

Pregabalin: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

October 2015

Abstract

Purpose

To examine the utilisation of pregabalin for neuropathic pain in the 24 months after PBS listing (1 March 2013 to 28 February 2015).

Data Source / methodology

Data for pregabalin was extracted from the DUSC and Department of Human Services (DHS) prescription databases from the date of listing of pregabalin on the Repatriation PBS (RPBS) Schedule (1 February 2008) to the most current available data (March 2015, inclusive).

Key Findings

- There were 294,747 and 433,324 PBS/RPBS patients treated with PBS subsidised pregabalin in the first two years of listing respectively. This was 39% and 58% higher than predicted. The number of actual patients in Year 2 exceeds the number of patients predicted for Year 5.
- The total number of prescriptions of pregabalin supplied in Year 1 (1,396,766) was similar to predicted, however utilisation in Year 2 (2,435,807 prescriptions) was 32% more than predicted.
- The greater than predicted number of patients and prescriptions in Year 2 did not translate to significantly greater than predicted PBS & RPBS (R/PBS) expenditure because there was;
 - a higher than expected discontinuation rate after the first prescription leading to lower than expected prescriptions per patient; and
 - lower than expected R/PBS expenditure per prescription due to lower than expected average daily dose and higher than expected average patient copayment (due to higher than expected proportion of non-concessional patients).
- Prescribing of pregabalin in clinical practice may not be optimal. A large number of patients do not have the dose of pregabalin up-titrated and persistence to therapy is poor.

Purpose of analysis

To examine the utilisation of pregabalin for neuropathic pain in the 24 months after listing (1 March 2013 to 28 February 2015). At its October 2014 meeting the DUSC requested a 24 month analysis of pregabalin utilisation including data on estimated co-administration 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.

Background

Pharmacology

Pregabalin is used to treat neuropathic pain, which is pain caused by an abnormality of, or damage to, the nerves. Pregabalin is also used to control epilepsy and belongs to a group of medicines called anticonvulsants. These medicines are thought to work by controlling brain chemicals which send signals to nerves so that seizures do not happen.¹ Pregabalin is an analogue of the neurotransmitter gamma-aminobutyric acid (GABA). In vitro studies show that it 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

If pregabalin has to be discontinued, it is recommended to withdraw it gradually over a minimum of one week.

¹ Lyrica (Pregabalin) Australian Consumer Medicine Information. Sydney: Pfizer Australia. February 2014. Available from <<https://www.ebs.tga.gov.au/>>. Accessed 17 August 2015.

² Lyrica (Pregabalin) Australian Approved Product Information. Sydney: Pfizer Australia. April 2014. Available from <<https://www.ebs.tga.gov.au/>>. Accessed 17 August 2015.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information)

Clinical Guidelines for Treatment of Neuropathic Pain

The Neuropathic Pain section of the Electronic Therapeutic Guidelines (eTG)³ notes 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. Use of N-methyl-D-aspartate (NMDA)-receptor antagonists, local anaesthetics and clonidine generally requires input from a pain specialist. Most drugs are used orally, but local anaesthetics (eg lignocaine) and NMDA-receptor antagonists (eg ketamine) can be administered parenterally or topically.

The eTG notes 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 eTG as analgesic adjuvants for neuropathic pain.

It may be necessary to use drugs from more than one class concurrently (eg a TCA, an antiepileptic drug and an opioid), although the evidence for benefit of combination therapy is limited.

Neuropathic pain is less responsive to opioids than nociceptive pain, so higher doses are generally required and adverse effects are more likely to be bothersome. This, together with the potential for addiction, make opioids a less attractive option than adjuvant analgesics.

PBS listing details as at 1 July 2015

The PBS listing details for pregabalin as at 1 July 2015 are shown in Table 1.

3 Neuropathic Pain [revised 2011 June]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; Accessed July 2015 <<http://online.tg.org.au/complete/desktop/index.htm>>.

Table 1: PBS listing of pregabalin

| Item | Name, form & strength, pack size | Max. quant. | Repeat s | DPMQ | Brand name and manufacturer |
|-------|----------------------------------|-------------|----------|---------|-----------------------------------|
| 2348N | Pregabalin 25 mg capsule, 56 | 56 | 5 | \$27.53 | Lyrica®, Pfizer Australia Pty Ltd |
| 2335X | Pregabalin 75 mg capsule, 56 | 56 | 5 | \$48.27 | Lyrica®, Pfizer Australia Pty Ltd |
| 2355Y | Pregabalin 150 mg capsule, 56 | 56 | 5 | \$68.48 | Lyrica®, Pfizer Australia Pty Ltd |
| 2363J | Pregabalin 300 mg capsule, 56 | 56 | 5 | \$97.05 | 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 consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

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)).

A drug audit survey included in the March 2012 submission found that the dose distribution of pregabalin (as part of combination therapy) was: 20.0% of patients taking total daily dosages of 75mg, 44.2% were taking 150mg, 17.5% were taking 300 mg and 12.5% were taking 600mg . The remaining 5.8% were taking total daily doses of 25, 50 or 450mg. The mean total daily dose was 224.6 mg, the median dose was 150 mg and the range was 25-600 mg.

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 differences. 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 combined PBS and RPBS (R/PBS) prescriptions of amitriptyline, gabapentin and carbamazepine of 112,255, 9,824 and 9,112 respectively was predicted.

Previous reviews by DUSC

Prior to the listing of pregabalin there were no medicines listed on the PBS schedule specifically for neuropathic pain. Gabapentin has been listed on the RPBS schedule (ie. for DVA patients only) since 1 August 2002 for treatment of refractory neuropathic pain not controlled by other drugs. 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.

A 12 month review was considered at the October 2014 DUSC meeting. DUSC noted that⁴;

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.

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 estimated co-administration 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.

For details of the DUSC consideration of the 12 month review of pregabalin refer to the Public Release Document from the October 2014 DUSC meeting.

⁴ DUSC Utilisation Analysis Public Release Documents, Pregabalin: 12 month predicted versus actual analysis, October 2014, <<http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/pregabalin-10-2014/>>

Methods

Data for pregabalin was extracted from the DUSC and Department of Human Services (DHS) prescription databases from the date of listing of pregabalin on the Repatriation PBS (RPBS) Schedule (1 February 2008) to the most current available data (March 2015, inclusive). Data was extracted for both the PBS and RPBS pregabalin items. The PBS items were listed on 1 March 2013 and the RPBS items were deleted from the Schedule on 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.

For the purpose of counting patients and performing other patient level analyses, PBS & RPBS (R/PBS) prescription data were extracted from the Department of Human Services (DHS) Prescription database for scripts supplied from February 2008.

The number of prevalent patients was determined by counting the number of people supplied at least one PBS prescription using person specific numbers (non-identifying) in the data for the specified time periods.

Patient initiation date was defined as the date of supply of the first PBS or RPBS prescription of pregabalin.

Data analysis was undertaken using SAS.

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).⁵

Estimated patient drug regimen analysis

The analysis was undertaken for patients who initiated treatment with pregabalin in the six month period March to August 2014 (inclusive). This cohort of patients was chosen because it shows the most recent patterns of use (more recent initiators would not have sufficient follow-up data). Also patients in this cohort initiated more than 12 months after the PBS listing of pregabalin, so the analysis is unlikely to be confounded by patients that have been grandfathered from private prescriptions.

Each patient's PBS prescription history was extracted for the period from March 2013 to March 2015 (inclusive) giving least 12 months pre-initiation and 7 months post-initiation

⁵ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

prescription history. The prescription history was filtered to contain medicines in the following ATC groups;

- M = Musculo-skeletal system
- N = Nervous system
- R05DA = Opium alkaloids and derivatives (e.g. codeine)
- C02AC01 = clonidine

A preliminary drug regimen analysis showed that there were a large number of different drugs supplied, resulting in a very large number of distinct drug regimens and regimen transitions around initiation to pregabalin. To reduce the number of distinct drug regimens, the drugs were grouped into the following drug groups;

Table 3: Drug groups used in drug regimen analysis

| Drug Group | ATC code | Drug name | |
|--------------------|-----------|---------------------|---------------------|
| Paracetamol, plain | N02BE01 | PARACETAMOL | |
| NSAID | M01AC06 | MELOXICAM | |
| | M01AH01 | CELECOXIB | |
| | M01AB05 | DICLOFENAC | |
| | M01AE02 | NAPROXEN | |
| | M01AE01 | IBUPROFEN | |
| | M01AB01 | INDOMETHACIN | |
| | M01AC01 | PIROXICAM | |
| | M01AE03 | KETOPROFEN | |
| | M01AG01 | MEFENAMIC_ACID | |
| | M01AE11 | TIAPROFENIC_ACID | |
| Pregabalin | N02BG | PREGABALIN | |
| Anticonvulsant | N03AG01 | VALPROATE | |
| | N03AF01 | CARBAMAZEPINE | |
| | N03AX11 | TOPIRAMATE | |
| | N03AX12 | GABAPENTIN | |
| | N03AX14 | LEVETIRACETAM | |
| | N03AX09 | LAMOTRIGINE | |
| | N03AB02 | PHENYTOIN | |
| | N03AE01 | CLONAZEPAM | |
| | N02BG | GABAPENTIN | |
| | N03AA03 | PRIMIDONE | |
| | N03AX18 | LACOSAMIDE | |
| | N03AF02 | OXCARBAZEPINE | |
| | N03AA02 | PHENOBARBITONE | |
| | N03AG04 | VIGABATRIN | |
| | N03AX15 | ZONISAMIDE | |
| | N03AG06 | TIAGABINE | |
| | N03AX03 | SULTHIAME | |
| | N03AX22 | PERAMPANEL | |
| | Tramadol | N02AX02 | TRAMADOL |
| | Opioid S4 | N02AA59 | PARACETAMOL_CODEINE |
| R05DA04 | | CODEINE | |
| N02BE51 | | PARACETAMOL_CODEINE | |
| N02AA | | CODEINE | |
| N02BA51 | | ASPIRIN_CODEINE | |

| | | |
|--------------------------------|-----------|--------------------|
| Opioid S8 | N02AA05 | OXYCODONE |
| | N02AE01 | BUPRENORPHINE |
| | N02AA55 | OXYCODONE_NALOXONE |
| | N02AB03 | FENTANYL |
| | N02AA01 | MORPHINE |
| | N02AA03 | HYDROMORPHONE |
| | N02AC | METHADONE |
| | N02AX06 | TAPENTADOL |
| | N02AC04 | DEXTROPROPOXYPHENE |
| | SNRI | N06AX21 |
| N06AX16 | | VENLAFAXINE |
| N06AX23 | | DESVENLAFAXINE |
| TCA (Tricyclic antidepressant) | N06AA09 | AMITRIPTYLINE |
| | N06AA16 | DOTHIEPIN |
| | N06AA12 | DOXEPIN |
| | N06AA10 | NORTRIPTYLINE |
| | N06AA02 | IMIPRAMINE |
| | N06AA04 | CLOMIPRAMINE |
| Other antidepressant | N06AB06 | SERTRALINE |
| | N06AX11 | MIRTAZAPINE |
| | N06AB10 | ESCITALOPRAM |
| | N06AB04 | CITALOPRAM |
| | N06AB03 | FLUOXETINE |
| | N06AB05 | PAROXETINE |
| | N06AB08 | FLUVOXAMINE |
| | N06AX18 | REBOXETINE |
| | N06AX03 | MIANSERIN |
| | N06AF04 | TRANLYCYPROMINE |
| | N06AF03 | PHENELZINE |
| | Clonidine | C02AC01 |

Drugs not in the above list were excluded from the drug regimen analysis. The drug groups in this list were chosen on the basis of the drug groups mentioned in the eTG⁶ and the more recent article “Neuropathic pain, A management update”⁷.

A preliminary analysis using these drug groups showed that paracetamol (plain) and NSAIDs were commonly part of patient drug regimens both pre and post initiation to pregabalin. However, as these drugs are also available over-the-counter (OTC), the number of patients with drug regimens that actually contained these drugs could be severely underestimated by this analysis of PBS prescription data. Thus it was decided to exclude these two drug groups from the analysis.

RPBS patients (defined as those who had one or more RPBS scripts in the period 12 months pre-initiation and 7 months post initiation) were identified in the six month cohort and were able to be analysed separately.

⁶ Neuropathic Pain [revised 2011 June]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; Accessed July 2015 <<http://online.tg.org.au/complete/desktop/index.htm>>.

⁷ Votrubic M, Thong I. Neuropathic pain—a management update. Aust Fam Physician. 2013;42:92–7 <<http://www.racgp.org.au/download/Documents/AFP/2013/March/201303votrubic.pdf>>

For more details see Appendix B: Detailed methodology to estimate drug regimens and regimen transitions.

Strength Sequence and Timing Analysis

To investigate dose, dose titration and persistence to therapy in the first few months, the strength sequence and timing of the first few scripts after initiation of pregabalin was analysed. It was decided to limit the analysis to only the first three prescriptions as more than this would generate too many sequence paths to present. There are 4 different strengths of pregabalin plus a category of "None" (for patients that discontinue before the 3rd script) which generated approximately $4 \times 5 \times 5 = 100$ different sequence paths for three scripts. An analysis of 4 scripts would have generated 500 sequence paths, too many to present. This analysis was performed for the cohort that initiated in the 3rd six month period after listing (ie. March to August 2014). This means that each patient had at least 7 months of follow-up to be supplied the three scripts. This is the cohort that was used for the estimated patient drug regimen analysis cohort and was chosen for similar reasons. That is, it shows the most recent patterns of use (more recent initiators would not have sufficient follow-up data) and this cohort initiated more than 12 months after the PBS listing of pregabalin, so the analysis is unlikely to be confounded by patients that have been grandfathered from private prescriptions. The median days between supplies of scripts were calculated. Scripts supplied on the same day were excluded from this calculation.

Estimated daily dose

As the prescribed dose is not available in the PBS dataset, it was estimated using the pregabalin treatment episodes generated as part of the estimated drug regimen analysis.

This method involves the following steps;

- discerning episodes of pregabalin treatment by detecting breaks in treatment;
- calculating the length of each episode of treatment;
- determining of the mass of drug supplied in the episode, across all strengths;
- calculate average dose per day across the episode = mass of drug / length of episode

The estimated daily dose for each patient episode was then summarised as a distribution, mean and weighted mean. This was done for three patient cohorts, that is, those who initiated in the 1st, 2nd and 3rd six month periods after listing of pregabalin (ie. March 2013).

Prescriber Type analysis

The prescriber type was determined from the Major Specialty field in the DHS prescription database.

