# Armodafinil: predicted versus actual analysis

## Drug utilisation sub-committee (DUSC)

***June 2019***


### Abstract

***Purpose***

To compare the predicted and actual utilisation of armodafinil for narcolepsy since it was PBS listed for this indication.

***Date of listing on the Pharmaceutical Benefits Scheme (PBS)***

Armodafinil for the treatment of narcolepsy was PBS listed on 1 November 2016.

***Data Source / methodology***

The analysis used data from the Department of Human Services (DHS) supplied prescriptions database.

***Key Findings***

- The number of patients on therapy for narcolepsy has increased from 2014 to 2018, inclusive.
- There was a 35.9% increase in patients new to narcolepsy therapy from 2017 to 2018.
- The listing of armodafinil has increased the total narcolepsy market, with the number of people starting PBS subsidised armodafinil being higher than the number of patients starting modafinil since its listing.
- The listing of armodafinil has increased the overall government expenditure for PBS-subsidised narcolepsy therapy.
- Dexamfetamine was the most used drug for narcolepsy by prescription volume and number of prevalent patients from 2015-2018, inclusive.
- There was a steep increase in the number of patients starting dexamfetamine for narcolepsy from 178 patients in the second quarter of 2018 to 465 patients in the fourth quarter of 2018.

# Purpose of analysis

To compare the predicted and actual utilisation of armodafinil for narcolepsy since it was PBS listed for this indication on 1 November 2016.

# Background

## Clinical situation

Narcolepsy is a disorder of sleep-wake regulation. It is characterised by chronic daytime sleepiness, which may lead to uncontrollable sleep attacks.[1] Excessive daytime sleepiness is the main symptom of narcolepsy. Other symptoms include sudden loss of muscle tone, usually associated with strong emotion (cataplexy), muscle paralysis on falling asleep or waking (sleep paralysis) and vivid hallucinations on falling asleep (hypnagogic) or waking (hypnopompic).[2] It is often extremely incapacitating, interfering with every aspect of life, in work and social settings. It usually begins between the ages of 10 and 20 years with the sudden onset of persistent daytime sleepiness, although it can also develop gradually.[3]

Narcolepsy is treated with a combination of behavioural and pharmacological approaches.[2] According to the Australian therapeutic guidelines, modafinil and armodafinil are first line drugs for the treatment of increasing alertness in narcolepsy. Other drugs that may be prescribed include dexamphetamine and methylphenidate.[1]

## Pharmacology

The exact mechanism through which armodafinil promotes wakefulness in unknown. Armodafinil is the R-enantiomer of modafinil (1:1 mixture of R and S enantiomers). It has wake promoting actions similar to sympathomimetic agents including amphetamine and methylphenidate, although the pharmacological profile is not identical to that of the sympathomimetic amines. In vitro armodafinil binds to the dopamine transporter and inhibits dopamine uptake.[4]

## Therapeutic Goods Administration (TGA) approved indications

Armodafinil is indicated:

- to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy;
- to treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where non-pharmacological interventions are unsuccessful or inappropriate; and

[1] General information on idiopathic hypersomnolence and narcolepsy. [revised 2017 Nov]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2019.
[2] Billiard M, Dauvilliers Y, Dolenc-Groselj L et al. European Handbook of neurological management. 2nd ed. Blackwell Publishing Ltd; 2011. Chapter 28, Management of narcolepsy in adults;p.513-28.
[3] Scammell TE. Narcolespy. N Engl J Med 2015;373:2654-62.

- as an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness.[4]

## Dosage and administration

The recommended dose of armodafinil for patients with narcolepsy is 150 mg or 250 mg given once daily in the morning.[4]

## PBS listing details

Armodafinil for the treatment of narcolepsy was PBS listed on 1 November 2016. Table 1 provides the PBS listing details as at 1 April 2019. Armodafinil has the same PBS restriction as modafinil.

**Table 1: PBS listing of Armodafinil**

| Item | Name, form & strength, pack size | Max. quant packs. | Rpts | DPMQ | Brand name and manufacturer |
|---|---|---|---|---|---|
| 10912H | Armodafinil, 150 mg tablet, 30 | 1 | 5 | $153.58 | Nuvigl |
| 10919Q | Armodafinil, 250 mg tablet, 30 | 1 | 5 | $250.41 | Nuvigil |
| 10922W | Armodafinil, 50 mg tablet, 30 | 2 | 5 | $106.17 | Nuvigil |

Source: Department of Health (2019), Schedule of Pharmaceutical Benefits.

***Restriction***

**Authority Required**

Narcolepsy

**Treatment Phase:** Initial treatment

**Treatment criteria:**

Must be treated by a qualified sleep medicine practitioner or neurologist.

**Clinical criteria:**

The treatment must be for use when therapy with dexamfetamine sulfate poses an unacceptable medical risk; OR

[4] Nuvigil (Armodafinil). Australian Approved Product Information. NSW: TEVA Pharma Australia Pty Ltd. Approved 26 November 2015. Most recent revision 17 July 2018. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-02888-1&d=201904011016933.>

The treatment must be for use when intolerance to dexamfetamine sulfate is of a severity to necessitate treatment withdrawal,

AND

Patient must have experienced excessive daytime sleepiness, recurrent naps or lapses into sleep occurring almost daily for at least 3 months,

AND

Patient must have a definite history of cataplexy; OR

Patient must have a mean sleep latency less than or equal to 10 minutes on a Multiple Sleep Latency Test (MSLT); OR

Patient must have an electroencephalographic (EEG) recording showing the pathologically rapid development of REM sleep,

AND

Patient must not have any medical or psychiatric disorder that could otherwise account for the hypersomnia.

