audit, General Practice Research Database (GPRN) and Bettering the Evaluation of Care of Health (BEACH)).

Add-on therapy to other medicines for neuropathic pain, movement of patients receiving pregabalin via the private market across to pregabalin through the PBS and a reduction in the use of other medicines for neuropathic pain including amitriptyline, gabapentin (outside of PBS restrictions) and carbamazepine through the PBS were also estimated.

Table 2: Estimated extent of use of pregabalin for the first five years of listing

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients supplied at least one PBS prescription	211,620 ^a	274,132 ^b	286,297 ^c	318,896 ^c	350,346 ^c
Number of packs per year	1,381,724	1,847,128	1,977,004	2,201,051	2,421,029

Source: Final agreed estimates based on financial years. *Estimates for the Risk Sharing Arrangement were converted to calendar years.*

^a49,144 newly diagnosed; 78,804 continuing from non-PBS supply (grandfathered); 83,672 previously lapsed.

^b27,257 newly diagnosed; 178,416 continuing on PBS from previous year; 68,459 previously lapsed.

^c newly diagnosed plus continuing from previous year.

The DUSC considered that the estimated prevalence of 3.7 % was highly uncertain as estimates based on overseas data are problematic with wide variations in the prevalence of chronic pain by country suggesting cultural or health system issues. The DUSC considered this uncertainty significantly affected the reliability of the overall estimates. The DUSC considered that a large number of patients were likely to seek treatment with pregabalin initially and that the submission underestimated this uptake.

The DUSC further considered that the total number of prescriptions per year was subject to several uncertainties with differing effects, including;

- The proportion who respond and continue on therapy was likely to be a substantial overestimate;
- The assumptions of substitution were considered unlikely to be realised, with add-on use expected to be much higher than the switching proposed; and
- The mean total daily dose of 225 mg pregabalin was high, and the average daily dose was likely to be lower.

In the March 2012 submission the cost off-sets for patients switching from amitriptyline, gabapentin or carbamazepine were reduced. In year 1 a reduction in R/PBS prescriptions of amitriptyline, gabapentin and carbamazepine of 112,255, 9,824 and 9,112 respectively was predicted.

Following the PBAC consideration, the sponsor offered a 16 % price decrease which resulted in a positive recommendation out of session by the PBAC.

A risk share arrangement was negotiated between the Government and the sponsor.

Previous reviews by the DUSC

Prior to the listing of pregabalin there were no medicines listed on the PBS specifically for neuropathic pain. This is the first review of pregabalin (12 months post listing).

Methods

Data for the number of prescriptions supplied and Government expenditure for pregabalin was extracted from the DUSC database from the date of listing on the PBS (1 March 2013) to the most current available data (March 2014). Data was also extracted for the RPBS pregabalin items prior to their deletion, effective 1 November 2013.

The DUSC database combines data on PBS prescriptions submitted to the Department of Human Services (DHS) for payment of a PBS/RPBS subsidy by the Government, with an estimate of under patient co-payment prescriptions based on dispensing data from a sample of pharmacies to the end of August 2012, replaced by actual under co-payment data from 1 April 2012. The DUSC database includes an estimate of private prescriptions based on dispensing data from a sample of pharmacies to the end of August 2012.

Patients initiating PBS pregabalin in the first twelve months of listing were counted from de-identified unique patient identification numbers (PINs).

All data were extracted based on the date of supply to the patient. The data differs from that available from the DHS (Medicare) PBS statistics website which is based on the date of processing and is only for subsidised R/PBS prescriptions (under patient co-payment not included).³

Results

Analysis of drug utilisation

Overall utilisation

Prescriptions

There were 1,389,678 prescriptions for pregabalin supplied in the first twelve months of listing. This figure includes PBS, including under co-payment prescriptions, and RPBS. Figure 1 shows the total number of prescriptions supplied by year and month of supply from March 2012 to March 2014. The data indicates that prescription numbers are currently increasing and have yet to stabilise.

³ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

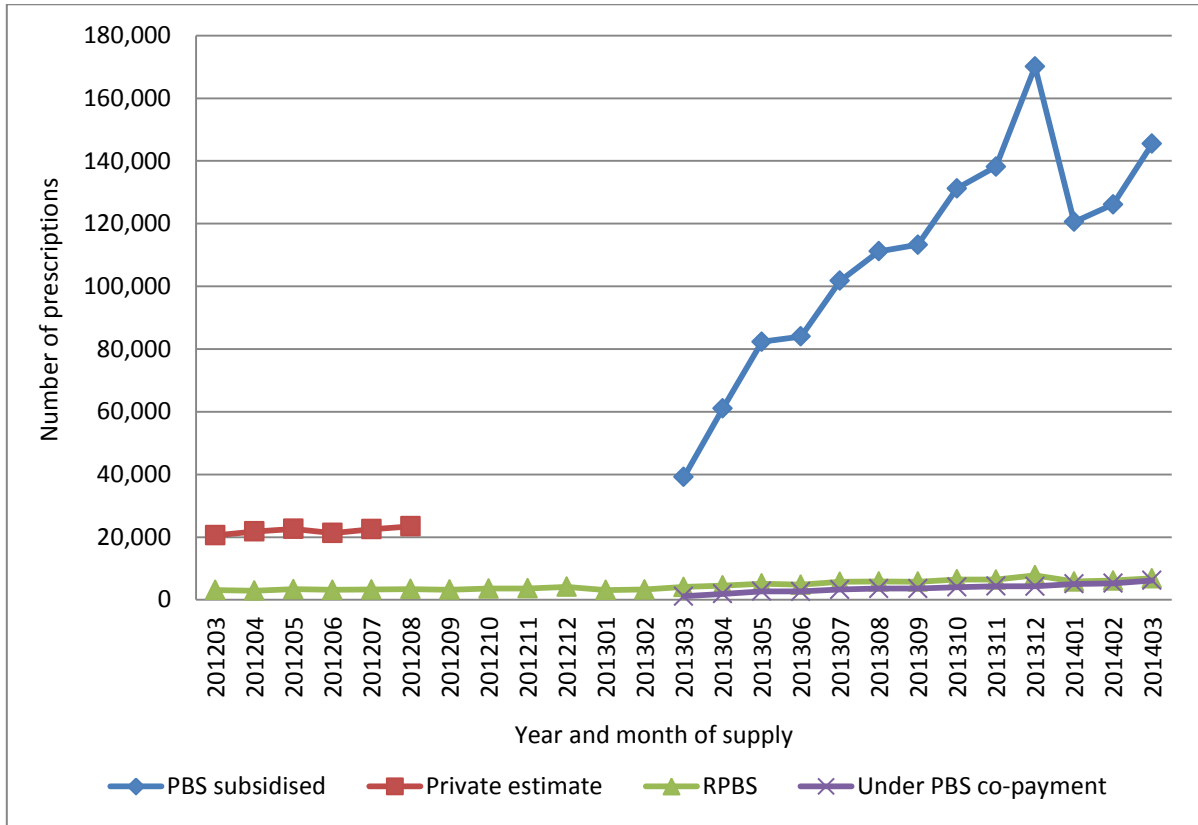


Figure 1: Number of prescriptions for pregabalin by year and month of supply, March 2012 to March 2014

Prescriptions by strength

Figure 2 shows the total number of prescriptions per month by strength. The most commonly supplied strength is 75 mg at 52 % of PBS prescriptions supplied in the first twelve months of listing.