Results

Analysis of drug utilisation

Patient count

The number of patients dispensed their first pregabalin PBS or RPBS item script from 1 February 2008 to March 2015 (inclusive) was determined. Figure 1 shows these results from December 2012. Monthly prevalent patients (ie. patients dispensed one or more scripts in a month) are also shown. Monthly prevalence based of prescription supply data is a slight underestimate of the prevalence of patients on pregabalin as not all patients will receive a supply in a month.

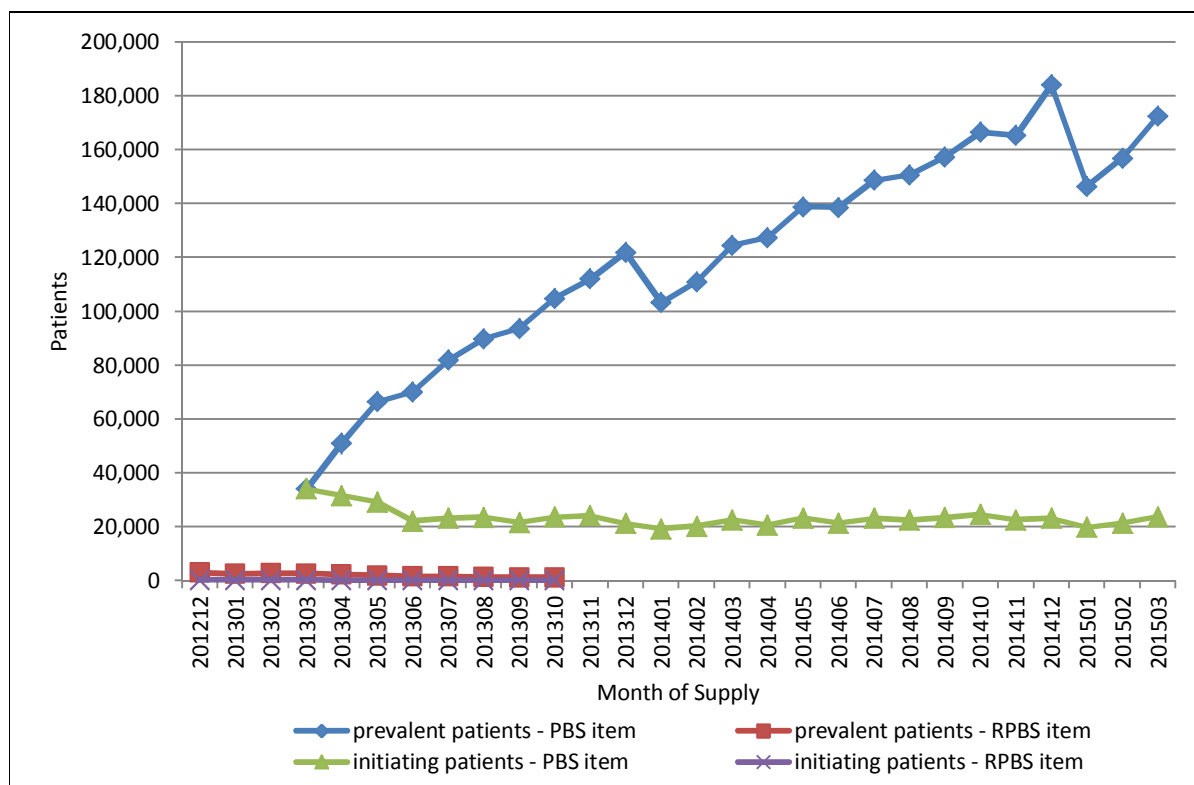


Figure 1: Initiating and prevalent pregabalin patients by item type (ie. PBS/RPBS)

The number of prevalent patients is continuing to trend upwards, while the number of initiating patients is stable at slightly over 20,000 per month.

Prescriptions

Figure 2 shows the total number of prescriptions supplied by script type and month of supply from March 2012 to March 2015.

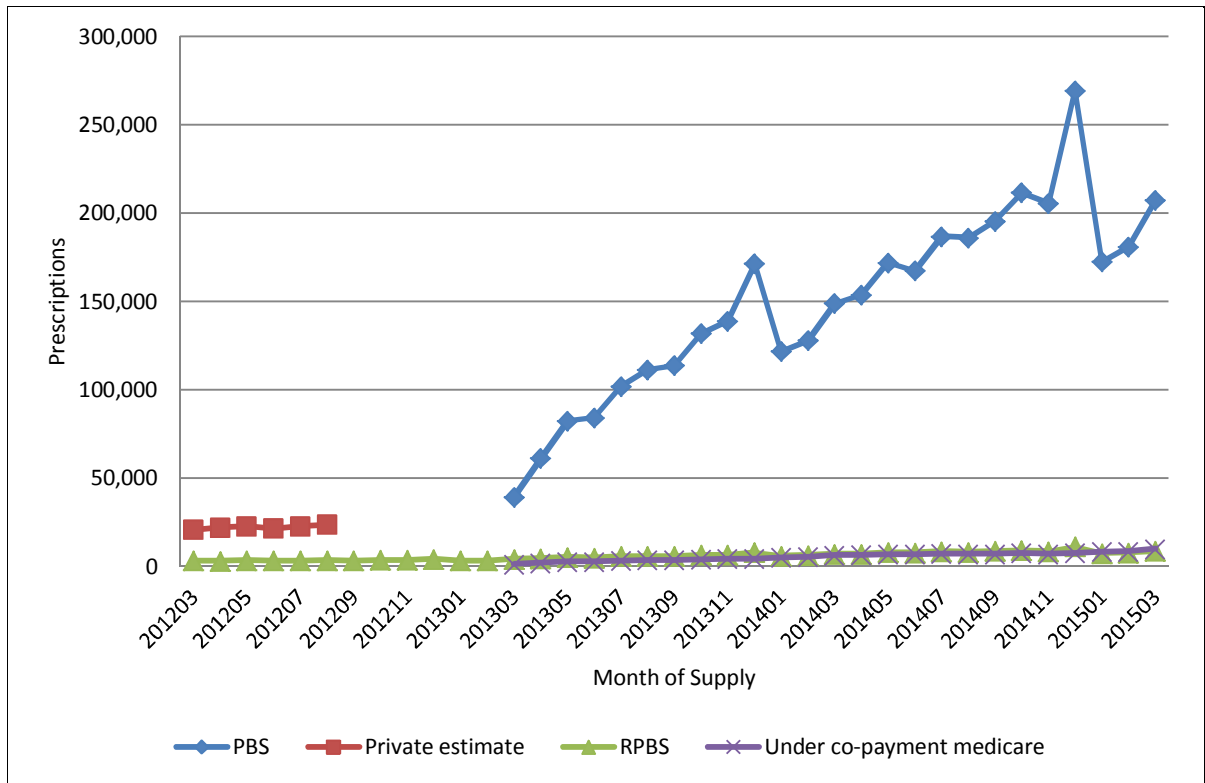


Figure 2: Number of prescriptions for pregabalin by month of supply

Prescription numbers have continued to increase rapidly in the second year of listing.

Prescriptions by strength

Figure 3 shows the total number of prescriptions per month by strength.

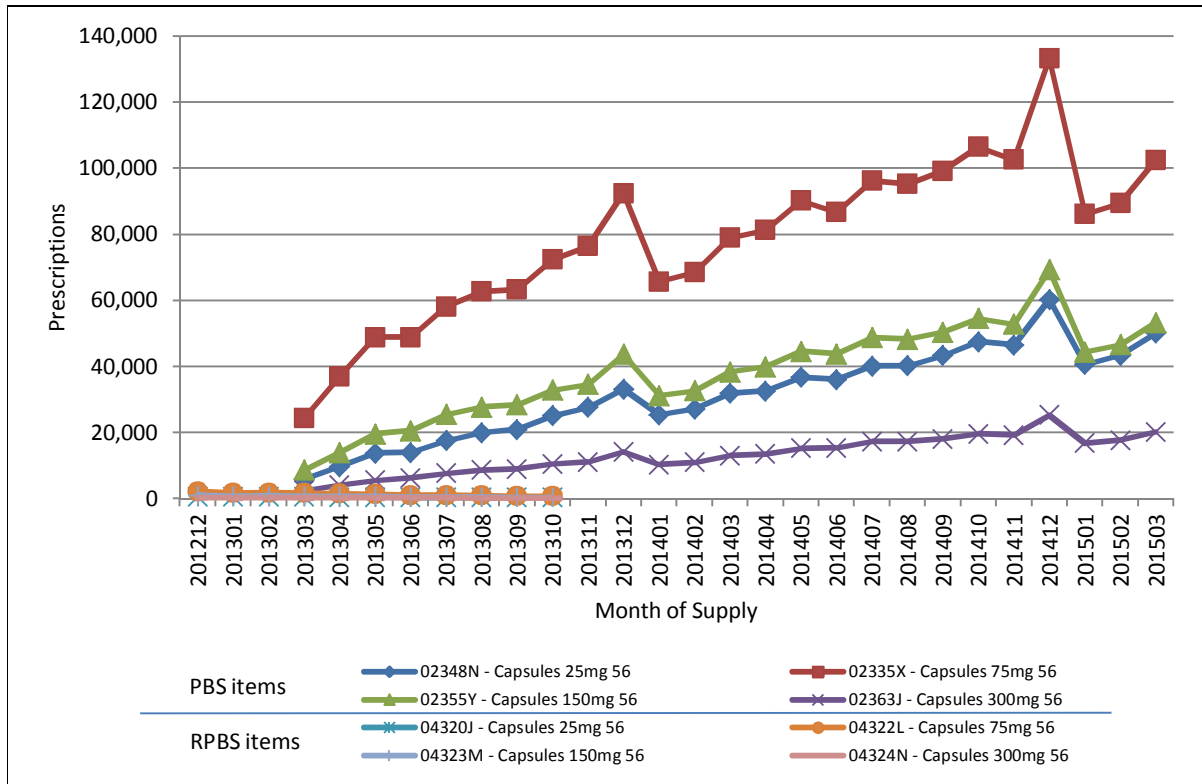


Figure 3: Prescriptions of pregabalin by strength

Note: The number 56 in the legend text refers to the number of capsules per pack

The most common strength is the 75 mg PBS item which accounted for 48% of prescriptions supplied in the two years since PBS listing.

The percentage distribution of strengths supplied is shown in Figure 4.

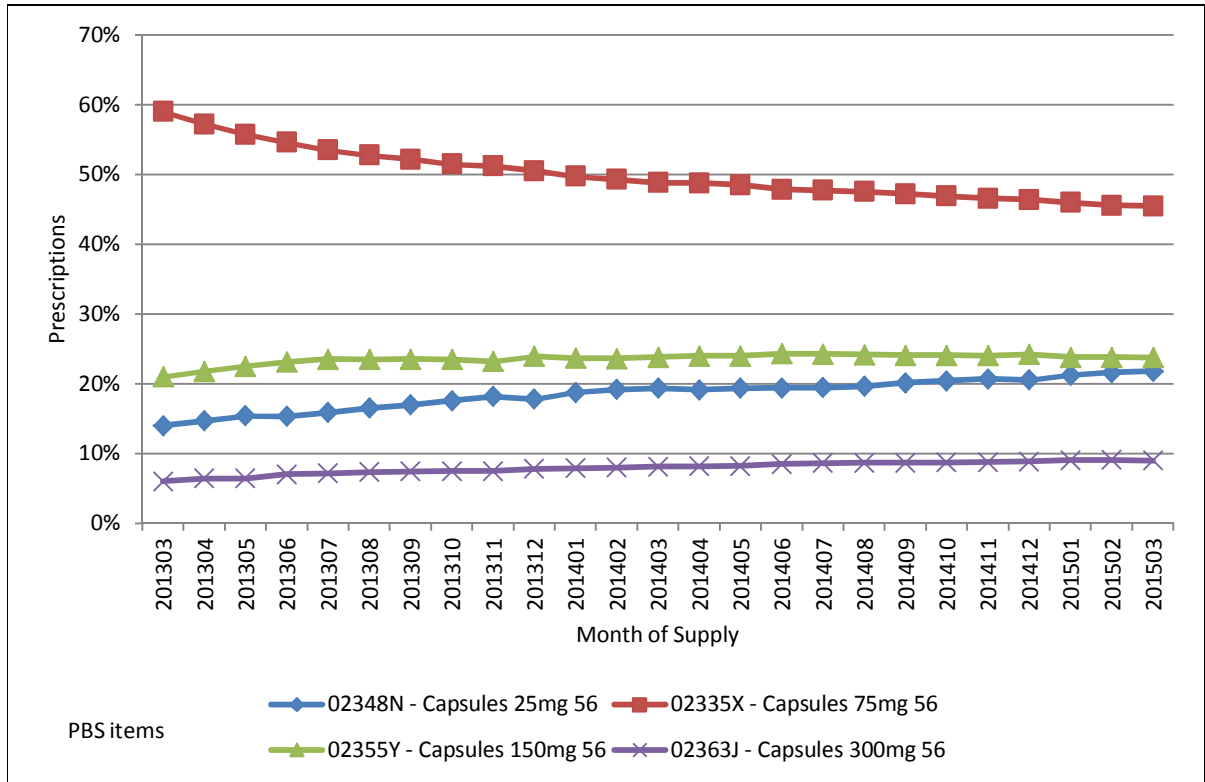


Figure 4: Distribution of prescriptions of pregabalin by strength

Note: RPBS items are not shown as they are low volume and were delisted at the end of October 2013.

Figure 4 shows a decreasing proportion of the 75mg strength (down to 45.4% in March 2015), an increasing proportion of the 25 and 300 mg strengths and the proportion of the 150mg strength is approximately flat.

At the October 2014 meeting DUSC considered that the 24 month review of pregabalin could include an analysis of the combination of strengths of pregabalin supplied. Figure 5 indicates that few patients are supplied multiple strengths of pregabalin at the same time.