The presence of any one of the following indicates treatment with dexamfetamine sulfate poses an unacceptable medical risk:

(a) a psychiatric disorder;

(b) a cardiovascular disorder;

(c) a history of substance abuse;

(d) glaucoma;

(e) any other absolute contraindication to dexamfetamine sulfate as specified in the TGA-approved Product Information.

The MSLT must be preceded by nocturnal polysomnography. Sleep prior to the MSLT must be at least 6 hours in duration.

**Treatment Phase:** Continuing treatment

**Clinical criteria:**

Patient must have previously received PBS-subsidised treatment with this drug for this condition.

For details of the current PBS listing refer to the PBS website.

## Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

### *Major submission for armodafinil- November 2015*

A submission for armodafinil was initially considered and rejected by the PBAC at its November 2015 meeting. The submission nominated modafinil as the comparator and the PBAC agreed that modafinil was appropriate, but considered that a comparison against the split dose regimen of modafinil was also relevant. The PBAC noted that there was no apparent unmet clinical need for armodafinil.[5]

This submission estimated the equi-effective doses as armodafinil [redacted] mg and modafinil [redacted] mg, and a dose relativity of [redacted] (armodafinil vs modafinil) based on mean doses used in five single arm studies. The PBAC considered that the basis for calculating the equi-effective doses was unreliable and that the equi-effective dose had not been adequately established in the submission.[5]

The PBAC noted that the submission estimated a net cost to the PBS from the listing of armodafinil. Considering the submission's claim of non-inferiority of armodafinil to modafinil and the cost minimisation approach taken, the PBAC considered that the listing of armodafinil should be cost neutral.[5]

The sponsor indicated it would offer a [redacted]% price reduction upon the listing of the first generic version of modafinil.[5]

### *Minor resubmission for armodafinil-March 2016*

A resubmission for armodafinil in narcolepsy was considered by PBAC at its March 2016 meeting. The resubmission presented data describing the differences between armodafinil and modafinil (Table 2). The resubmission proposed that these differences were substantive enough to have a clinical impact and that patients not responding to one drug may respond to the other therapy.[6]

[5] Department of Health (2015), PBAC Meeting Public Summary Documents: Armodafinil, Updated 10 April 2016. Accessed on 2 April 2019, at: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-11/files/armodafinil-psd-november-2015.pdf

[6] Department of Health (2016), PBAC Meeting Public Summary Documents: Armodafinil, Updated 01 July 2016. Accessed on 2 April 2019, at: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/armodafinil-psd-march-2016.pdf

**Table 2: Comparison of key properties of armodafinil and modafinil**

| | Armodafinil | Modafinil |
|---|---|---|
| **ATC Code** | N06BA13 | N06BA07 |
| **Enantiomers** | contains solely the R-enantiomer of modafinil | contains both the "R" and "S" enantiomers of modafinil |
| **Strengths** | 50, 150 and 250 mg | 100 mg |
| **Dosing** | Starting Dose: 150mg<br>Narcolepsy: 150 mg or 250 mg given once daily in the morning. | Starting Dose: 200mg<br>Narcolepsy: 200 to 400 mg/day, given as a single dose in the morning, or as two divided doses, in the morning and at noon.<br>Doses of 400 mg/day have been well tolerated, but there is no statistically significant evidence that this dose confers additional benefit beyond that of the 200 mg dose. It is proposed that split dosing may be appropriate for patients who experience a late afternoon dip in wakefulness at a proposed dosing of 400mg spilt into 200mg in the morning and 200mg at noon.<br>For patients who require more than 200 mg/day, the dose should be increased, to a maximum of 400 mg/day, in increments of 100 mg as needed and tolerated. |
| **Recommended Starting Dose** | 150mg | 200 mg |
| **Cmax** | 2.99 µg/mL after a 100 mg dose<br>5.9 µg/mL after a 250 mg dose | 3.3 mg/mL after a 200 mg dose |

The resubmission used the maximum dose (250 mg daily) instead of the weighted average dosing, and presented the revised equi-effective doses of armodafinil 250 mg and modafinil 348.55 mg, resulting in a dose relativity of 5:7. The sponsor proposed a further price reduction of approximately [redacted]% based on the revised therapeutic relativity presented in the resubmission.[6]

The PBAC recommended an Authority Required listing for armodafinil for the treatment of narcolepsy on a cost-minimisation basis with modafinil. In making its recommendation, the PBAC considered that the revised equi-effective doses presented in the re-submission were reasonable.[6]

The PBAC maintained its previous view that there was no apparent unmet clinical need for armodafinil. The PBAC noted the resubmission's claims of differences in plasma concentrations and dose response, however the PBAC was not convinced that these differences would result in armodafinil having any appreciable clinical advantage over modafinil.[6]

The PBAC noted that over time, armodafinil may cease to be cost-effective due to decreases in the modafinil price as a result of patent expiry and the introduction of generic versions of modafinil. The PBAC noted that at some point in the future, the Minister may wish to seek advice from the PBAC regarding the ongoing cost-effectiveness of armodafinil.[6]

The PBAC noted that the resubmission proposed cost savings to Government upon the listing of armodafinil, however considered that these savings will not be realised if the price of modafinil decreases over time.[6]

***Minor submission for modafinil-November 2008***

A submission from the Australian Sleep Association (ASA) and the Australian New Zealand Association of Neurologists (ANZAN) joint working party for instatement of modafinil as first line therapy for narcolepsy was considered by the PBAC at its November 2008 meeting.[7]

The PBAC did not accept the premise of the submission that from a medical and legal view, dexamfetamine can no longer be considered the standard of care for treatment of this lifelong condition, and was not an appropriate comparator for modafinil in the first-line setting. The PBAC noted that the absence of a systematic review of the evidence in support of this statement was a significant impediment to its deliberations. Additionally, the comment made both in the Pre-Sub-Committee response and in a hearing that not all patients currently on dexamfetamine will switch to modafinil appeared to contradict the first statement.[7]