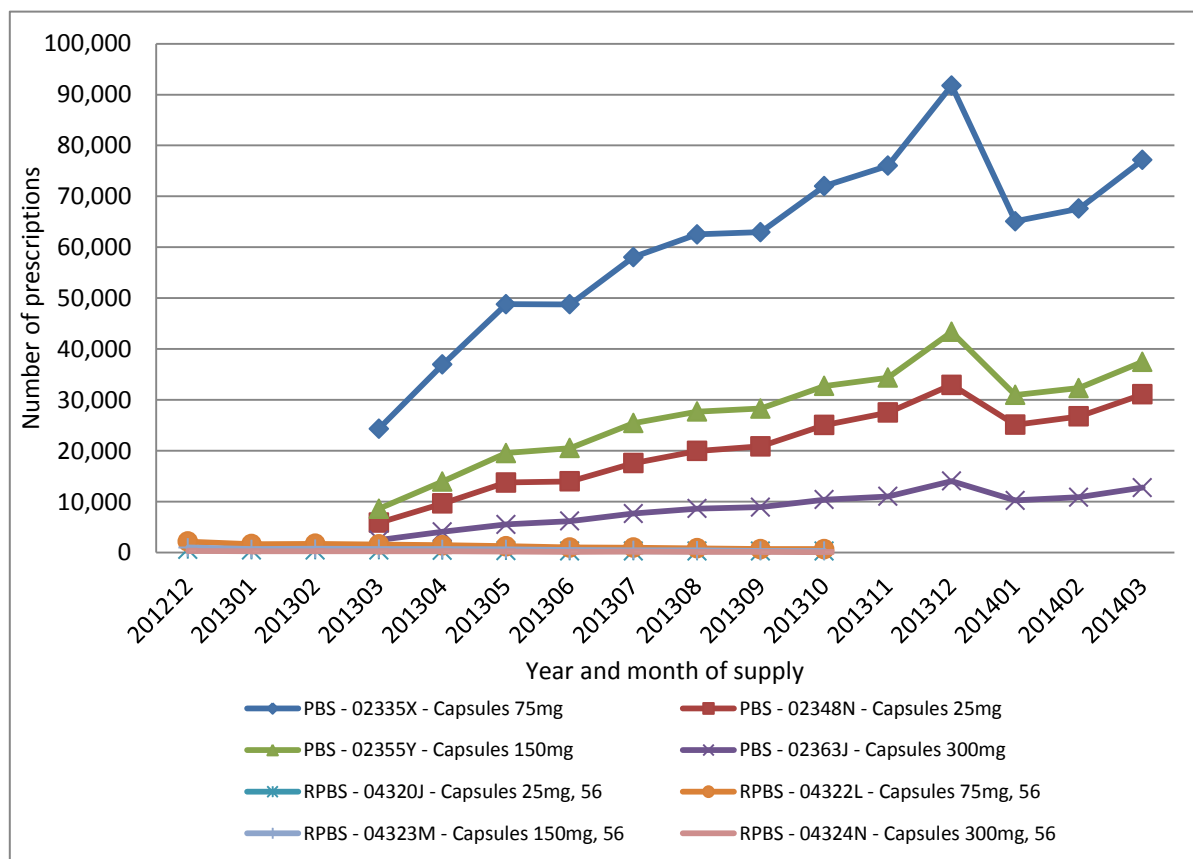


Figure 2: Number of PBS and RPBS prescriptions of pregabalin by strength, year and month of supply, March 2012 to March 2014

The proportions of pregabalin by strength supplied appear consistent over the first year of listing. Patients initiating PBS subsidised pregabalin in year 1 will be a mix of patients including those moving from pregabalin supplied via the private market, dose titration in patients new to treatment, add-on therapy, re-initiators and switching from other medicines used to treat neuropathic pain (PBS or non-PBS subsidised). The data in Figure 2 also includes continuing patients. Two snapshots were taken of pregabalin strengths supplied to explore whether the proportions of strengths varied over the period, possibly reflecting a changing mix of patients. The proportions of prescriptions by strength are shown in Table 3 below, with the early snapshot of three months post listing (June 2013) and seven months post listing (October 2013). October 2013 was taken as the second snapshot, as the RPBS items were deleted on 1 November 2013. The snapshots confirmed that the proportions of prescriptions for pregabalin by strength were fairly stable over the time period.

Table 3: Percentages of strengths of pregabalin supplied

Month of supply	pregabalin 25 mg (%)	pregabalin 75 mg (%)	pregabalin 150 mg (%)	pregabalin 300 mg (%)	Total
March 2013 to February 2014 total PBS	239,255 (17.4 %)	714,940 (52.1 %)	318,019 (23.2 %)	100,250 (7.3 %)	1,372,464
June 2013 total (PBS/RPBS)	14,315 (15.6 %)	49,794 (54.4 %)	21,036 (23 %)	6,387 (7 %)	91,532
June 2013 PBS	13,993 (15.63 %)	48,771 (54.49 %)	20,533 (22.94 %)	6,210 (6.94 %)	89,507
June 2013 RPBS	322 (15.9 %)	1023 (50.5 %)	503 (24.8 %)	177 (8.7 %)	2025
October 2013 total (PBS/RPBS)	25,350 (17.9 %)	72,751 (51.3 %)	33,109 (23.4 %)	10,545 (7.4 %)	141,755
October 2013 PBS	25,065 (17.9 %)	72,035 (51.3 %)	32,757 (23.4 %)	10,427 (7.4 %)	140,284
October 2013 RPBS	285 (19.4 %)	716 (48.7 %)	352 (23.9 %)	118 (8 %)	1,471

Prescriptions by patient category

Figure 3 shows the number of prescriptions by patient category.