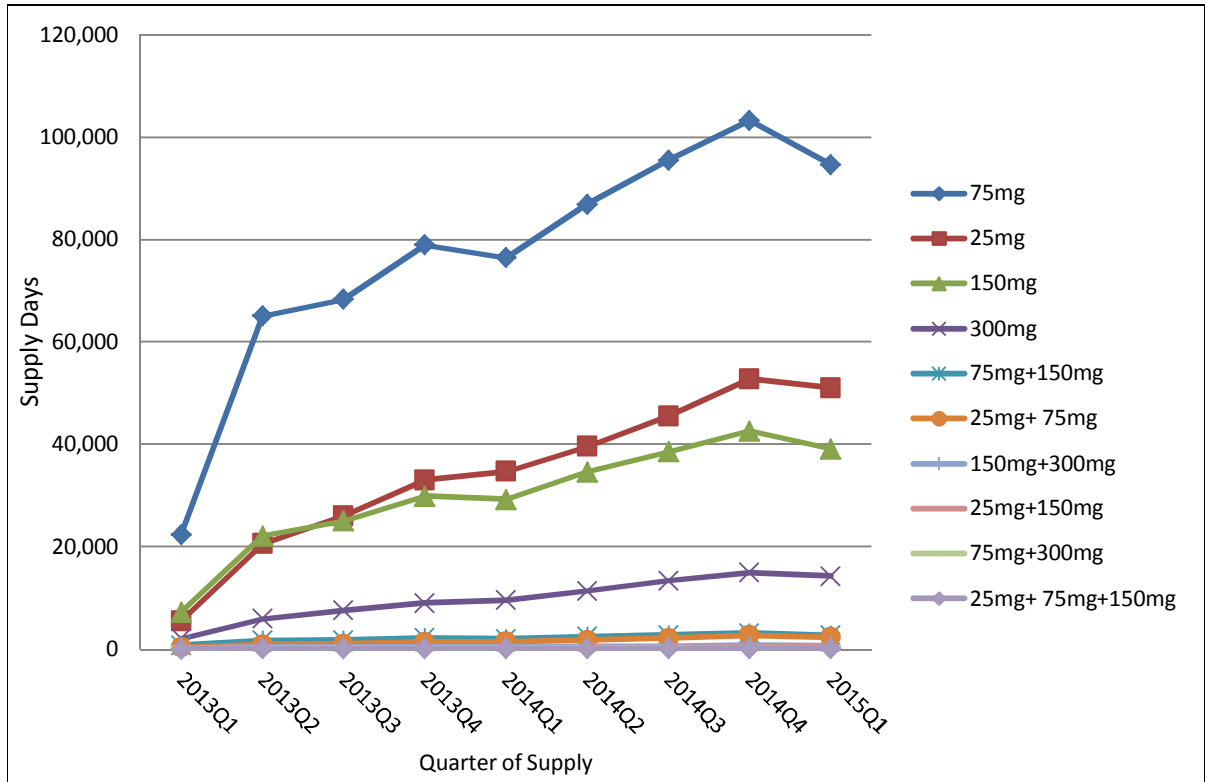


Figure 5: Strengths of pregabalin supplied on original prescriptions on the same day

Note: only the top ten strength combinations are shown

Figure 5 shows that there are relatively few instances of supply of the two or more strengths of pregabalin from original prescriptions on the same day. Only 3.0% percent of supply days in 2015 Q1 had instances of a combination of strengths supplied. This is probably because as patients up titrate, they are more likely to need a single strength to achieve the higher dose, not a combination of strengths.

Analyses of prescription strength sequence and estimated daily dose are presented later in this report.

Analysis of actual versus predicted utilisation

Table 4 compares the predicted and actual use of pregabalin in each of the first 2 years of listing.

Table 4: Predicted vs Actual utilisation

| | | Year1 | Year 2 |
|------------------------------------|----------------------|----------------|----------------|
| | | Mar13 to Feb14 | Mar14 to Feb15 |
| Patients | Predicted (P) | 211,620 | 274,132 |
| | Actual (A) | 294,747 | 433,324 |
| | % Difference (A-P)/P | +39% | +58% |
| Prescriptions | Predicted (P) | 1,381,724 | 1,847,128 |
| | Actual (A) | 1,396,766 | 2,435,807 |
| | % Difference (A-P)/P | +1% | +32% |
| Scripts per patient | Predicted (P) | 6.53 | 6.74 |
| | Actual (A) | 4.74 | 5.62 |
| | % Difference (A-P)/P | -27% | -17% |
| R/PBS expenditure | Predicted (P) | \$ ██████████ | \$ ██████████ |
| | Actual (A) | \$ 60,970,537 | \$ 106,374,363 |
| | % Difference (A-P)/P | ██████% | ██████% |
| Mean R/PBS expenditure per script | Predicted (P) | \$ █████ | \$ █████ |
| | Actual (A) | \$44 | \$44 |
| | % Difference (A-P)/P | ██████% | ██████% |
| Mean R/PBS expenditure per patient | Predicted (P) | \$ █████ | \$ █████ |
| | Actual (A) | \$207 | \$245 |
| | % Difference (A-P)/P | ██████% | ██████% |

The number of patients supplied pregabalin was 39% and 58% higher than expected in Year 1 and 2 respectively. However this only translated to prescriptions being 1% and 32% higher than expected in Year 1 and 2 respectively. This was because the mean scripts per patient were lower than expected (27% and 17% lower in Year 1 and 2 respectively).

Mean R/PBS expenditure per script was █████% and █████% lower than expected in Year 1 and 2 respectively. This could be due to;

- the actual dose being lower than predicted (this issue is investigated further in the dose analysis section below) and/or;
- the proportion of General (ie. non-concessional) scripts being higher than predicted. General scripts result in lower R/PBS expenditure because of a higher patient copayment.

The proportion of General scripts was 22.2% and 20.9% in Year 1 and 2 respectively. The submission assumed this proportion would be 10.9% based on the patient category distribution for gabapentin scripts from June 2011 to May 2012 (date of processing). This difference would have made the average copayment larger than expected and so contributed to the less than expected R/PBS expenditure per script.

Changes in the use of other medicines 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 2015 are shown in Figure 6. 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.

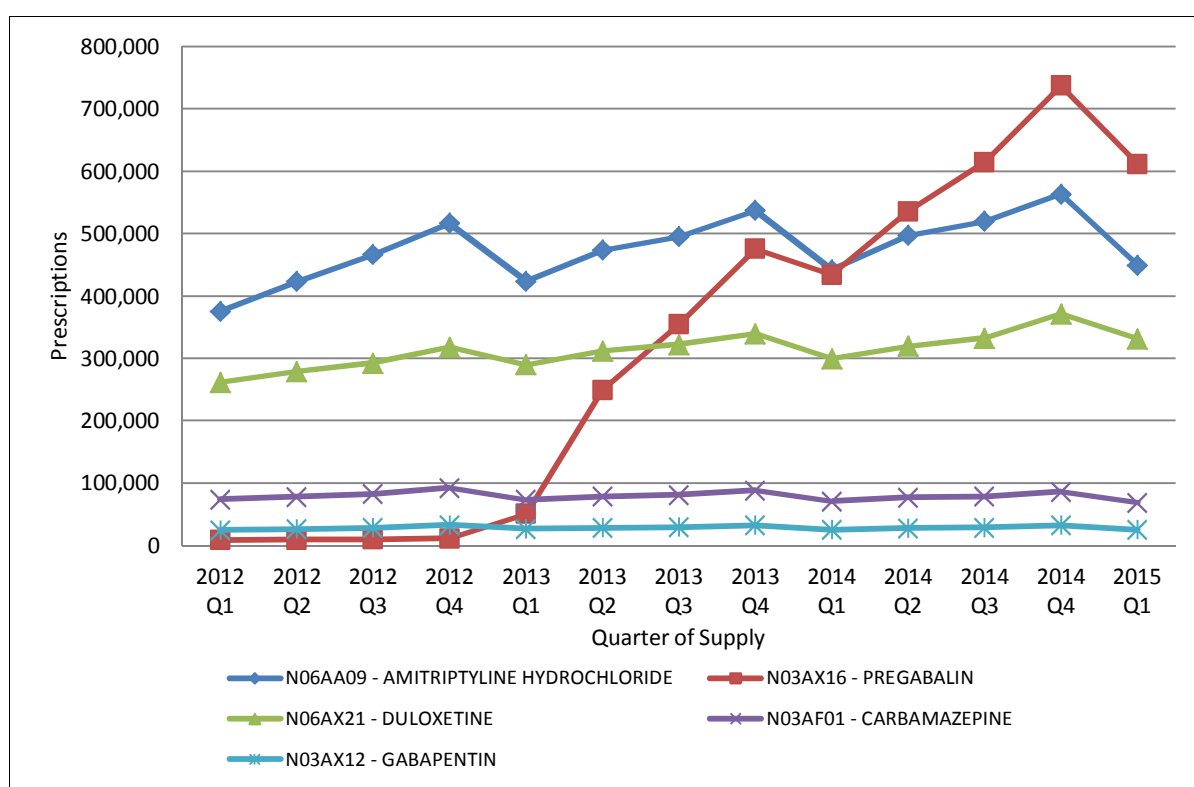


Figure 6: Prescriptions for pregabalin, amitriptyline, gabapentin, duloxetine and carbamazepine

The prescriptions supplied for amitriptyline, gabapentin, carbamazepine and duloxetine appear largely unchanged by the listing of pregabalin. The submission predicted a reduction of 112,255 prescriptions of amitriptyline in the first year of listing of pregabalin due to substitution. This magnitude of decline should be observable in Figure 6, but it does not appear to have happened. However as clinical guidelines recommend tricyclic antidepressants for neuropathic pain, and PBS eligibility for pregabalin requires patients to be refractory to treatment with other drugs, there is an ongoing role for amitriptyline in management of this condition.

Estimated Patient Drug Regimens and Regimen Transitions

The estimated patient drug regimen transitions at the point of initiation to pregabalin are shown in the table below. These are for patients who initiated pregabalin in the six month period March to August 2014 (inclusive). See the Methods section for more details regarding this analysis.

Table 5: Estimated drug regimen transitions at initiation to pregabalin

| Pre-initiation (week=-1) | Post-initiation (week=0) | Switch or Add? | Patients | % patients | Rank |
|--------------------------------|---|----------------|----------|------------|------|
| None | Pregabalin | Add | 50,076 | 37.5% | 1 |
| Opioid_S8 | Opioid_S8+Pregabalin | Add | 7,536 | 5.6% | 2 |
| Other_antidepressant | Other_antidepressant+Pregabalin | Add | 6,588 | 4.9% | 3 |
| Opioid_S4 | Opioid_S4+Pregabalin | Add | 3,969 | 3.0% | 4 |
| None | Opioid_S8+Pregabalin | Add | 3,881 | 2.9% | 5 |
| Opioid_S4 | Pregabalin | Switch | 3,182 | 2.4% | 6 |
| TCA | Pregabalin+TCA | Add | 3,078 | 2.3% | 7 |
| SNRI | Pregabalin+SNRI | Add | 3,043 | 2.3% | 8 |
| Opioid_S8 | Pregabalin | Switch | 2,606 | 2.0% | 9 |
| Tramadol | Pregabalin+Tramadol | Add | 2,383 | 1.8% | 10 |
| None | Opioid_S4+Pregabalin | Add | 2,161 | 1.6% | 11 |
| Opioid_S8+Other_antidepressant | Opioid_S8+Other_antidepressant+Pregabalin | Add | 2,083 | 1.6% | 12 |
| TCA | Pregabalin | Switch | 1,917 | 1.4% | 13 |
| None | Pregabalin+Tramadol | Add | 1,579 | 1.2% | 14 |
| Tramadol | Pregabalin | Switch | 1,400 | 1.0% | 15 |
| Opioid_S8+TCA | Opioid_S8+Pregabalin+TCA | Add | 1,136 | 0.9% | 16 |
| Opioid_S8+SNRI | Opioid_S8+Pregabalin+SNRI | Add | 1,126 | 0.8% | 17 |
| Other_antidepressant | Pregabalin | Switch | 866 | 0.6% | 18 |
| Opioid_S4+Other_antidepressant | Opioid_S4+Other_antidepressant+Pregabalin | Add | 797 | 0.6% | 19 |
| Opioid_S4+Opioid_S8 | Opioid_S4+Opioid_S8+Pregabalin | Add | 783 | 0.6% | 20 |
| Opioid_S4+Opioid_S8 | Opioid_S8+Pregabalin | Switch | 750 | 0.6% | 21 |
| Anticonvulsant | Anticonvulsant+Pregabalin | Add | 710 | 0.5% | 22 |
| None | Pregabalin+TCA | Add | 634 | 0.5% | 23 |
| Opioid_S8+Other_antidepressant | Other_antidepressant+Pregabalin | Switch | 575 | 0.4% | 24 |
| Other_antidepressant | Opioid_S8+Other_antidepressant+Pregabalin | Add | 553 | 0.4% | 25 |
| Opioid_S4+Other_antidepressant | Other_antidepressant+Pregabalin | Switch | 516 | 0.4% | 26 |
| Opioid_S4+Opioid_S8 | Pregabalin | Switch | 485 | 0.4% | 27 |
| None | Opioid_S8+Pregabalin+Tramadol | Add | 448 | 0.3% | 28 |
| Opioid_S8+Tramadol | Opioid_S8+Pregabalin+Tramadol | Add | 443 | 0.3% | 29 |
| None | Other_antidepressant+Pregabalin | Add | 443 | 0.3% | 30 |
| Opioid_S8+TCA | Opioid_S8+Pregabalin | Switch | 439 | 0.3% | 31 |
| Anticonvulsant | Pregabalin | Switch | 438 | 0.3% | 32 |
| Opioid_S4+SNRI | Opioid_S4+Pregabalin+SNRI | Add | 420 | 0.3% | 33 |
| Opioid_S4 | Opioid_S4+Opioid_S8+Pregabalin | Add | 419 | 0.3% | 34 |
| Opioid_S8+Tramadol | Opioid_S8+Pregabalin | Switch | 418 | 0.3% | 35 |
| Other | Other | | 25,733 | 19.3% | |
| Total | | | 133,614 | 100% | |

Table 5 shows that the most common transition is to initiate pregabalin without having been on any drugs (considered in this analysis) beforehand. It should be remembered that paracetamol (in plain products) and NSAIDs were excluded from this analysis because they are available over the counter and so have incomplete capture in the data (see Methods section). The most common addition was to add pregabalin to a strong opioid (ie. Opioid_S8) and the most common switch was to substitute pregabalin for a weak opioid (ie. Opioid_S4).

Oxycodone was the most common strong opioid that pregabalin was added to. The most common weak opioid substituted by pregabalin was codeine in a combination product with paracetamol.

To summarise pregabalin initiation transitions;

- 45.2% (n=60,372) of patients initiated pregabalin without being on a PBS drug regimen (excluding paracetamol and NSAIDs) just prior to initiation (50,076 of these initiate onto pregabalin monotherapy).
- 33.2% (n=44,410) of patients add pregabalin to an existing PBS drug regimen; and
- 21.6% (n=28,832) of patients substitute at least one drug in their regimen.

45.2% of patients were not on a drug regimen just prior to initiation of pregabalin, but this does not mean they had not tried and stopped treatment on one or more of the drug groups in the past. Table 6 shows the drug groups (excluding paracetamol and NSAIDs) tried by these patients in the 12 months prior to their initiation to pregabalin.