The PBAC recalled that the incremental benefit (efficacy and safety) of modafinil over dexamfetamine had not been previously established in the first-line setting. It was the large difference between the prices of the two drugs that forced the PBAC to consider the construct of the second-line indication and a comparison with placebo to be developed for modafinil in order for the product to be made available to patients.[7]

The PBAC further considered that the omission of economic analyses was inappropriate. It was noted that modafinil and dexamfetamine have drug costs of $3327 vs. $318 per year, respectively, for life long therapy and uncertain relative net clinical effect, particularly in the long term.[7]

The PBAC acknowledged the letter provided by the ASA suggesting that there was a clinical need for the restriction to be broadened. However the criteria in the current restriction were based upon internationally accepted standards and no data or references were provided in support of the claims made in the Pre-Sub-Committee response regarding the proportion of narcolepsy patients currently being denied modafinil treatment as a result of requirements related to the MSLT.[7]

[7] Department of Health (2008), PBAC Meeting Public Summary Documents: Modafinil, Updated 19 MAR 2009. Accessed on: 02 April 2019, at: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2008-11/pbac-psd-modafinil-nov08.pdf

The PBAC therefore rejected the application because of insufficient evidence to support the claim that placebo rather than dexamfetamine is the appropriate comparator for modafinil in the first line setting and because of insufficient evidence to substantiate the claim that eligible patients are being denied treatment under the current restriction.[7]

The PBAC indicated its willingness to hold further dialogue with the working party and other relevant stakeholders on the restriction's diagnostic criteria.[7]

### Approach taken to estimate utilisation

The November 2015 submission used a market-share approach to estimate the use and costs of listing armodafinil on the PBS.[5]

### Previous reviews by the DUSC

DUSC reviewed the 12 month predicted versus actual use of modafinil at the September 2006 meeting. At 12 months, actual number of PBS prescriptions of modafinil supplied was [redacted] compared to the predicted [redacted] prescriptions. DUSC considered this justified the concerns raised previously by DUSC regarding difficulties in estimating patient numbers for narcolepsy. DUSC also noted that the wording of the restriction was effective in limiting uptake to the desired patient population.[8]

## Methods

Prescription data for armodafinil, modafinil and dexamfetamine were extracted from the Department of Human Services (DHS) PBS prescription claim database for the period April 2005 to February 2019, inclusive. This database contains data on PBS prescriptions submitted to DHS for payment of a R/PBS subsidy by the Government. The prescription data were used to determine the number of prescriptions supplied and for the R/PBS expenditure and prescriber type analyses.

Prescriber type was attributed to the de-identified approval number of the prescriber by the DHS and was based on the major field of specialty, derived from the combination of the current registered specialty and the most Medicare services provided per quarter. Prescribers can work in several different specialties but are allocated by DHS to one major field of specialty per quarter.

The R/PBS prescription data were also used to determine the number of incident (new to pharmacological treatment) and prevalent (number treated) patients. Patient counts were based on de-identified unique patient identification numbers (PINs) from the prescription data.

Location and drug sequence analyses were undertaken for all patients supplied dexamfetamine, modafinil and armodafinil. The rate of people supplied narcolepsy therapy standardised per 1,000 population in each state and territory was calculated based on the

[8] Drug Utilisation Sub-Committee. DUSC predicted versus actual analysis of modafinil. Canberra: Australian Department of Health: 2006. Unpublished.

Australian Bureau of Statistics (ABS) Quarterly Population Estimates by State/Territory in September 2018 data and the DHS database. For the sequence of treatment analysis, unique patient counts were derived for each sequence of treatment.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available DHS Medicare date of processing data. The publicly available DHS Medicare data only includes subsidised R/PBS prescriptions with prescriptions under the patient co-payment not included.