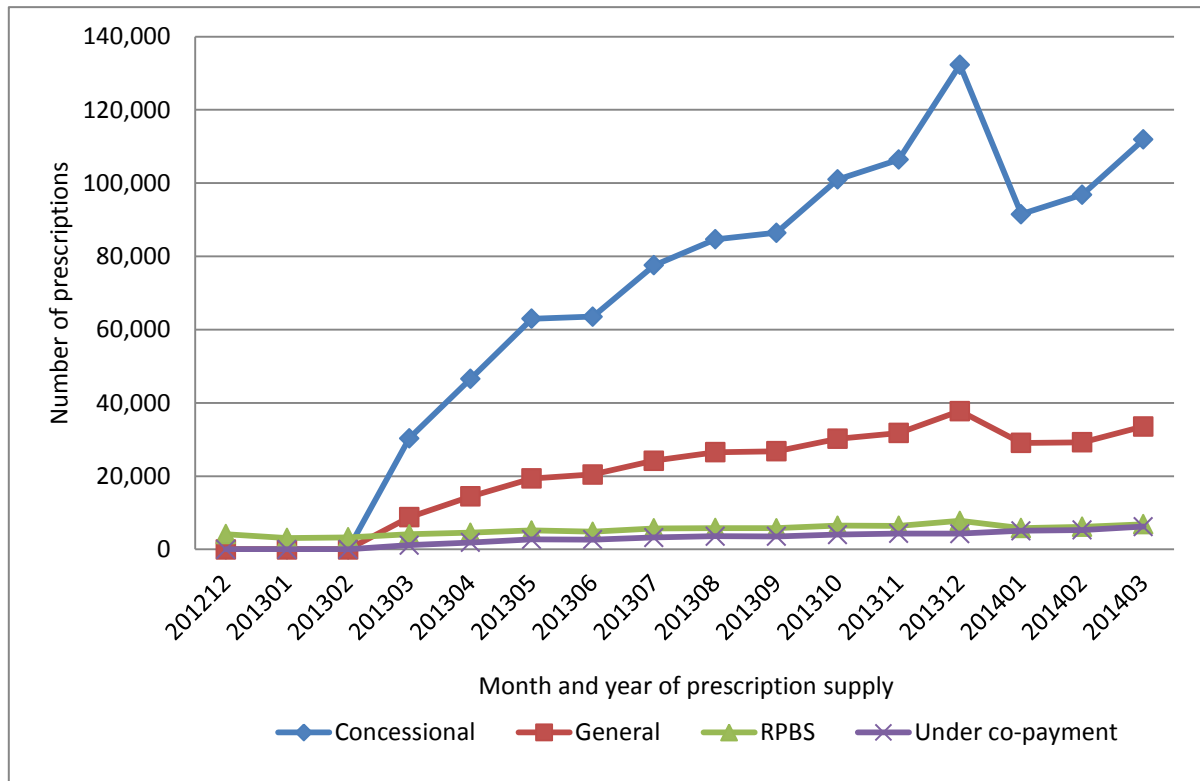


Figure 3: Number of prescriptions by patient category, December 2012 to March 2014

Over the first year of PBS listing of pregabalin 70.5 % of prescriptions were concessional benefits, 21.5 % were general benefits, 5 % were RPBS and 3 % were under the patient co-payment. Only the 25 mg capsules are priced under the general patient co-payment.

Patient count

The number of patients initiating pregabalin in the first year of listing from 1 March 2013 to the end of February 2014 is shown in Figure 4. RPBS patients are also shown until the deletion of the RPBS items in November 2013.