Table 6: Drug groups tried anytime in the 12 months prior to pregabalin initiation for patients on no treatment in the week before pregabalin initiation.

| Drug Groups | Patients | % Patients | Ranks |
|---------------------------------|----------|------------|-------|
| None | 36,893 | 60.8% | 1 |
| Opioid_S4 | 5,510 | 9.1% | 2 |
| Opioid_S8 | 4,169 | 6.9% | 3 |
| Tramadol | 2,268 | 3.7% | 4 |
| TCA | 1,783 | 2.9% | 5 |
| Opioid_S4, Opioid_S8 | 1,470 | 2.4% | 6 |
| Other_antidepressant | 1,365 | 2.3% | 7 |
| Opioid_S8, Tramadol | 922 | 1.5% | 8 |
| Opioid_S4, Tramadol | 667 | 1.1% | 9 |
| SNRI | 577 | 1.0% | 10 |
| Opioid_S4, TCA | 446 | 0.7% | 11 |
| Anticonvulsant | 409 | 0.7% | 12 |
| Opioid_S8, TCA | 409 | 0.7% | 13 |
| Opioid_S4, Opioid_S8, Tramadol | 376 | 0.6% | 14 |
| Opioid_S4, Other_antidepressant | 327 | 0.5% | 15 |
| Other | 2,781 | 5.0% | |
| Total | 60,372 | 100.0% | |

Table 6 shows that the vast majority of patients not on any PBS medicines just prior to initiation of pregabalin had not used other medicines in the preceding 12 months.

The estimated patient drug regimens in the 7 months pre and post initiation to pregabalin are shown in the Figure 7. The patient cohort is the same as that used for the drug regimen transition analysis in Table 5.

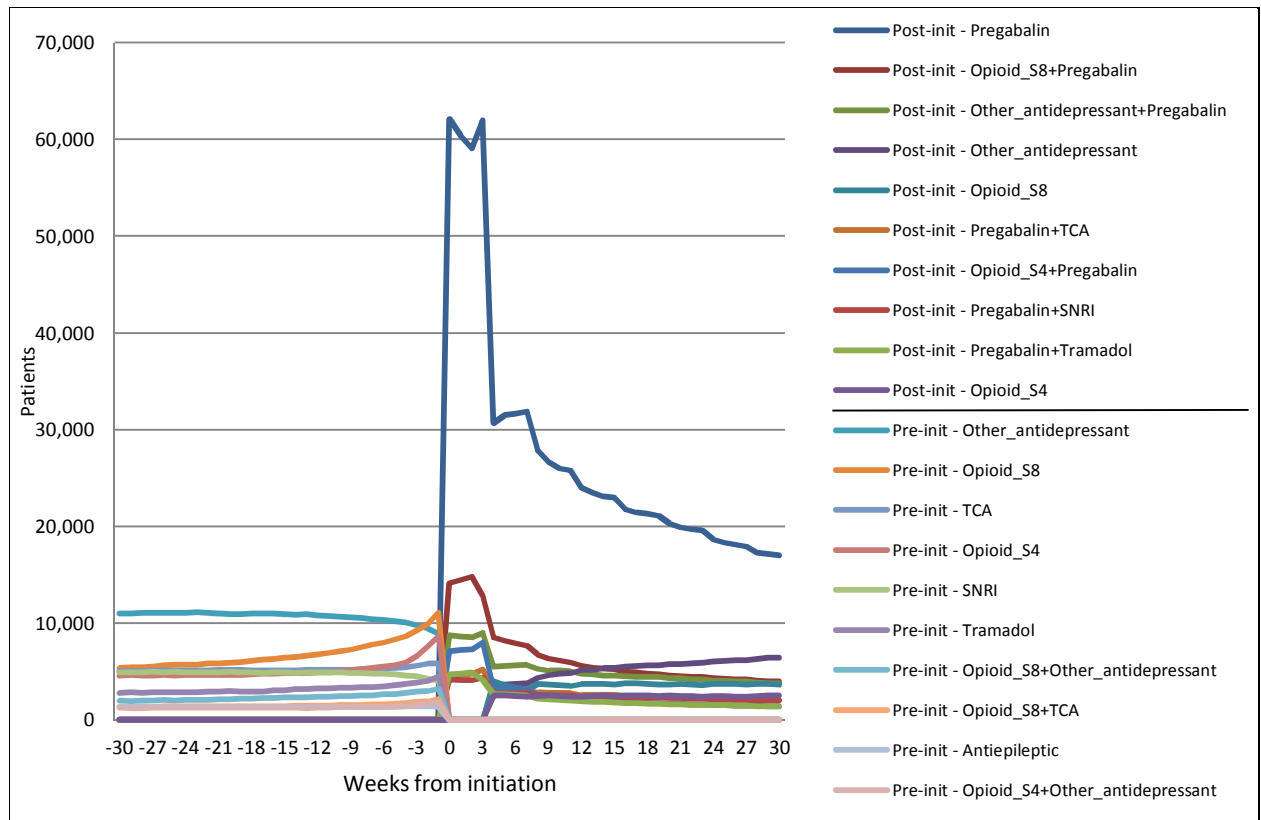


Figure 7: Estimate drug regimens pre and post initiation to pregabalin

Figure 7 shows that in the weeks before initiation to pregabalin, the number of patients on opioids (ie. Opioid_S8, Opioid_S4 and Tramadol) increased. The number of patients on tricyclic antidepressants (TCA) also increased slightly, however the number of patients on SNRI and other antidepressants decreased. After initiation to pregabalin the discontinuation rate is high. Approximately half (50.4%) of the patients that initiated onto pregabalin monotherapy were not deemed to be on pregabalin monotherapy 5 weeks after initiation (ie. either the patient only had the initiating script or there was a break in therapy after the initiating script) and 43.9% of patients that initiated onto any regimen containing pregabalin (ie. mono or combination therapy) were not deemed to be on a regimen containing pregabalin 5 weeks after initiation.

An analysis using the 10% PBS sample included in the Sponsor's response to the 12 month PvA analysis of pregabalin considered that the average persistence with pregabalin was 82% after 14 months. The methodology used to produce this result is not clear, for example the cohorts and lookback periods were not defined. In addition, the analysis was likely limited by the short period of data available at the time of the analysis. In their response to the 24 month PvA analysis the Sponsor clarified their methodology, and re-ran their

analysis with a slightly modified method (ie. they excluded grandfathered patients because it is not possible to measure their persistence rate) and using prescription data up to the end of March 2015. This re-analysis gave a persistence rate of 56% at 12 months, which was less than the 82% after 14 months reported in their first analysis.

DVA patients were assessed separately because treatment patterns may vary because gabapentin is available for neuropathic pain through the RPBS and because pregabalin was available for neuropathic pain through the RPBS prior to its listing on the PBS. There were 3,905 patients in the 6 month cohort (N=133,614) analysed in this section that had at least one RPBS script in the period March 2013 to March 2015 inclusive (ie. 2.9% RPBS patients). These patients were analysed separately and the results are shown in Appendix A. These show that the RPBS patient estimated drug regimens and transitions are not substantially different from the whole cohort and so are unlikely to have biased the results.

Figure 8 shows the estimated drug regimens by calendar week from March 2014 to February 2015 (inclusive) for all regimens that contain pregabalin. The analysis includes all pregabalin patients, not just the six month initiator cohort used for the previous analyses.

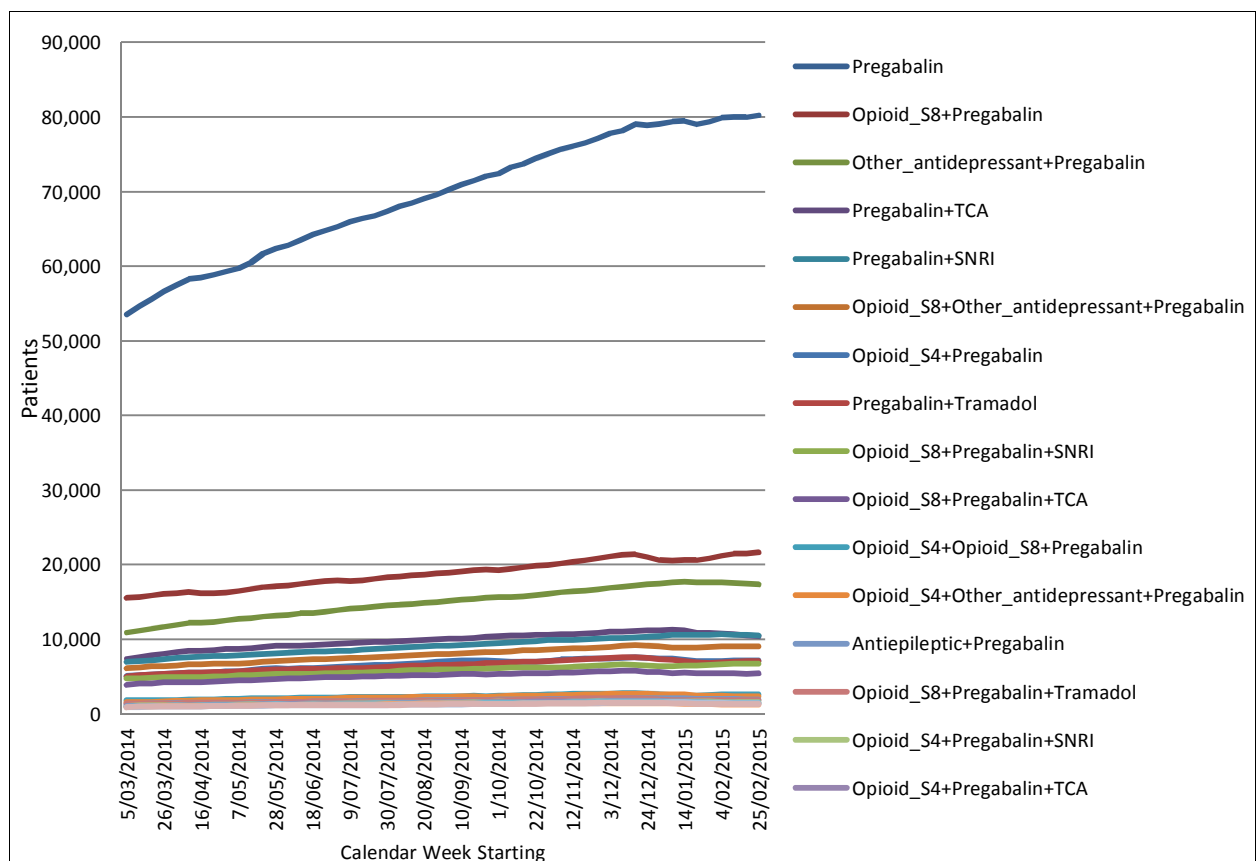


Figure 8: Estimated drug regimens containing pregabalin by calendar week

At the start of the last week in Figure 8 (ie. 25/2/2015), there were a total of 212,993 patients estimated to be on pregabalin. 80,214 (37.7 %) were estimated to be on

pregabalin alone and the remainder (62.3%) were estimated to be on pregabalin in combination with another drug group. The most common combination was with a strong opioid (Opioid_S8, 21,633 patients, 10.2% of all patients). The distribution of estimated drug regimens as at 25/2/2015 is shown in the table below.

Table 7: Estimated patient drug regimens containing pregabalin as at 25/2/2015

| Estimated drug regimen | Patients | % Patients |
|---|----------|------------|
| Pregabalin | 80,214 | 37.7% |
| Opioid_S8+Pregabalin | 21,633 | 10.2% |
| Other_antidepressant+Pregabalin | 17,391 | 8.2% |
| Pregabalin+SNRI | 10,480 | 4.9% |
| Pregabalin+TCA | 10,403 | 4.9% |
| Opioid_S8+Other_antidepressant+Pregabalin | 9,019 | 4.2% |
| Opioid_S4+Pregabalin | 7,153 | 3.4% |
| Pregabalin+Tramadol | 7,084 | 3.3% |
| Opioid_S8+Pregabalin+SNRI | 6,680 | 3.1% |
| Opioid_S8+Pregabalin+TCA | 5,397 | 2.5% |
| Opioid_S4+Opioid_S8+Pregabalin | 2,566 | 1.2% |
| Opioid_S4+Other_antidepressant+Pregabalin | 2,341 | 1.1% |
| Anticonvulsant+Pregabalin | 1,934 | 0.9% |
| Opioid_S8+Pregabalin+Tramadol | 1,850 | 0.9% |
| Opioid_S4+Pregabalin+SNRI | 1,590 | 0.7% |
| Other_antidepressant+Pregabalin+Tramadol | 1,502 | 0.7% |
| Opioid_S4+Pregabalin+TCA | 1,417 | 0.7% |
| Other_antidepressant+Pregabalin+TCA | 1,361 | 0.6% |
| Opioid_S4+Opioid_S8+Other_antidepressant+Pregabalin | 1,322 | 0.6% |
| Pregabalin+TCA+Tramadol | 1,233 | 0.6% |
| Other | 20,423 | 9.6% |
| Grand Total | 212,993 | 100.0% |

Strength Sequence and Timing Analysis

The Product Information (PI) and Australian Medicine Handbook⁸ recommended dose of pregabalin is initially 75mg twice daily; if required, an increase after 3 to 7 days to 150mg twice daily, and to a maximum of 300mg twice daily after a further 7 days if required.

The eTG recommended dose of pregabalin is 75 mg orally, daily; increase to twice daily after 2 or 3 days and then more slowly up to 300 mg twice daily⁹.

Table 8 shows that the 75mg capsule was the most common strength used for initiation to pregabalin (59%). The most common 1st → 2nd strength sequences and the median days to supply of the 2nd script were;

- 75→75mg (39,256, 30.0% of cohort, 31 days)
- 75→None (29,316, 22.4% of cohort)
- 25→25mg (21,202, 16.2% of cohort, 28 days)
- 25→75mg (6,752, 5.1% of cohort, 20 days)
- 75→150mg (5,685, 4.3% of cohort, 21 days)

It can be seen the 1st → 2nd strength sequence of 75→150mg capsules, corresponding to the first titration described by the PI (ie. 150→300mg daily dose after an interval of 3 to 7 days), is the 5th most frequent one in clinical practice. When the median days to supply of the 2nd scripts are less than 28 (eg. 25→75mg or 75→150mg) it is likely that dose up titration is occurring. If the titration of 150→300mg per day occurred after 6 days then the first script would last 17 days (ie. 6 days x 2 capsules per day + 11 days at 4 capsules per day = 56 capsules). The above result indicates that the extent of up titration is approximately 9.4% (ie. 5.1% + 4.3%) of patients.