# Results

## Analysis of drug utilisation

### *Overall utilisation*

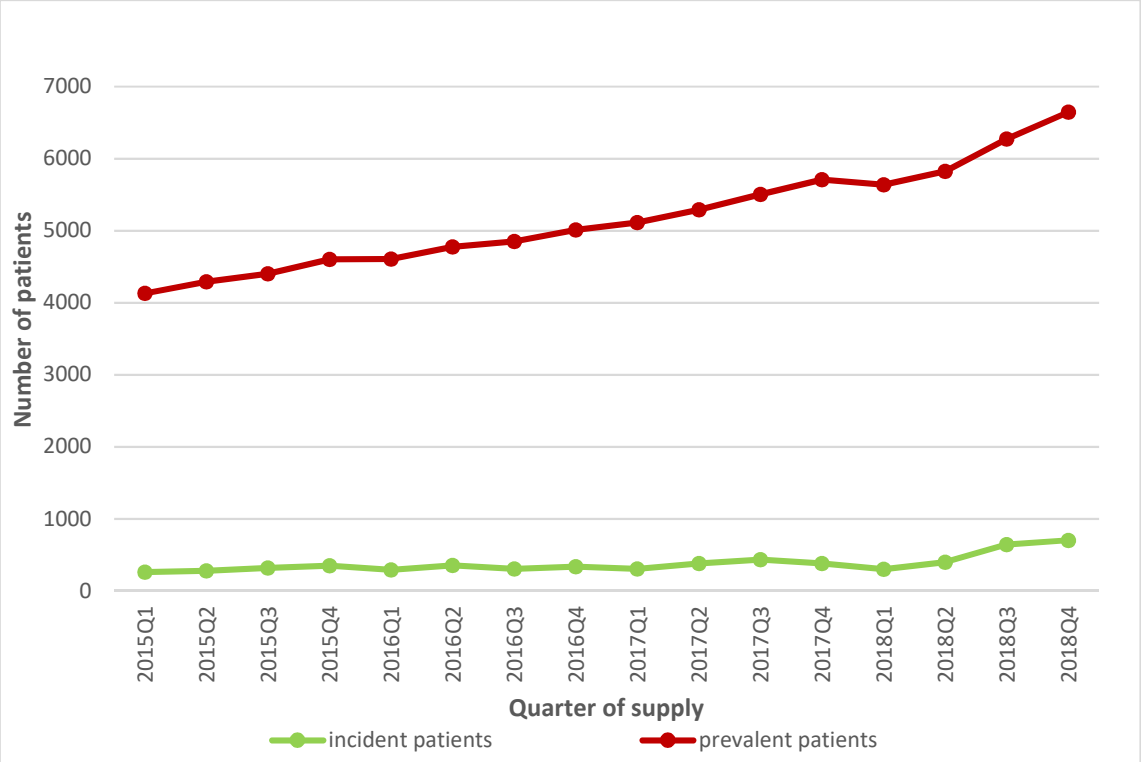


**Figure 1: Number of incident and prevalent patients to narcolepsy therapy (dexamfetamine, modafinil and armodafinil)**

Source: DHS PBS prescription database, extracted April 2019

The number of patients incident and prevalent to PBS subsidised narcolepsy therapy in the two years before and the two years after the PBS listing of armodafinil (1 November 2016) is presented in Figure 1.

**Table 4: Number and percentage growth of patients incident and prevalent to all narcolepsy therapy**

| Calendar Year | Prevalent patients (% growth from previous year ) | Incident patients (% growth from previous year) |
|---|---|---|
| **2014** | 5,258 | 1,062 |
| **2015** | 5,804 (10.38%) | 1,210 (13.94%) |
| **2016** | 6,449 (11.11%) | 1,293 (6.86%) |
| **2017** | 7,256 (12.51%) | 1,506 (16.47%) |
| **2018** | 8,454 (16.51%) | 2,047 (35.92%) |

Source: DHS PBS prescription database, extracted April 2019

Table 4 shows the number of patients incident and prevalent to narcolepsy therapy per calendar year from 2014 to 2018. The total number of patients on therapy for narcolepsy increased over the four-year period. The number of incident patients to narcolepsy therapy also increased over the same period, with a 35.9% increase in the number of incident patients between 2017 and 2018.

***Changes in the use of other drugs***

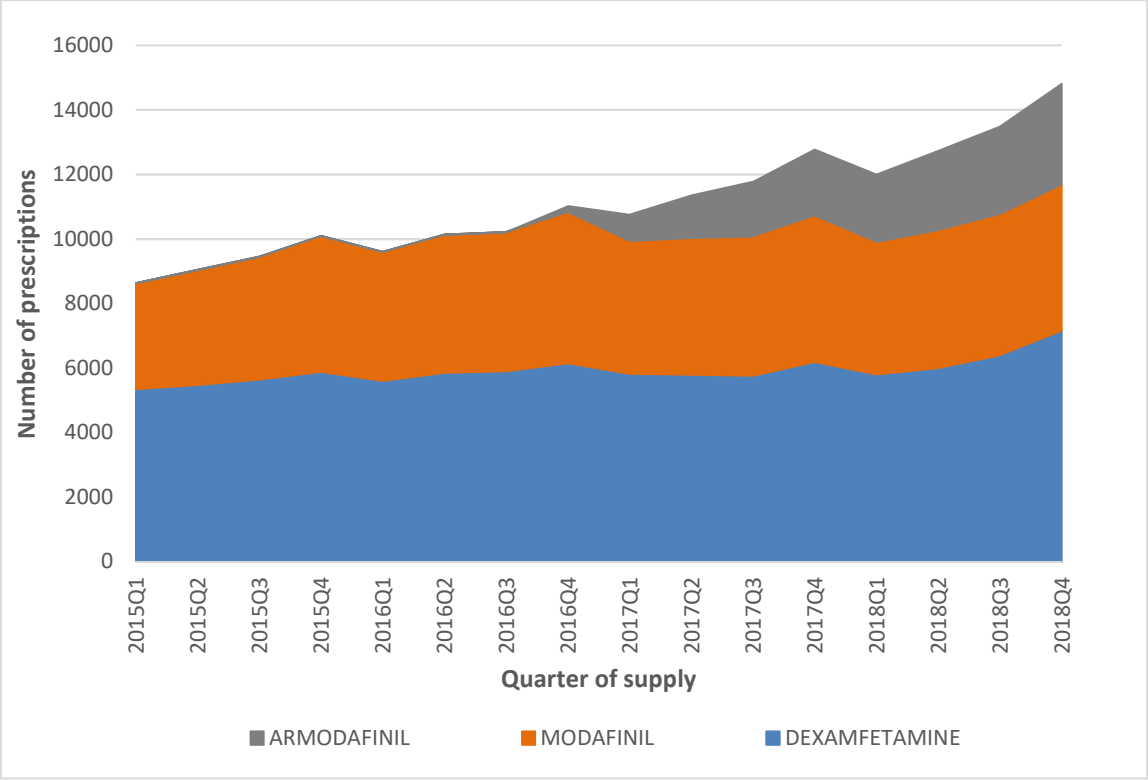


**Figure 2: Number of PBS/RPBS dexamfetamine, modafinil and armodafinil prescriptions supplied per quarter**

Source: DHS prescription database, extracted April 2019

Figure 2 illustrates the use of PBS listed medicines for narcolepsy since the first quarter of 2015. Dexamfetamine was the most used drug for narcolepsy by prescription volume over the period. The listing of armodafinil appears to have increased the total market.