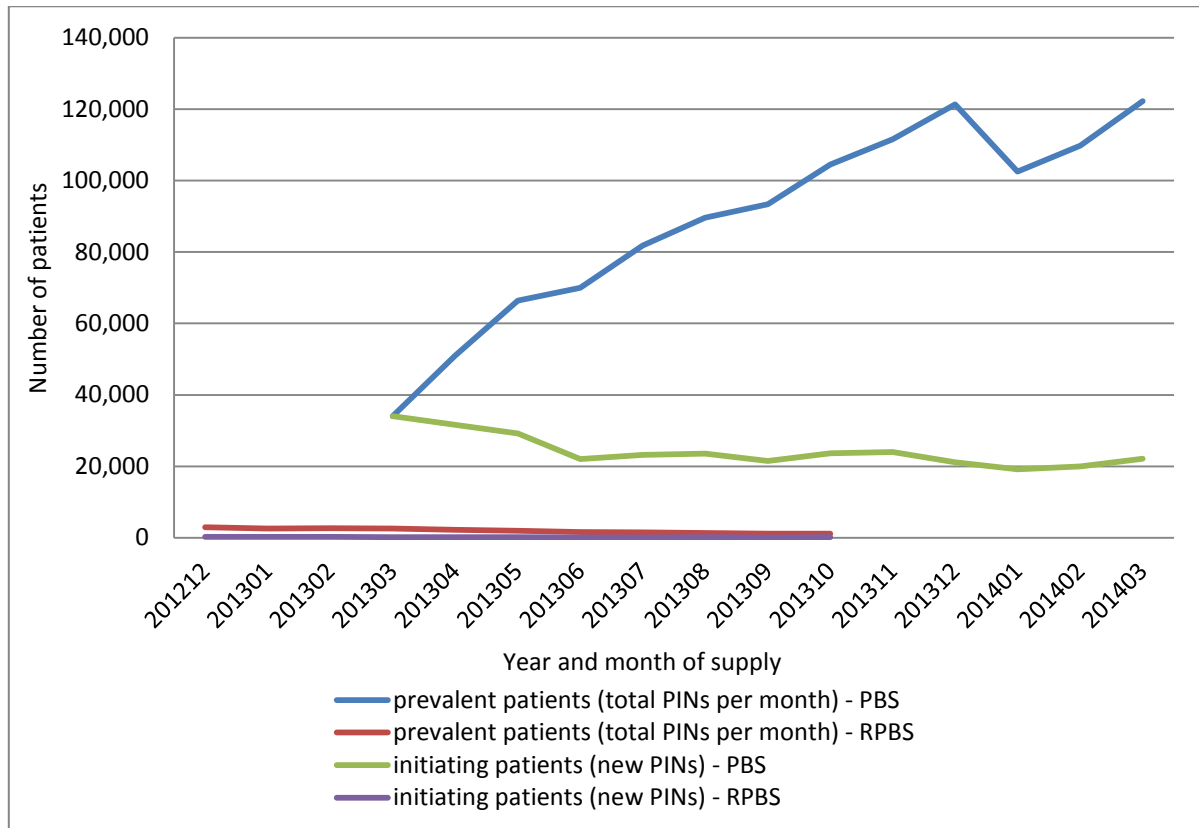


Figure 4: Number of patients initiating pregabalin in the first year of listing, March 2013 to end February 2014

PIN = patient identification number

In the first twelve months of PBS listing 294,274 PBS/RPBS patients (293,265 PBS) received at least one prescription for pregabalin. There were around 30-34,000 initiators in each of the first three months of listing, reducing to around 22-24,000 in each of the next six months.

Changes in the use of other medicines for neuropathic pain

The Neurology Therapeutic Guidelines (TG)⁴ note that neuropathic pain is usually refractory to simple analgesics, including non-steroidal anti-inflammatory drugs and treatment usually requires the use of analgesic adjuvants such as tricyclic antidepressants (TCAs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and antiepileptic drugs. The TG note that the choice of analgesic adjuvant is largely dependent on consideration of efficacy, adverse effects and cost. Other indications (e.g. need for sedation) or contraindications (e.g. prostatism, cognitive impairment) may also influence the choice of drug. Amitriptyline, gabapentin, duloxetine or pregabalin are recommended by the TG as analgesic adjuvants for neuropathic pain.

The total prescription numbers for amitriptyline (unrestricted PBS listing), gabapentin (Authority required streamlined PBS listing for partial epileptic seizures), duloxetine (restricted benefit PBS listing for major depressive disorders) and carbamazepine (unrestricted PBS listing) for Q1 2012 through to Q1 2014 are shown in Figure 5. This data is provided to investigate if the listing of pregabalin has had an effect on the prescription volumes for these agents. Carbamazepine is included as the submission estimated a proportion of switching from carbamazepine to pregabalin and an associated cost off-set. The submission also predicted substitution of pregabalin for amitriptyline and gabapentin. The submission did not include cost offsets for switching from duloxetine to pregabalin.