The most common 1st → 2nd → 3rd strength sequences and the median days to between the supply of the 2nd and 3rd scripts were;

- 75→75→75mg (27,882, 21.3% of cohort, 30 days)
- 25→25→25mg (14,869, 11.4% of cohort, 28 days)
- 150→150→150mg(3,240, 2.5% of cohort, 29 days)
- 75→150→150mg(3,207, 2.5% of cohort, 29 days)

These strength sequences imply that many patients are initiating on the 75mg capsule (dose = 150mg/day) and not up titrating to using the 150mg capsule. In addition, many patients are initiating and then not continuing to a second or third prescription. 35.9% (n=

⁸ *Australian Medicines Handbook*. Adelaide: Australian Medicines Handbook Pty Ltd; 2015, p692.

⁹ Neuropathic Pain [revised 2011 June]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; Accessed July 2015 <<http://online.tg.org.au/complete/desktop/index.htm>>.

47,004) of patients discontinued after one script and a further 13.0% (n=16,981) discontinued after two scripts. In the Estimated Patient Drug Regimens section above it was estimated that 43.9% of patients that initiated onto any pregabalin regimen (ie. mono or combination therapy) were not deemed to be on a pregabalin regimen 5 weeks after initiation. This means that 35.9% of patients had only one script for pregabalin and 8.0% (ie. 43.9% - 35.9%) of patients were estimated to have had a break in pregabalin treatment (ie. they had more than one script, but had a break in treatment after the first script).

Table 8: Strength sequence and median time to supply of first three prescriptions

| Strength of pregabalin capsules | | | Not supplied on same day as previous script | | | Supplied on the same day as previous script | |
|---------------------------------|---------------------|----------|---|-----------------------------------|--------------------------|---|------------|
| Script 1 | Script 2 | Script 3 | Patients | % Patients (% of previous script) | days to supply (median)* | Patients | |
| 25 mg | 25 mg | 25 mg | 14,869 | 70% | 28 | 434 | |
| | | 75 mg | 2,311 | 11% | 14 | 436 | |
| | | 150 mg | 181 | 1% | 13 | | |
| | | 300 mg | 7 | 0% | 11 | | |
| | | None | 3,834 | 18% | - | | |
| | 25 mg Total | | | 21,202 | 49% | 28 | 870 |
| | 75 mg | 25 mg | 1,400 | 21% | 23 | | |
| | | 75 mg | 3,184 | 47% | 29 | 50 | |
| | | 150 mg | 613 | 9% | 21 | | |
| | | 300 mg | 39 | 1% | 14 | | |
| | | None | 1,516 | 22% | - | | |
| | 75 mg Total | | | 6,752 | 16% | 20 | 50 |
| | 150 mg | 25 mg | 39 | 9% | 16 | 18 | |
| | | 75 mg | 40 | 9% | 25 | 44 | |
| | | 150 mg | 230 | 51% | 27 | 1 | |
| | | 300 mg | 28 | 6% | 20 | 2 | |
| | | None | 114 | 25% | - | | |
| | 150 mg Total | | | 451 | 1% | 21 | 65 |
| | 300 mg | 25mg | 3 | 10% | 11 | | |
| | | 75mg | 3 | 10% | 6 | 1 | |
| | | 150mg | 4 | 13% | 34 | | |
| | | 300mg | 16 | 53% | 35 | | |
| | | None | 4 | 13% | - | | |
| 300 mg Total | | | 30 | 0% | 16 | 1 | |
| None Total | | | 15,012 | 35% | - | | |
| 25 mg Total | | | 43,447 | 33% | | 986 | |

| Strength of pregabalin capsules | | | Not supplied on same day as previous script | | | Supplied on the same day as previous script | |
|---------------------------------|---------------------|----------|---|-----------------------------------|--------------------------|---|------------|
| Script 1 | Script 2 | Script 3 | Patients | % Patients (% of previous script) | days to supply (median)* | Patients | |
| 75 mg | 25 mg | 25mg | 1,193 | 43% | 30 | 18 | |
| | | 75mg | 538 | 19% | 24 | 181 | |
| | | 150mg | 62 | 2% | 19 | | |
| | | 300mg | 4 | 0% | 14 | 1 | |
| | | None | 988 | 35% | - | | |
| | 25 mg Total | | | 2,785 | 4% | 28 | 200 |
| | 75 mg | 25mg | 762 | 2% | 29 | | |
| | | 75mg | 27,882 | 71% | 30 | 709 | |
| | | 150mg | 2,469 | 6% | 20 | | |
| | | 300mg | 192 | 0% | 13 | | |
| | | None | 7,951 | 20% | - | | |
| | 75 mg Total | | | 39,256 | 51% | 31 | 709 |
| | 150 mg | 25mg | 69 | 1% | 29 | 19 | |
| | | 75mg | 998 | 18% | 22 | 413 | |
| | | 150mg | 3,207 | 56% | 29 | 34 | |
| | | 300mg | 311 | 5% | 20 | 18 | |
| | | None | 1,100 | 19% | - | | |
| | 150 mg Total | | | 5,685 | 7% | 21 | 484 |
| | 300 mg | 25mg | 2 | 0% | 104 | | |
| | | 75mg | 64 | 15% | 17 | 12 | |
| 150mg | | 35 | 8% | 14 | | | |
| 300mg | | 234 | 55% | 28 | 1 | | |
| None | | 93 | 22% | - | | | |
| 300 mg Total | | | 428 | 1% | 15 | 13 | |
| None Total | | | 29,316 | 38% | - | | |
| 75 mg Total | | | 77,470 | 59% | | 1,406 | |
| 150 mg | 25 mg | 25mg | 58 | 28% | 23 | 5 | |
| | | 75mg | 23 | 11% | 14 | 38 | |
| | | 150mg | 50 | 25% | 22 | | |
| | | 300mg | 2 | 1% | 134 | 1 | |
| | | None | 71 | 35% | - | | |
| | 25 mg Total | | | 204 | 2% | 32 | 44 |
| | 75 mg | 25mg | 60 | 4% | 23 | | |
| | | 75mg | 378 | 26% | 30 | 12 | |
| 150mg | | 556 | 39% | 29 | | | |

| Strength of pregabalin capsules | | | Not supplied on same day as previous script | | | Supplied on the same day as previous script |
|---------------------------------|---------------------|--------------|---|-----------------------------------|--------------------------|---|
| Script 1 | Script 2 | Script 3 | Patients | % Patients (% of previous script) | days to supply (median)* | Patients |
| | | 300mg | 48 | 3% | 29 | |
| | | None | 395 | 27% | - | |
| | 75 mg Total | | 1,437 | 16% | 24 | 12 |
| | 150 mg | 25mg | 45 | 1% | 38 | 14 |
| | | 75mg | 210 | 5% | 28 | 87 |
| | | 150mg | 3,240 | 74% | 29 | 95 |
| | | 300mg | 152 | 3% | 20 | 23 |
| | | None | 746 | 17% | - | |
| | 150 mg Total | | 4,393 | 50% | 29 | 219 |
| | 300 mg | 25mg | 7 | 2% | 13 | |
| | | 75mg | 10 | 3% | 20 | 15 |
| | | 150mg | 98 | 26% | 30 | |
| | | 300mg | 195 | 52% | 28 | 4 |
| | | None | 63 | 17% | - | |
| | 300 mg Total | | 373 | 4% | 20 | 19 |
| | | | | | | |
| None Total | | 2,456 | 28% | - | | |
| 150 mg Total | | 8,863 | 7% | | 294 | |
| 300 mg | 25 mg | 25mg | 1 | 25% | 33 | |
| | | 75mg | 3 | 75% | 21 | 1 |
| | 25 mg Total | | 4 | 0% | 196 | 1 |
| | 75 mg | 25mg | 2 | 3% | 18 | |
| | | 75mg | 18 | 28% | 30 | |
| | | 150mg | 2 | 3% | 105 | |
| | | 300mg | 21 | 33% | 28 | |
| | | None | 21 | 33% | - | |
| | 75 mg Total | | 64 | 6% | 22 | |
| | 150 mg | 25mg | 2 | 3% | 96 | 1 |
| | | 75mg | 6 | 9% | 31 | 4 |
| | | 150mg | 27 | 40% | 30 | |
| | | 300mg | 18 | 27% | 28 | 7 |
| | | None | 14 | 21% | - | |
| | 150 mg Total | | 67 | 6% | 18 | 12 |
| 300 mg | 25mg | 2 | 0% | 128 | | |
| | 75mg | 13 | 2% | 28 | 1 | |
| | 150mg | 22 | 3% | 26 | | |

| Strength of pregabalin capsules | | | Not supplied on same day as previous script | | | Supplied on the same day as previous script |
|---------------------------------|---------------------|----------|---|-----------------------------------|--------------------------|---|
| Script 1 | Script 2 | Script 3 | Patients | % Patients (% of previous script) | days to supply (median)* | Patients |
| | | 300mg | 649 | 86% | 28 | 22 |
| | | None | 71 | 9% | - | |
| | 300 mg Total | | 757 | 68% | 28 | 23 |
| | | | | | - | |
| | None Total | | 220 | 20% | - | |
| 300 mg Total | | | 1,112 | 1% | | 36 |
| Grand Total | | | 130,892 | 100% | | 2,722 |

* The Script 2 Total rows contain the median days to supply of Script 2 after Script 1. The Script 1 Total rows do not have a median days to supply as there was no prior script

Estimated Dose Analysis

The dose analysis results are summarised in the following two figures and table.

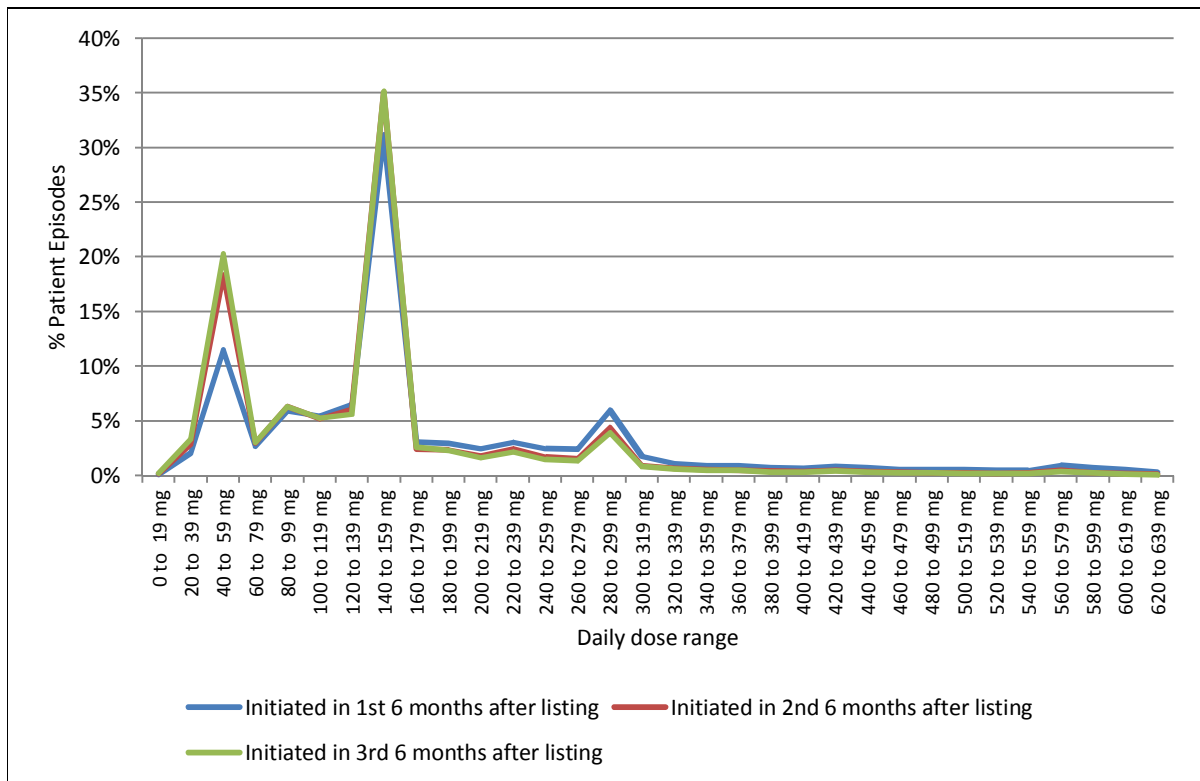


Figure 9: Estimate of daily dose by initiation cohort

Note: excluding outliers with an average dose >= 640 mg/day (6,384 patients were excluded, 1.17% of all patients).

Figure 9 shows that the three most common daily doses are approximately 150mg, 50mg and 300mg respectively. It also shows that the patients in the first cohort had a relatively higher frequency of high doses and lower frequency of low doses. This probably reflects patients responding to and established on treatment in the private market moving to PBS supply.

Since it is anticipated that patients may go on and off therapies for neuropathic pain, and it is not known whether patients who reinitiate after a break (ie. start a new episode of treatment) would re-commence on a low dose of pregabalin and up-titrate, an analysis of dose according to treatment episode was also undertaken. Episodes are defined as a break of two standard coverage days (SCD) or more between the coverage end date of one script and the supply of the next. SCD is the median time to re-supply and is 27 days for pregabalin (see Appendix B for more detail).