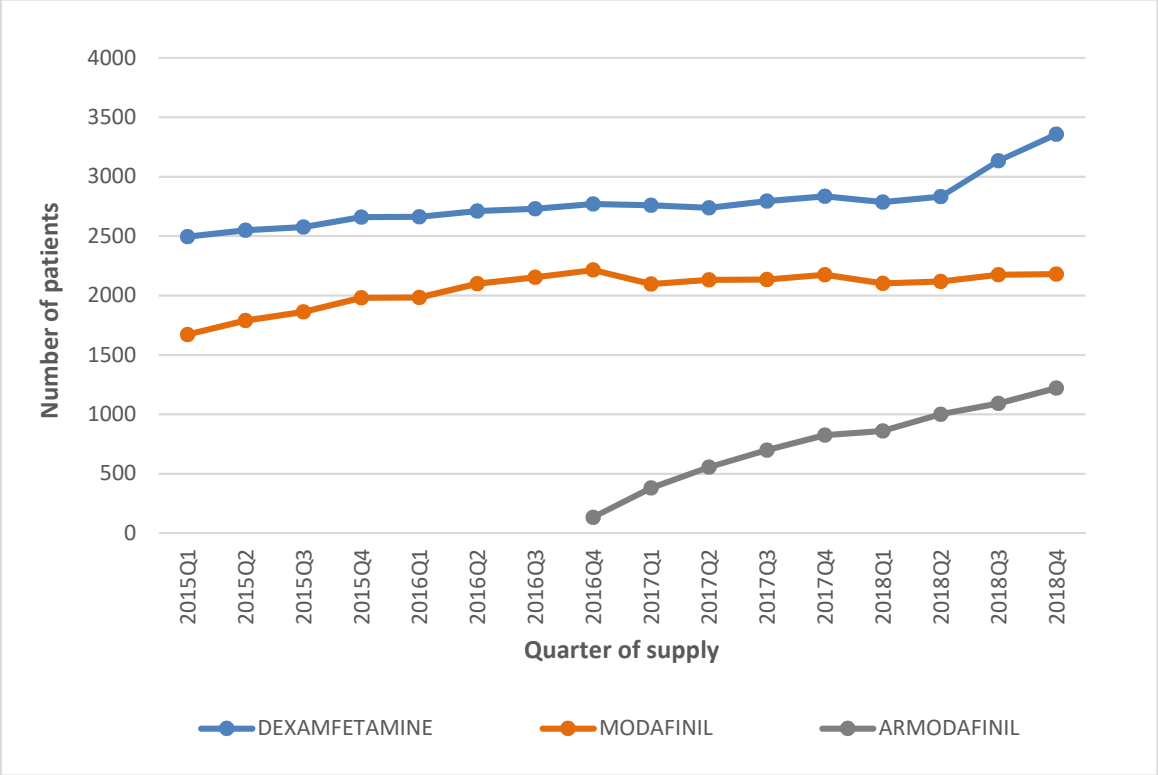


**Figure 3: Prevalent patients by drug by quarter**

Source: DHS PBS prescription database, extracted April 2019

Figure 3 depicts the number of patients supplied each narcolepsy medicine by quarter, from the first quarter of 2015 to fourth quarter 2018. Patients may be double-counted if they are supplied more than one narcolepsy medicine in the same quarter. Dexamfetamine was the most commonly supplied narcolepsy medicine over this period. The number of patients supplied dexamfetamine increased at a higher rate between second and fourth quarter of 2018. The use of modafinil was increasing at a steady rate until the listing of armodafinil, and then the number of patients decreased marginally and started to plateau. There has been a steady increase in the number of patients supplied armodafinil since it was PBS listed in the fourth quarter of 2016.