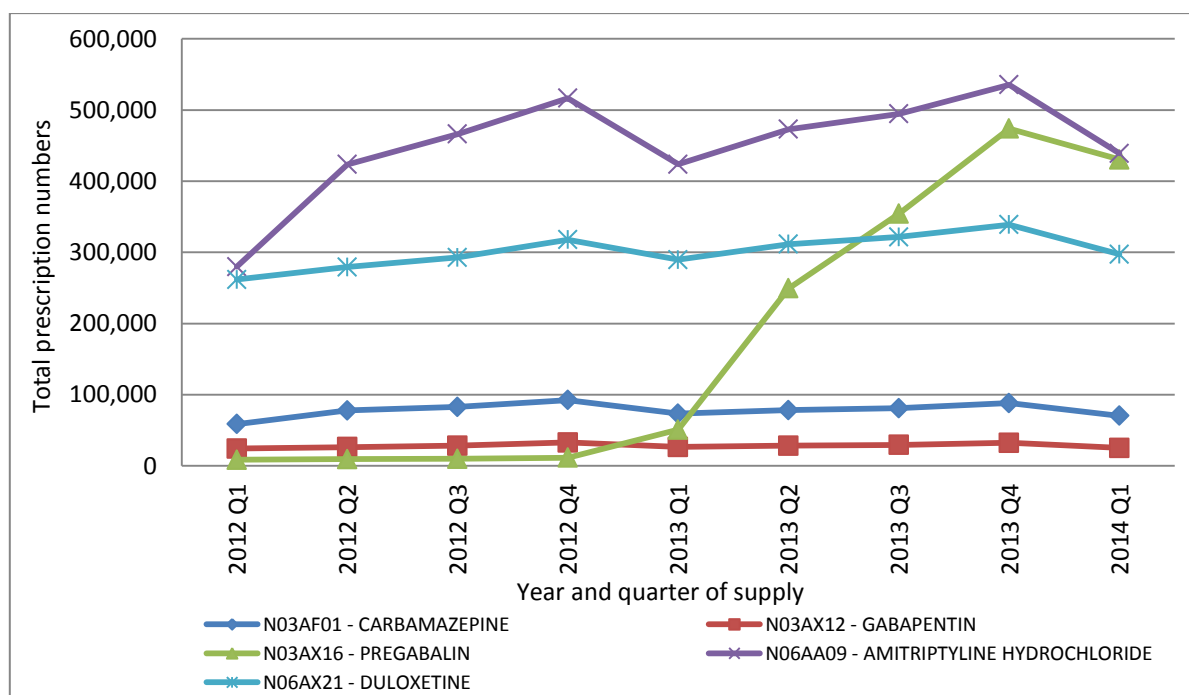


Figure 5: Total PBS/ RPBS prescription numbers by year and quarter for pregabalin, amitriptyline, gabapentin, duloxetine and carbamazepine, Q1 2012 to Q1 2014.

*Under co-payment data included from 1 April 2012.

⁴ Neuropathic Pain [revised 2011 June]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2014 Mar. Accessed 2014 Aug 14 <<http://online.tg.org.au/complete/desktop/index.htm>>.

The PBS/RPBS prescriptions supplied for amitriptyline, gabapentin, carbamazepine and duloxetine appear largely unchanged by the listing of pregabalin.

Analysis of expenditure

The PBS/ RPBS expenditure in the first twelve months of listing was \$60.7 million. Figure 6 illustrates PBS/RPBS expenditure per month from March 2012 (one year before listing) to March 2014 (most current data available). The expenditure prior to the 1 March 2013 listing date is for pregabalin supplied through the RPBS.