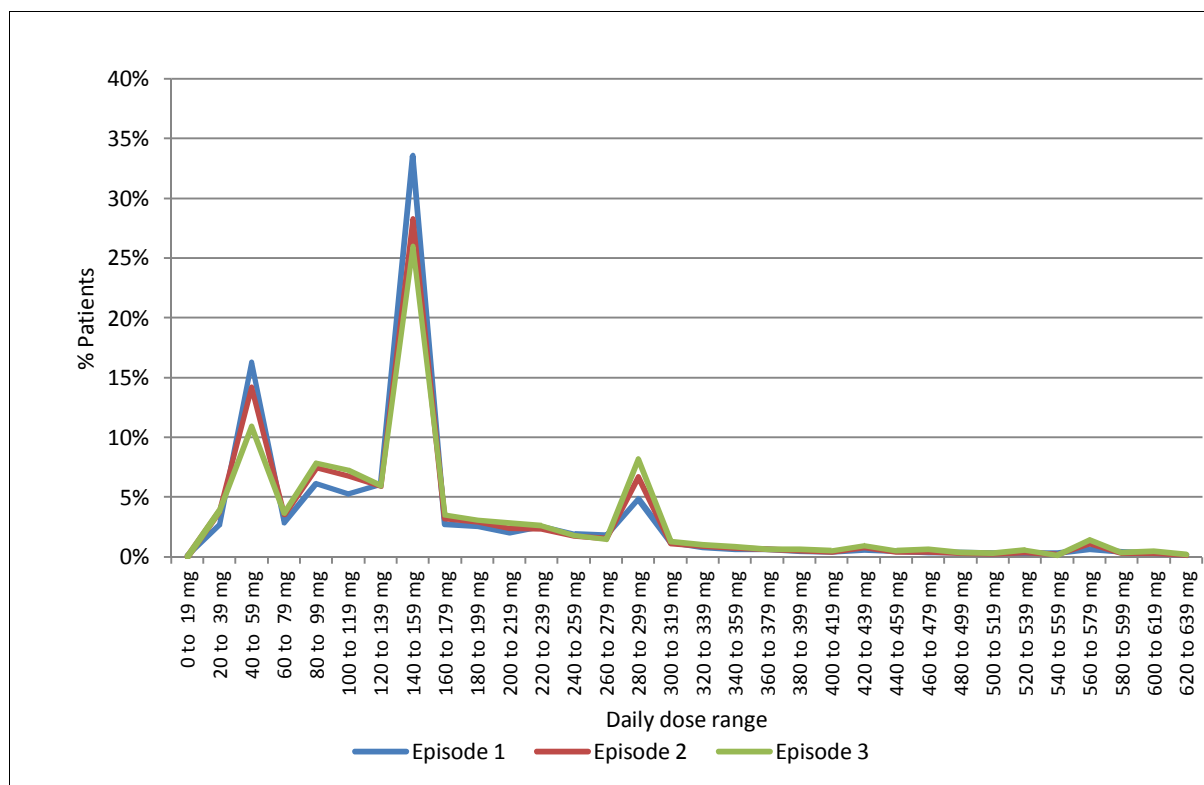


Figure 10: Estimate of daily dose by episode

Note: excluding outliers with an average dose \geq 640 mg/day (6,384 patients were excluded, 1.17% of all patients).

Figure 10 shows that patient first episodes had a relatively higher frequency of low doses and lower frequency of high doses. This may be due to the fact that a first episode contains the titration period. This leads to a lower average dose for first episodes, as shown in Table 8 (but only for the 2nd and 3rd initiation cohorts. In the 1st cohort the average dose is approximately equal across the episodes. Again, this may be due to more patients grandfathered from the private market in this cohort).

Table 9: Estimated Average Daily Doses of pregabalin

| Initiation Cohort | Episode* | Patients | Average Dose (mg/day) | Weighted** Average Dose (mg/day) |
|---|----------|----------|-----------------------|----------------------------------|
| Initiated in 1st 6 months after listing | 1 | 163,938 | 181 | 229 |
| | 2 | 47,571 | 171 | 183 |
| | 3 | 13,490 | 176 | 172 |
| Initiated in 2nd 6 months after listing | 1 | 128,214 | 149 | 182 |
| | 2 | 29,252 | 153 | 157 |
| | 3 | 5,645 | 167 | 155 |
| Initiated in 3rd 6 months after listing | 1 | 132,863 | 142 | 165 |
| | 2 | 18,752 | 155 | 150 |
| | 3 | 1,432 | 173 | 155 |

Note: excluding outliers with an average dose > 640 mg/day (6,384 patients were excluded, 1.17% of all patients).

* Episodes greater than 3 are not displayed because of low patient numbers in the subsequent episodes.

** Weighted by the length of each episode

The weighted average dose in Table 9 has regard to the length of treatment in each episode. For example, the average dose for episode 1 and cohort 1 is 181 mg/day and the weighted average dose is 229 mg/day. This means that the higher dose episodes are also on average longer and this increases the weighted average dose relative to the episode average.

The cohort 1 weighted average dose of 229 mg/day was quite close to the 225 mg/day assumed in the submission. The doses are lower for the later cohorts 2 & 3. This probably reflects cohort 1 including many patients established on pregabalin in the private market moving to PBS subsidised therapy, and possibly also that the early cohort patients include those with high unmet clinical need and who may need higher doses.

The trend across episodes is inconsistent between cohorts and measures (ie. weighted vs non-weight average dose). The non-weighted average dose is higher in later episodes for cohorts 2 & 3.

The percentages of patients having one or more breaks in treatment (ie. more than one episode of treatment), calculated from the figures in Table 9, were 29%, 22% and 14% for cohorts 1, 2 and 3 respectively. The percentages are lower for each cohort because the follow-up time decreases. Each cohort is followed up until the end of March 2015, thus patients have an average follow-up time of 22.5, 16.5 and 10.5 months in cohorts 1, 2 & 3 respectively. These breaks in treatment also contribute to the lower than expected scripts per patient (see Table 4).

In case the results for Episode 1 are heavily influenced by the titration period in the first month of use, the analysis presented in Table 9 was repeated excluding the first script. The results are shown in Table 10.

Table 10: Estimated Average Daily Doses, excluding the first script from Episode 1

| Initiation Cohort | Episode* | Patients | Average Dose (mg/day) | Weighted** Average Dose (mg/day) |
|---|----------|----------|-----------------------|----------------------------------|
| Initiated in 1st 6 months after listing | 1 | 130,040 | 198 | 235 |
| Initiated in 2nd 6 months after listing | 1 | 88,817 | 166 | 191 |
| Initiated in 3rd 6 months after listing | 1 | 85,616 | 162 | 178 |

Note: excluding outliers with an average dose > 640 mg/day (6,384 patients were excluded, 1.17% of all patients).

** Weighted by the length of each episode

Table 10 shows that both the average dose and the weighted average dose increases if the first script is excluded from the analysis, however the increases are not large. That is, a maximum of 14% (ie. average dose changes from 142 to 162mg per day) in the case of those who initiated in the 3rd 6 months after listing. This result is consistent with the result of the Strength Sequence and Timing Analysis which estimated that the extent of up titration was small.

Patient Age Analysis

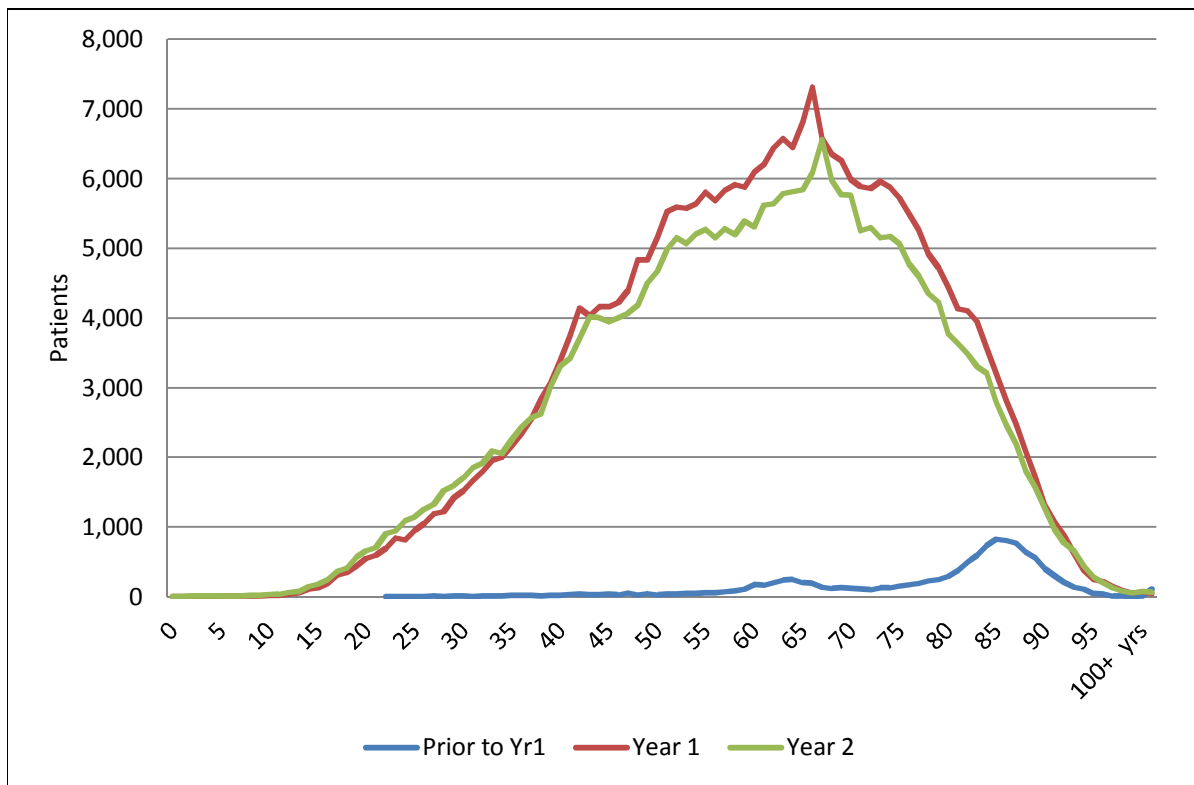


Figure 11: Patient age at initiation to pregabalin by year since general PBS listing

Note: "Prior to Yr1" = all initiations to the RPBS items (listed from February 2008) prior to general PBS listing in March 2013.

Figure 11 shows that slightly more patients initiated in Year 1 compared to Year 2. The median ages were 83, 62, 61 years in the periods Prior to Yr1, Year 1 and Year 2 respectively. An unusual feature is the sharp peak of initiators in Year 1 and Year 2 just after the age of 65 years. This may be related to patients qualifying for PBS concession cards at this age. Figure 12 shows initiators in Year 2 by age and initiating script type.

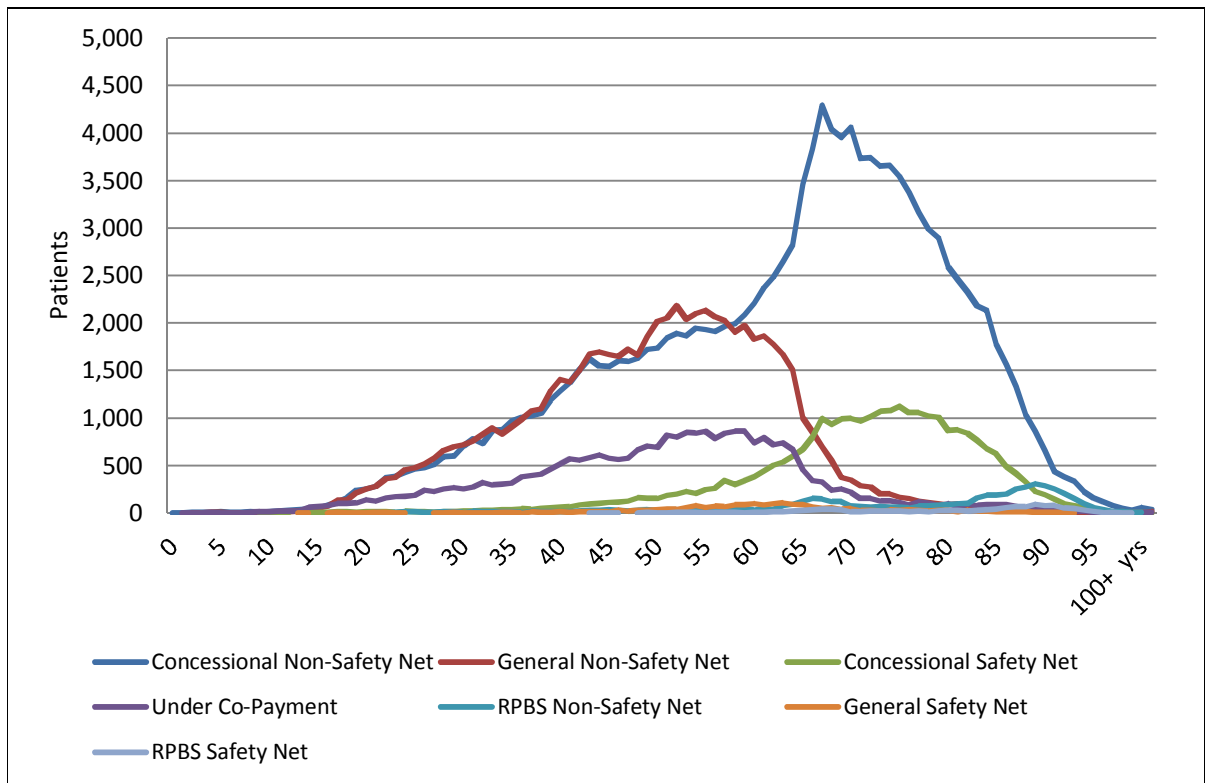


Figure 12: Patient age at initiation to pregabalin in Year 2 by initiating script type

Patients can qualify for Concessional Non-Safety Net scripts if they qualify for a Pensioner Concession Card, Commonwealth Seniors Health Card or a Health Care Card. People can qualify for the Commonwealth Seniors Health Card from age 65 years and for the Pensioner Concession Card from age 60 if they are receiving a CentreLink allowance (the most common one being the age pension from age 65 years).

Prescriber Type Analysis

Table 11 shows the distribution by prescriber major specialty of pregabalin original prescriptions (ie. does not include supply of repeats) supplied in the first two years after PBS listing (ie. March 2013 to February 2015)

Table 11: Original prescriptions by prescriber major specialty

| Major Specialty | Scripts | % Scripts | Rank |
|--------------------------------|----------------|------------------|-------------|
| Vocationally Registered GP | 1,017,860 | 73.4% | 1 |
| Non-Vocationally Registered GP | 114,737 | 8.3% | 2 |
| GP Trainee | 58,037 | 4.2% | 3 |
| GP Unclassified | 28,235 | 2.0% | 4 |
| Rheumatology | 22,355 | 1.6% | 5 |
| Neurology | 18,740 | 1.4% | 6 |
| Surgery | 18,718 | 1.4% | 7 |
| Palliative Medicine | 16,643 | 1.2% | 8 |
| Internal Medicine | 14,852 | 1.1% | 9 |
| Rehabilitation Medicine | 10,595 | 0.8% | 10 |
| Other | 65,410 | 4.7% | |
| Total | 1,386,182 | 100.0% | |

GPs prescribed 87.9%, specialists 12.0% and nurse practitioners 0.1% of original pregabalin prescriptions.

Discussion

In the advice provided to the March 2011 PBAC meeting the DUSC considered that the total number of prescriptions per year was subject to several uncertainties with differing effects, including:

1. A large number of patients were likely to seek treatment with pregabalin initially and that the submission underestimated this uptake.
2. The proportion who respond and continue on therapy was likely to be a substantial overestimate.
3. The assumptions of substitution were considered unlikely to be realised, with add-on use expected to be much higher than the switching proposed.
4. The mean total daily dose of 225 mg pregabalin was high, and the average daily dose was likely to be lower.