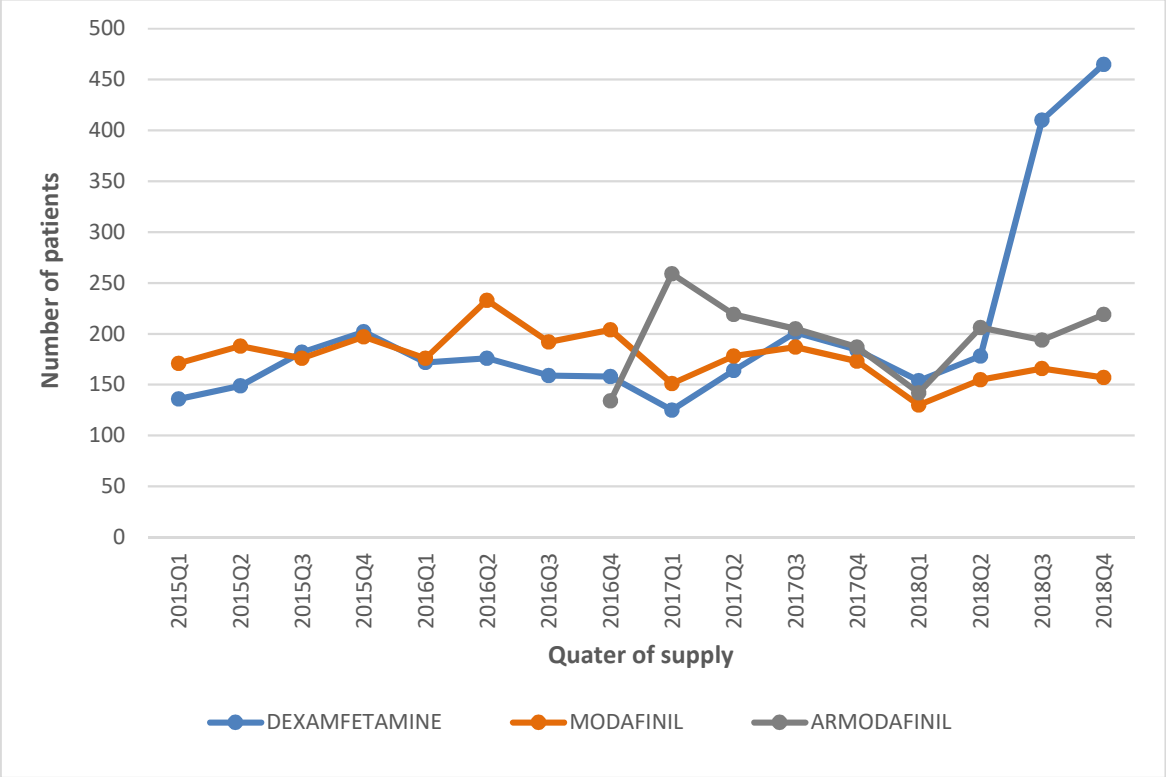


**Figure 4: Initiating patients by drug by quarter**

Source: DHS prescription database, extracted April 2019

The number of patients initiating each PBS-subsidised narcolepsy medicine per quarter is shown in Figure 4. Patients may be double-counted within a quarter if they have switched between narcolepsy medicines. There was a steep increase in the number of patients starting dexamfetamine from 178 patients in the second quarter of 2018 to 465 patients in the fourth quarter of 2018. Since the listing of armodafinil, the number of patients initiating armodafinil is higher than the number of patients starting modafinil.

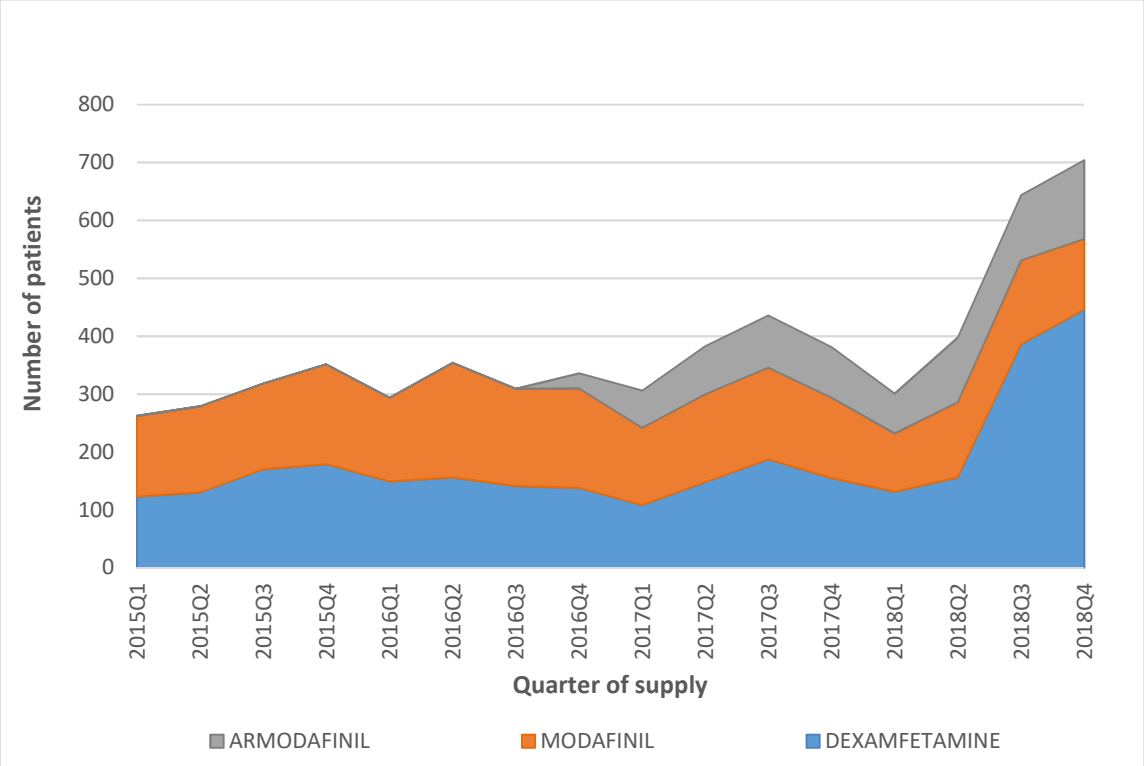


**Figure 5: Patients incident to narcolepsy therapy per quarter**

Source: DHS PBS prescription database, extracted April 2019

Figure 5 shows the number of new patients per quarter by their first ever PBS-subsidised narcolepsy medicine. The listing of armodafinil increased the overall market, with the number of people starting narcolepsy therapy with armodafinil surpassing the number starting with modafinil in the fourth quarter of 2018. The listing of armodafinil had minimal effect on the number of people initiating therapy for narcolepsy with dexamfetamine and modafinil. A similar number of new patients started therapy for narcolepsy with dexamfetamine and modafinil until the second quarter of 2018, when there was a steep increase in the number of people initiating therapy with dexamfetamine.