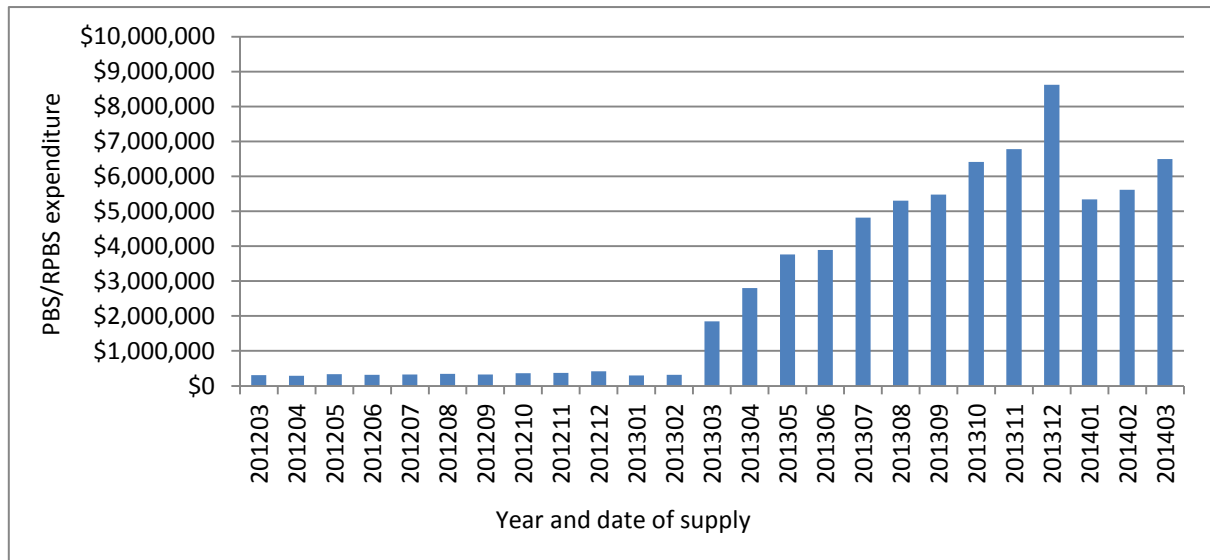


Figure 6: PBS/RPBS Expenditure by year and date of supply, March 2012 to March 2014

Analysis of actual versus predicted utilisation

The submission's estimated extent of use and the actual utilisation for pregabalin are compared in Table 4.

Table 4: Predicted and actual extent of use of pregabalin

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated number of patients	211,620	274,132	286,297	318,896	350,346
Actual number of patients	294,274	N/A	N/A	N/A	N/A
Estimated number of packs per year	1,381,724	1,847,128	1,977,004	2,201,051	2,421,029
Actual number of prescriptions per year	1,389,678	N/A	N/A	N/A	N/A

The number of prescriptions for pregabalin in the first twelve months of PBS listing was similar to predicted, however the data indicates that utilisation is yet to stabilise and that prescription numbers are increasing.

In the first twelve months of listing 294,274 patients were supplied with at least one prescription for pregabalin through the PBS. It was estimated that 211,620 patients in year 1 rising to 274,132 in year 2 would be treated with pregabalin. The number of patients starting treatment with PBS subsidised pregabalin in the first year of listing was higher than that estimated in the submission, however it is unclear at this time point if patients are continuing on treatment with pregabalin, and if so for how long, and if pregabalin is being used intermittently. The DUSC noted that the sponsor of pregabalin suggested that the persistence rate for continuation on therapy was high, based on a 10 % sample of PBS data.

The most commonly supplied strength of pregabalin is 75 mg (around half of all prescriptions), and the second most commonly prescribed strength is 150 mg. The submission concluded that the mean total daily dose of pregabalin used in Australia in practice is 225 mg. Analysis was not undertaken to determine if patients were supplied multiple strengths of pregabalin, nor which combination of strengths. This type of analysis is better undertaken when a longer period of data is available. The proportions of pregabalin supplied by strength appear fairly consistent over the first year of listing.

The PBS/RPBS prescription volumes for amitriptyline, gabapentin, carbamazepine and duloxetine appear largely unchanged by the listing of pregabalin. The DUSC suggested that this could indicate that there is co-administration of pregabalin with these agents rather than switching. The DUSC considered that pregabalin is also likely to be used in combination with opioids in the treatment of neuropathic pain and that data investigating

co-prescribing with opioids would also be informative to include in the 24 month review of pregabalin.

DUSC actions

- The DUSC considered that a subsequent analysis of pregabalin should be undertaken when there is 24 months of utilisation data available. The DUSC requested that the 24 month analysis include data on co-prescription with other medicines including amitriptyline, gabapentin, opioids and anti-epileptics, age, average dose, dose escalation (including the combination of strengths of pregabalin supplied), and persistence.
- The DUSC referred the report to the PBAC for information.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsor's comment

Pfizer Australia Pty Ltd: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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