The analyses in this report demonstrate that.

1. There were 294,747 and 433,324 PBS/RPBS patients treated with PBS subsidised pregabalin in the first two years of listing respectively. This was 39% and 58% higher than predicted. The number of actual patients in Year 2 exceeded the number of patients predicted for Year 5.
2. The submission assumed that 75% of the patients who receive initiation therapy will be considered responders and will receive continuation therapy. This was based on the Patient Global Impression of Change (PGIC), a secondary outcome measure in many of the pregabalin clinical studies referenced in the March 2012 submission. The proportion of patients who were minimally improved or better ranged from 63% to 82%. It was assumed, in practice, that 75% of the patients who receive initiation therapy will be considered responders and will receive continuation therapy. The submission Section E spreadsheet estimates assumed that 25% of patients discontinue after the supply of one prescription. Figure 7 shows that the discontinuation rate after one prescription for patients who initiated onto pregabalin (mono or combination therapy) is 43.9%, which is substantially higher than the 25% assumed in the submission. This statistic also helps explain why scripts per patient are less than expected (see Table 4).
3. The submission assumed that of the patients who initiate pregabalin, 92.5% switch from and 7.5% will add to prior drug treatment (defined as amitriptyline, gabapentin or carbamazepine). This was based on the proportion of patients taking amitriptyline, gabapentin or carbamazepine and also the proportion of these drugs which were estimated to be used in combination with pregabalin in the 2011 Drug Audit (Attachment 2 of the submission to the March 2012 PBAC). A summary of Table 5 shows that 45.2% of patients initiate pregabalin without being on a prior drug regimen (excluding paracetamol and NSAIDs), 33.2% of patients add pregabalin to an existing drug regimen and 21.6% of patients substitute at least one drug in their regimen. Since the submission substantially over estimated the switching rate (ie. 92.5% predicted vs 21.6% actual), the drug cost offsets would have been overestimated in the submission.
4. The submission Section E priced the mean dose of 225mg per day using the price for the monthly supply of the 75 and 150mg packs. The submission stated that "The mean total daily dose of pregabalin used in Australia in practice is 225 mg, which is the weighted

average of the pregabalin doses used from all data sources". Table 9 shows that 225mg was a reasonable estimate of the weighted average dose for the first episode of treatment of the patients who initiated PBS therapy in the first 6 months after listing (ie. 229 mg/day). Patients who initiated after this had lower weighted average doses (eg. 165mg for the first episode of treatment for patient who initiated in the third 6 months after listing). Patients in the first cohort probably include a high proportion of patients established on pregabalin in the private market transitioning to PBS therapy and a group of patients with unmet clinical need.

The total number of prescriptions of pregabalin supplied in the first year of PBS listing (1,396,766) was similar to predicted, however utilisation in the second year of PBS listing (2,435,807 prescriptions) was 32% more than predicted.

The R/PBS expenditure in Year 2 was similar to that expected, despite the more than expected number of patients and scripts. This is due to the;

- higher than expected discontinuation rate (resulting in fewer than expected scripts per patient);
- the lower than expected weighted average dose (165mg/day for 1st episodes of treatment initiated in the first 6 months of Year 2 compared to 225mg/day assumed in the submission); and
- the higher than expected average patient copayment.

DUSC consideration

DUSC considered that the submission:

1. Under-estimated the number of patients treated.

There were 294,747 and 433,324 PBS/RPBS patients treated with PBS subsidised pregabalin in the first two years of listing respectively. This was 39% and 58% higher than predicted. The number of actual patients in Year 2 exceeded the number of patients predicted for Year 5.

2. Over-estimated the proportion of patients who would respond and continue on therapy.

The submission assumed that 75% of the patients who receive initiation therapy will be considered responders and will receive continuation therapy. The submission Section E spreadsheet estimates assumed that 25% of patients discontinue after the supply of one prescription. Figure 7 shows that the discontinuation rate after one prescription for patients who initiated onto pregabalin (mono or combination therapy) is 43.9%, which is substantially higher than the 25% assumed in the submission. This statistic also helps explain why prescriptions per patient are less than expected (see Table 4).

3. Over-estimated the proportion of patients that would switch from amitriptyline, gabapentin or carbamazepine to pregabalin.

The submission assumed that of the patients who initiate pregabalin, 92.5% switch from and 7.5% will add to prior drug treatment (defined as amitriptyline, gabapentin or carbamazepine). A summary of Table 5 shows that 45.2% of patients initiate pregabalin without being on a prior drug regimen (excluding paracetamol and NSAIDs), 33.2% of

patients add pregabalin to an existing drug regimen and 21.6% of patients substitute at least one drug in their regimen. Since the submission substantially over estimated the switching rate (ie. 92.5% predicted vs 21.6% actual), the drug cost offsets would have been overestimated in the submission.

4. Over-estimated the mean daily dose of pregabalin

The submission Section E priced the mean dose of 225mg per day using the price for the monthly supply of the 75 and 150mg packs. The submission stated that “The mean total daily dose of pregabalin used in Australia in practice is 225 mg, which is the weighted average of the pregabalin doses used from all data sources”. Table 9 shows that 225mg was a reasonable estimate of the weighted average dose for the first episode of treatment of the patients who initiated PBS therapy in the first 6 months after listing (ie. 229 mg/day). Patients who initiated after this had lower weighted average doses (eg. 165mg for the first episode of treatment for patient who initiated in the third 6 months after listing). Patients in the first cohort probably include a high proportion of patients established on pregabalin in the private market transitioning to PBS therapy and a group of patients with unmet clinical need.

5. Under-estimated the average patient copayment

This was due to higher than expected proportion of non-concessional patients

DUSC noted that:

- The first four of the above five points were identified in the DUSC advice provided to the March 2011 PBAC meeting.
- The combination of the under and over-estimates mentioned above led to an under-estimate of the number of prescriptions supplied in Year 2 of listing (ie. 32% more than predicted), [REDACTED] (ie. [REDACTED])
- Utilisation is continuing to trend upwards
- DUSC noted that the Sponsor’s Pre-Subcommittee Response (PSCR) included updated information on the prevalence of neuropathic pain. This estimated the prevalence of **neuropathic pain** to be 8.5%, which is higher than the 3.7% for **chronic neuropathic pain** used in the 2011 submission.

DUSC considered that the results of the analysis raised some Quality Use of Medicine (QUM) questions. These were:

- Is pregabalin being used for other conditions?

The PBAC had anticipated huge potential for use outside of the proposed restriction. From the results of the current analysis, DUSC was concerned that the higher than expected number of patients might indicate pregabalin use for conditions other than neuropathic pain. Table 11 shows that pregabalin is most frequently prescribed by GPs but rheumatologists were the highest prescribers of all specialists. DUSC considered that this may indicate treatment of fibromyalgia, which is outside the PBS restriction. Based on the high discontinuation rate after one script, DUSC also considered that pregabalin may be being prescribed for acute pain. The sponsor noted that these were

the DUSC's interpretations of the data and the sponsor does not agree with these interpretations as they consider there is no evidence to support these conclusions.

- Is pregabalin being used without the trial of other agents?
The PBS restriction states that the condition must be refractory to treatment with other drugs. The analysis indicated that 45.2% of patients initiated pregabalin without being on a prior drug regimen (excluding paracetamol and NSAIDs). DUSC noted that the PSCR stated that these patients may have been refractory to OTC or PBS paracetamol or NSAIDs and so have fulfilled the restriction criteria. However the submission assumed that all new pregabalin patients would switch from the treatment with amitriptyline, gabapentin or carbamazepine and this was the basis of the PBAC recommendation. Thus if the 45.2% of patients were all on a regimen containing paracetamol or an NSAIDs prior to initiation to pregabalin, this is a significantly different scenario to that envisaged in the submission.
- Are people discontinuing due to adverse effects?
The analysis estimated the discontinuation rate after one script to be 43.9% which is higher than the 25% assumed in the submission. One possible explanation for this is that the adverse effects (the four most common listed in the PI being dizziness, somnolence, vision blurred and fatigue) were greater than expected.
- Are people obtaining adequate benefit from the dose prescribed?
An alternative explanation for the high discontinuation rate is that the dose prescribed may not be adequate and so the patient discontinues due to lack of effect. The analysis found a lower than predicted average dose and related to this was a low percentage of patients showing evidence of up-titrating from 75mg to 150mg capsules. DUSC considered that the lack of up-titration could be related to the postulated greater than expected adverse effects. DUSC noted that the PSCR stated that "patients who are receiving adequate benefit from, and are tolerating the 75 mg twice daily dose do not necessarily need to be up-titrated despite the recommendation in the product information. 150 mg/day is a therapeutic dose and if a patient remains on this dose it suggests they are receiving the optimal dose to manage their pain. Further to this, the sponsor provides ongoing education and support materials to prescribers including information on appropriate dosing and up-titrating to achieve the optimal tolerated dose." DUSC noted that while both explanations may have some plausibility, the data are insufficient to determine the reason.
- Is there a knowledge gap around reaching optimal effective dose that needs to be addressed?
DUSC considered that such a knowledge gap may exist and decided to refer the report to NPS MedicineWise. DUSC also noted that there has been recent literature regarding the possible abuse of pregabalin that may also be appropriate to include in a prescriber education campaign.
- DUSC noted that the "regimen transition at initiation" analysis (see Table 5) indicated that the listing of pregabalin had not resulted in a significant reduction of strong opioid use (S8) or reduction in use of other neuropathic pain medicines. The DUSC therefore considered that pregabalin may not be reaching the populations with the most need for alternatives to current treatments.

DUSC commended the Secretariat for the quality of the analyses and considered that the assessment of the accuracy of submission cost offsets via the “regimen transition at initiation” analysis to be novel to DUSC analyses.

Actions undertaken by the Secretariat

This report was provided to the Sponsor of pregabalin (Pfizer Australia) for comment, including the opportunity to comment on the report prior to consideration by the DUSC.

DUSC actions

The DUSC requested that the report be provided to the PBAC and to NPS MedicineWise.

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.

Sponsors' comments

- Pfizer Australia Pty Ltd

Pfizer acknowledges that the DUSC Review provides a comprehensive assessment of the current use of pregabalin in neuropathic pain. Pfizer also welcomes the PBAC's request that NPS MedicineWise provide education on the appropriate use of pregabalin and the PBS subsidised indication.

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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Appendices

Appendix A: DVA patient analysis

Table A.1: Estimated drug regimen transitions at initiation to pregabalin

| Pre-initiation (week=-1) | Post-initiation (week=0) | Switch or Add? | Patients | % patients | Rank |
|--------------------------------|---|----------------|----------|------------|------|
| None | Pregabalin | Add | 1,222 | 31.3% | 1 |
| Opioid_S8 | Opioid_S8+Pregabalin | Add | 347 | 8.9% | 2 |
| Other_antidepressant | Other_antidepressant+Pregabalin | Add | 252 | 6.5% | 3 |
| Opioid_S4 | Opioid_S4+Pregabalin | Add | 119 | 3.0% | 4 |
| Opioid_S8+Other_antidepressant | Opioid_S8+Other_antidepressant+Pregabalin | Add | 111 | 2.8% | 5 |
| None | Opioid_S8+Pregabalin | Add | 104 | 2.7% | 6 |
| Opioid_S8 | Pregabalin | Switch | 99 | 2.5% | 7 |
| TCA | Pregabalin+TCA | Add | 76 | 1.9% | 8 |
| SNRI | Pregabalin+SNRI | Add | 72 | 1.8% | 9 |
| Tramadol | Pregabalin+Tramadol | Add | 59 | 1.5% | 10 |
| Opioid_S4 | Pregabalin | Switch | 58 | 1.5% | 11 |
| TCA | Pregabalin | Switch | 48 | 1.2% | 12 |
| Opioid_S8+TCA | Opioid_S8+Pregabalin+TCA | Add | 41 | 1.0% | 13 |
| Other_antidepressant | Pregabalin | Switch | 33 | 0.8% | 14 |
| Opioid_S4+Other_antidepressant | Opioid_S4+Other_antidepressant+Pregabalin | Add | 29 | 0.7% | 15 |
| None | Opioid_S4+Pregabalin | Add | 26 | 0.7% | 16 |
| Tramadol | Pregabalin | Switch | 26 | 0.7% | 17 |
| Opioid_S8+SNRI | Opioid_S8+Pregabalin+SNRI | Add | 23 | 0.6% | 18 |
| Opioid_S4+Other_antidepressant | Other_antidepressant+Pregabalin | Switch | 21 | 0.5% | 19 |
| Anticonvulsant | Anticonvulsant+Pregabalin | Add | 20 | 0.5% | 20 |
| None | Pregabalin+Tramadol | Add | 18 | 0.5% | 21 |
| Opioid_S8+Tramadol | Opioid_S8+Pregabalin+Tramadol | Add | 17 | 0.4% | 22 |
| Other_antidepressant | Opioid_S8+Other_antidepressant+Pregabalin | Add | 17 | 0.4% | 23 |
| Opioid_S8+Other_antidepressant | Other_antidepressant+Pregabalin | Switch | 15 | 0.4% | 24 |
| Opioid_S4+Opioid_S8 | Opioid_S4+Opioid_S8+Pregabalin | Add | 13 | 0.3% | 25 |
| Opioid_S8+Tramadol | Opioid_S8+Pregabalin | Switch | 13 | 0.3% | 26 |
| Anticonvulsant | Pregabalin | Switch | 13 | 0.3% | 27 |
| TCA | Opioid_S8+Pregabalin+TCA | Add | 12 | 0.3% | 28 |
| Opioid_S4+Opioid_S8 | Opioid_S8+Pregabalin | Switch | 12 | 0.3% | 29 |
| Anticonvulsant+Opioid_S8 | Anticonvulsant+Opioid_S8+Pregabalin | Add | 11 | 0.3% | 30 |
| Other_antidepressant+Tramadol | Other_antidepressant+Pregabalin+Tramadol | Add | 11 | 0.3% | 31 |
| Opioid_S8+TCA | Opioid_S8+Pregabalin | Switch | 11 | 0.3% | 32 |
| Opioid_S4 | Opioid_S4+Opioid_S8+Pregabalin | Add | 10 | 0.3% | 33 |
| None | Other_antidepressant+Pregabalin | Add | 10 | 0.3% | 34 |
| Other | Other | | 936 | 24.0% | |
| Total | | | 3,905 | 100% | |