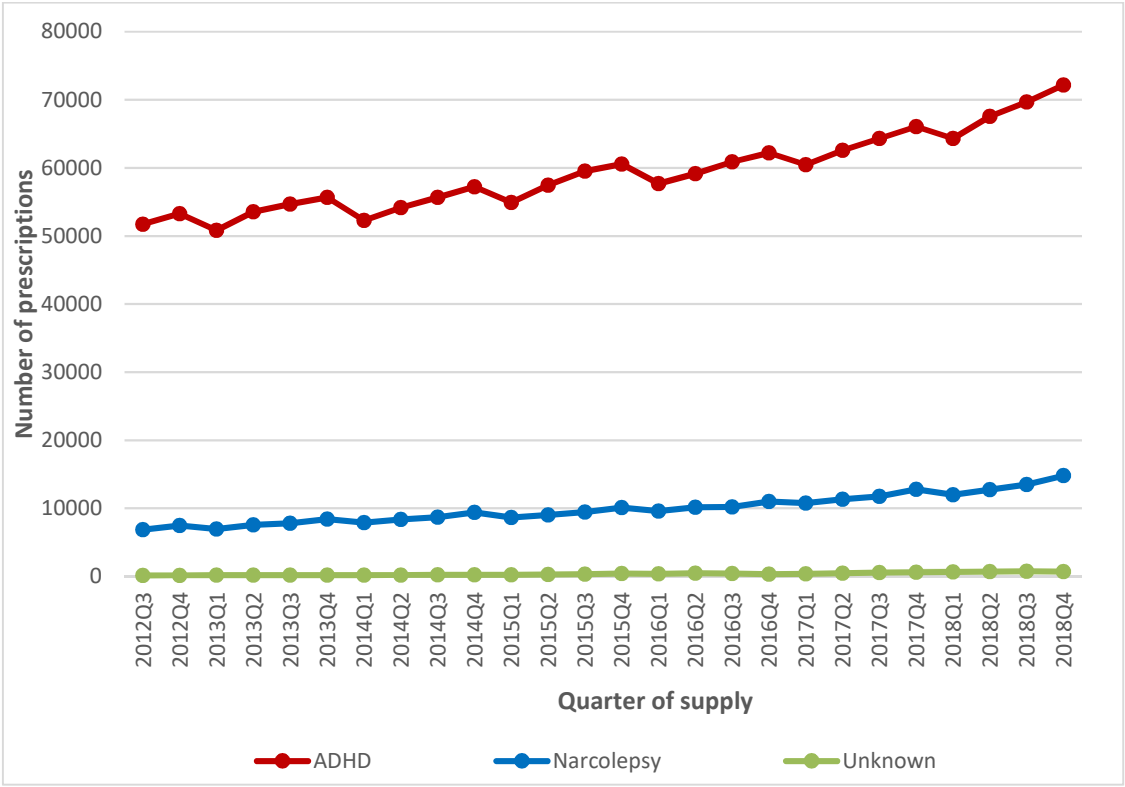


**Figure 6: Number of prescriptions of dexamfetamine by indication by quarter**

Source: DHS PBS prescription database, extracted April 2019

Analysis of dexamfetamine use in narcolepsy showed a steep increase in the number of people using dexamfetamine from the second quarter of 2018. Further analysis of the overall use of PBS-subsidised dexamfetamine showed that there was an increase in the volume of prescriptions of dexamfetamine supplied for Attention Deficit Hyperactivity Disorder (ADHD) by 8% and for narcolepsy by 13.6% between 2017 to 2018 (Figure 6).