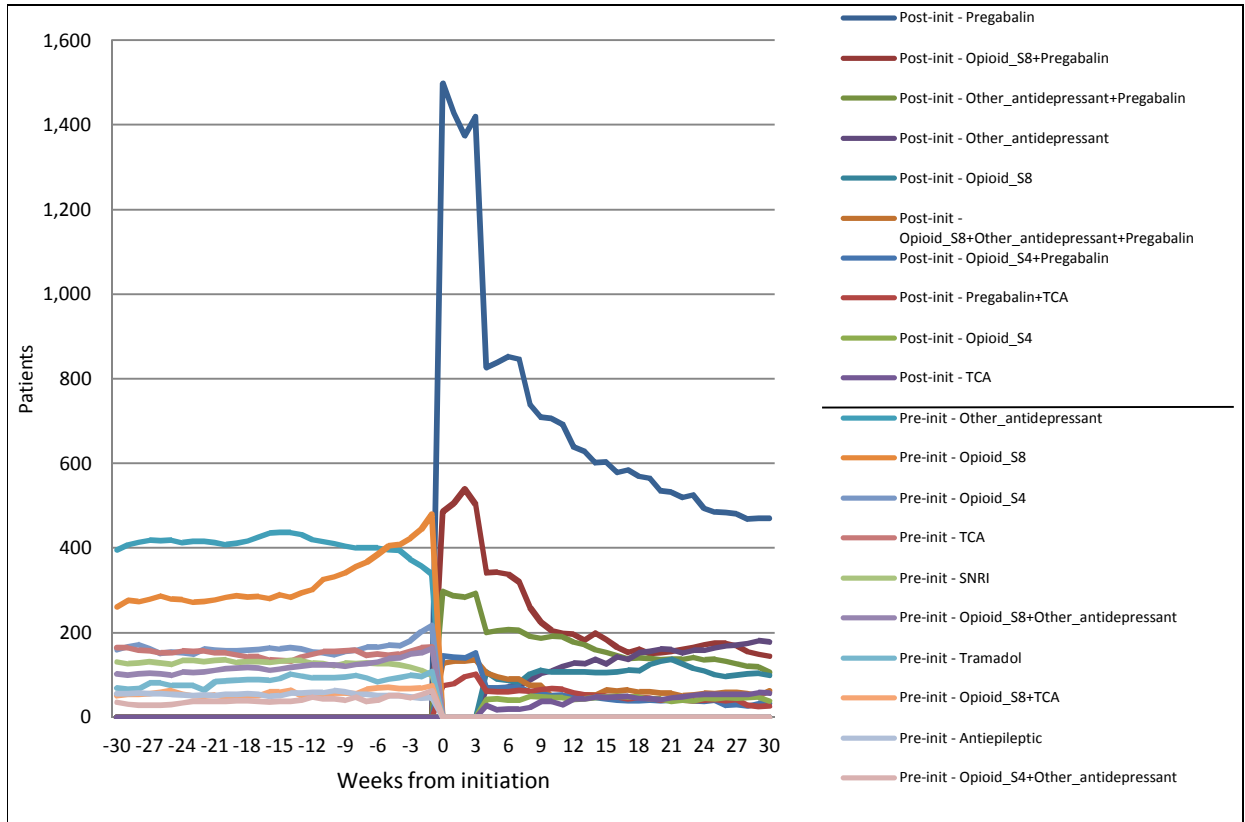


Figure A.1: Estimate drug regimens pre and post initiation to pregabalin

Appendix B:

Detailed methodology to estimate drug regimens and regimen transitions

Drug treatment regimens are estimated from prescription supply dates

The prescription data contains date of supply of each prescription, but no information on whether or not medicines should be (or were) co-administered. Thus co-administration was estimated from the data in the following way;

Step 1:

Determine the estimated medication coverage days for **each** drug or drug group.

This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode of treatment for each drug or drug group.

Step 2:

Determine the estimated medication coverage days **across all** drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every day in the data period.

Similar methods have been used for assessing medicine use in Australian populations.^{10,11} Hallas¹² describes the method and provides references to early variants.

Figure B.1 illustrates the method specified above. The standard coverage days (SCD) for each drug A, B & C have been shortened to 5 days to enable the figure to fit on one page. The Step 1 process results in the production of the episodes (pink bars) and the Step 2 process results in the production of the treatment regimen (blue bar). The days in this illustration are days from initiation (applicable to an incident patient analysis) but they can also be calendar days (applicable to a prevalent patient analysis).

In this illustration, a break in treatment is defined as a coverage gap of 2 or more SCDs (i.e. the patient has not received re-supply at two consecutive expected refill dates. The first gap in drug A coverage (from days -39 to -35) is not deemed to be a break in the drug A Episode 1 as the estimated gap in coverage is only 1 x SCD. The 2nd gap in drug A coverage from days -29 to -20 is deemed to be a break in treatment and the end of Episode 1 because the gap in estimated coverage is 2 x SCD.

The two prescriptions for drug B supplied on day -9 are interpreted as dose escalation of drug B, if each prescription is for a different strength. The two prescriptions are deemed to

¹⁰ Pratt N, Roughead EE, Ramsay E, Salter A, Ryan P 2011 "Risk of hospitalization for hip fracture and pneumonia associated with antipsychotic prescribing in the elderly: a self-controlled case-series analysis in an Australian health care claims database" *Drug Saf.* 34(7):567-75. doi: 10.2165/11588470-000000000-00000.

¹¹ Vitry AI, Roughead EE, Preiss AK, Ryan P, Ramsay EN, Gilbert AL, Caughey GE, Shakib S, Esterman A, Zhang Y, McDermott RA 2010 "Influence of comorbidities on therapeutic progression of diabetes treatment in Australian veterans: a cohort study" *PLoS One.* 5(11):e14024. doi: 10.1371/journal.pone.0014024.

¹² Hallas J. 2005 "Drug utilization statistics for individual-level pharmacy dispensing data" *Pharmacoepidemiol Drug Saf.* 14:455-463. doi: 10.1002/pds.1063.

be necessary to supply one SCD period and not used to extend the drug coverage period. If each prescription of drug B were for the same strength then this would be interpreted as “stockpiling” and assumed to extend the drug coverage period (see Details of Methodology below for details)

Drug C is a 3rd line agent and initiated on day 0 (by definition). The basic method imputes a short period of B+C, but a refinement of the method includes the calculation of an adjusted treatment regimen which removes short periods of overlap when it is likely that a switch has occurred before prior medicine is deemed to be fully used.

The final method for estimating the drug treatment regimen includes several refinements which are explained in below. Briefly they are:

1. Calculation of the treatment regimen on a weekly rather than daily basis.
2. Calculation of drug treatment regimen transitions – including an adjustment to allow for switching when the prior medication is not fully used.
3. Adjustment to allow for stockpiling of medication, both same-day supply and supplies on different days.
4. Change in the rules for prescriptions whose coverage spans the initiation data;
- removal of stockpiling rule
5. Estimating if a patient is continuing or stopping after their last script

Details of Methodology

1. Calculation of the treatment regimen

Drug treatment regimens are estimated from prescription supply dates in the following way;

Step 1:

Determine the estimated medication coverage days for **each** drug or drug group.

This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode for each drug or drug group.

Step 2:

Determine the estimated medication coverage days **across all** drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every day in the data period.

Step 2 above was modified so that the treatment regimen was estimated on a weekly rather than daily basis. This modification was deemed necessary to keep the data volume at a manageable level. This modification means that if the a medication coverage start date falls in a particular calendar week (for prevalent patient analysis) or week since initiation (for initiation analysis) then the medication is deemed to cover that week. The same rule was applied to the medication coverage end date.

2. Drug regimen transitions - including an adjustment to allow for switching when the prior medication is not fully used

Once estimated drug regimens have been determined for every week, then transitions can be computed.

These are useful for determining patient behaviour upon initiation of a drug; e.g. $A \rightarrow A+B$ (adding to existing therapy), $A \rightarrow B$ (switching) or $\text{None} \rightarrow A$ (starting therapy).

The transitions can be;

- A. previous drug regimen \rightarrow drug regimen at week x, or
- B. drug regimen at week -1 \rightarrow drug regimen at week x

Option A has the advantage that it can be calculated at any week, whereas Option B can only be calculated after initiation (i.e. from week 0). The main advantages of Option B are that it can easily be used to adjust the drug regimen in the first few weeks after initiation to allow for switching when the prior medication is not fully used. That is, if a patient switches from A to B, in the first few weeks after initiation to drug B the drug regimen may be incorrectly estimated to be A+B if the patient still has drug A "on hand" (i.e. some is unused) when drug B is initiated.

The regimen transitions are adjusted so that if a regimen transition corresponding to a switch (e.g. $A \rightarrow B$) is detected within the first X weeks after initiation (e.g. at week Y), then all weeks between the initiation (i.e. week 0) and week Y are modified to the switch transition (i.e. $A \rightarrow B$). This means some instances of " $A \rightarrow A+B$ " (apparent co-administration after a switch) are modified to " $A \rightarrow B$ " from week 0 to week Y (where $Y \leq X$). The value of X is the 1 week + SCD (expressed in weeks) for the drug or drug group that is being substituted.

This means that if a drug A was supplied 1 day before an initiation to drug B and then there were no further supplies of drug A, then there would be apparent co-administration of A and B from week 0 to week X-1 and in week X the drug regimen would be drug B only and considered a switch. Thus the regimens from weeks 0 to X-1 would be modified to be drug B only. If a switch is first detected in week X+1 then the A script would have been supplied in week 0 (i.e. at or after initiation to drug B) and this would mean that the transition was not a switch, but an add. Thus the logic is only applied to weeks 0 to X.

A transition is considered a switch if a drug in the regimen prior to initiation (the week=-1 regimen) is not in the regimen post initiation (i.e. the week=0 regimen).

After this transition adjustment, the drug regimens can also be adjusted by using the regimen after the arrow in the adjusted regimen transition. That is, if a transition gets adjusted from $A \rightarrow A+B$ to $A \rightarrow B$ in week Y then the adjusted drug regimen for week Y changes from A+B to B. Thus even though the drug regimen is calculated first, its adjustment is dependent on both the regimen transition and adjusted regimen transition. Thus the sequence of calculations is;

1. drug regimens
2. drug regimen transitions around initiation
3. adjusted drug regimen transitions
4. adjusted drug regimens

The above adjustment process is reliant on having regard to drug initiations. If the analysis is for prevalent drug regimens only (i.e. regimens by calendar week and not relative to an initiation date) then the above adjustment is not possible. This is not a major problem as the overestimation of co-administration (e.g. $A \rightarrow A+B$ instead of $A \rightarrow B$) is greatest in the month after initiation. In a prevalent patient analysis, patient initiations (to any and all drugs) are spread out in time (i.e. all patients do not generally initiate in the same week), and so the overestimation is also spread out over time and so minimised. In an initiating patient analysis, all over-estimations occur at the same time (as time is relative to the initiation week) and so the overestimation is significant and so needs to be adjusted for. In theory in a prevalent patient analysis, it is possible to do an initiation analysis for every drug and so find adjusted drug regimens that can then be re-expressed in calendar weeks. In practice this is too resource intensive and is unlikely to be make a significant difference to the prevalent patient drug regimens.

3. Adjustment to allow for stockpiling of medication, both same-day supply and supplies on different days

The two step methodology outlined in point 1 and refined by logic in point 2 above did not take into account the phenomenon of stockpiling. This often occurs towards the end of the calendar year when a Safety Net card holder fills prescriptions more frequently than expected, so as to stockpile the medicine and avoid a higher co-payment in the next calendar year when they lose Safety Net eligibility. Stockpiling can also occur at other times of the year. Step 1 can impute higher rates of breaks in episodes around February. This is likely to be due to the stockpiling effect and not due to genuine breaks in treatment. Thus the rule to estimate the prescription coverage end date was modified to be the greater of;

- the predicted coverage end date of the previous prescription plus the standard coverage days (SCD); and,
- the actual refill date of the previous prescription plus the SCD.

This way of calculating the prescription coverage end date takes into account medication stockpiling (i.e. early supply). The logic of the break rule remained unchanged, that is;

- a break was where a prescription was supplied 2 x SCD or more after the coverage end date of the previous prescription for the same drug or drug group.

Application of this refinement results in the reduction of the extent of seasonality in the number of breaks in episodes.

If multiple prescriptions of the same drug (but not the same strength) or drug group are supplied on the same day, it was assumed that these were necessary for the prescribed dose for the SCD and not for an extension of coverage.

If multiple prescriptions of the same drug are supplied it is generally for two different strengths to enable the prescribed dose to be administered. If two prescriptions for the same strength (as opposed to increased quantity for a single script) are supplied, the method assumes this is similar to stockpiling (i.e. same day stockpiling) and the predicted coverage end date is extended to be the greater of;

- the predicted coverage end date of the previous prescription plus $n \times$ SCD; and,
 - the actual refill date of the previous prescription plus $n \times$ SCD
- where n = number of prescriptions on the same day.

A special case of multiple prescriptions being supplied on the same day is Regulation 24 prescriptions.

If the original and repeat prescriptions were supplied under Regulation 24 on the same day, then this was assumed to extend the coverage period (i.e. coverage period = prescriptions x SCD).

4. Change in the rules for prescriptions whose coverage spans the initiation data; - removal of stockpiling rule

It was found that the stockpiling rule could result in the script coverage end date getting considerably ahead of the script supply date. This is the intent of the rule, however when a new drug B was initiated the stockpiling rules was resulting in the imputation that the new

drug B was being added to an existing drug A, when in all probability it was substituting drug A. To correct for this, the script coverage rule was changed so that if the script coverage period for a drug A script included the initiation date for drug B, then the stockpiling rule would not apply to the drug A script (i.e. its coverage would be from its supply date to the supply date + SCD). The rationale for this change is that even if patient has a lot of drug A on hand, the decision by the prescriber to initiate a new drug means that a switch could have occurred.

5. Estimating if a patient is continuing or stopping after their last script

If the last script in a patients script history is supplied within 2 x SCD of the end of the data period then the treatment is estimated to be continuing at the end of the data period (i.e. the episode coverage end date is set to the end date of the data period). Otherwise the treatment episode is estimated to have stopped and the episode coverage end date is equal to If the last script in a patients script history plus 1 x SCD.

Table B.1: Standard Coverage Days used in this analysis

| Drug or Drug Group | Standard Coverage Days (i.e. Median time to re-supply by any item of the same drug or drug group) |
|---------------------------|--|
| Anticonvulsant | 34 |
| Clonidine | 37 |
| Opioid_S4 | 27 |
| Opioid_S8 | 14 |
| Other_antidepressant | 29 |
| Pregabalin | 27 |
| SNRI | 28 |
| TCA | 32 |
| Tramadol | 17 |