***Prescribers***

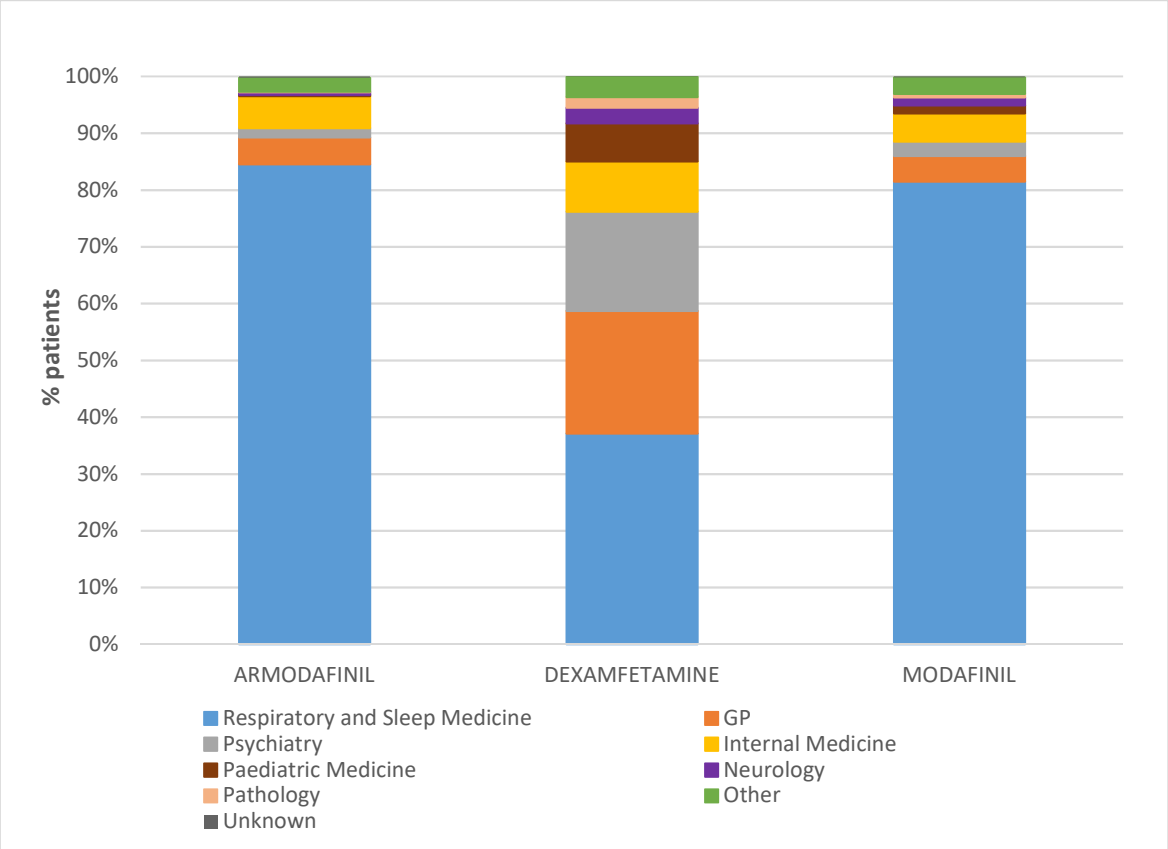


**Figure 7: Patients incident to narcolepsy therapy by drug and prescriber in 2018**

Source: DHS PBS prescription database, extracted April 2019

Dexamfetamine is classified as a Schedule 8 medicine under the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Schedule 8 medicines are controlled drugs that require additional restrictions in manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.[9] Each State and Territory has regulations that stipulate the conditions under which medical practitioners are able to prescribe dexamfetamine for narcolepsy. The PBS restriction for modafinil and armodafinil requires that a qualified sleep medicine practitioner or neurologist prescribe the initial treatment, but there is no prescriber restriction for continuing treatment.

Figure 7 shows the type of prescribers initiating PBS subsidised narcolepsy therapy. The largest proportion of armodafinil and modafinil prescriptions supplied to patients starting narcolepsy therapy were written by respiratory and sleep medicine specialists. Specialists in respiratory and sleep medicine, followed by GPs and psychiatrists, most commonly

[9] Department of Health. Standard for the Uniform Scheduling of Medicines and Poisons February 2019. Available from https://www.legislation.gov.au/Details/F2019L00032/Html/Text#_Toc532805033

prescribed first prescriptions to patients supplied dexamfetamine as their first narcolepsy therapy.

***Utilisation by State/Territory***

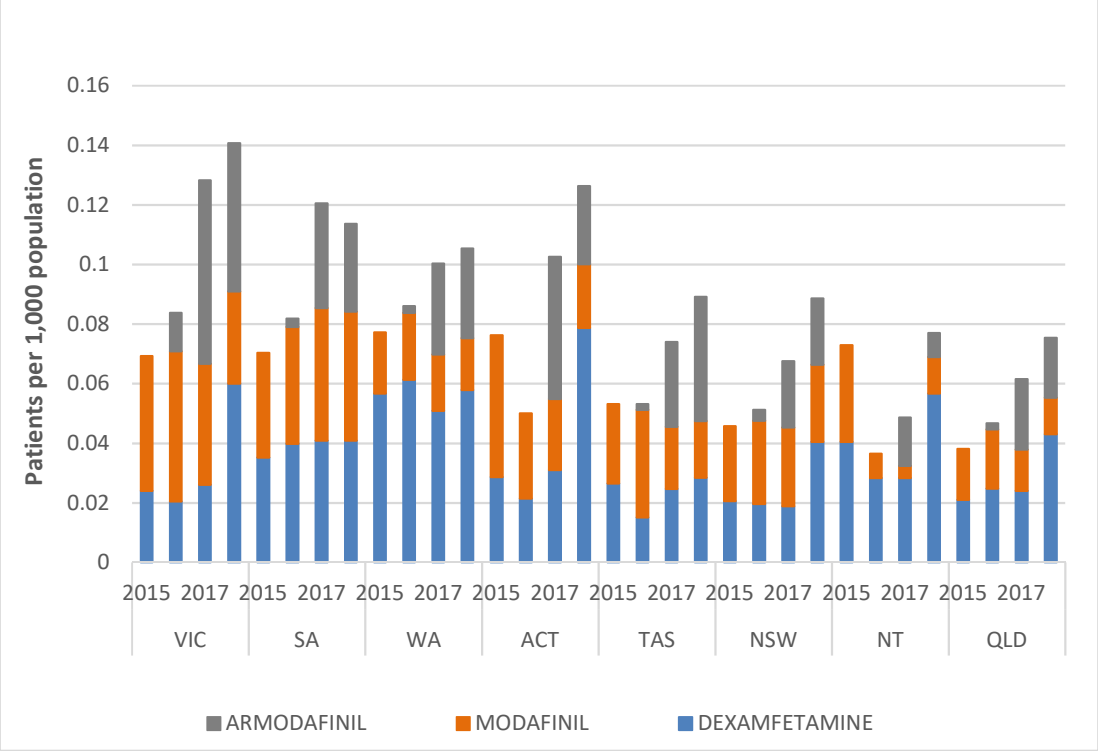


**Figure 8: Incident patients per 1,000 population by drug and state 2015-2018**

Source: DHS prescription database, extracted April 2019

Figure 8 illustrates the number of new patients supplied a PBS subsidised medicine for narcolepsy per 1,000 population, adjusted to account for the population size of each State and Territory in 2018. The rate of new patients starting dexamfetamine for narcolepsy has increased in all states except for Western Australia where there was some fluctuation over the four-year period. A larger difference can be seen in the rate of dexamfetamine supplied to new patients between 2017 and 2018 in Victoria, Australian Capital Territory, New South Wales, Northern Territory and Queensland. There has been considerable uptake of armodafinil in South Australia, Western Australia, Australian Capital Territory, Tasmania and Victoria, with Victoria having the highest rate of new patients starting armodafinil in the first 24 months after listing.

### *Sequence of therapy*

**Table 5: Drug initiation sequence for narcolepsy therapy**

| Drug initiation sequence | PERCENT |
|---|---|
| DEXAMFETAMINE | 52.4 |
| MODAFINIL | 25.9 |
| DEXAMFETAMINE -> MODAFINIL | 5.7 |
| ARMODAFINIL | 5.6 |
| MODAFINIL -> ARMODAFINIL | 4.2 |
| MODAFINIL -> DEXAMFETAMINE | 3.1 |
| DEXAMFETAMINE -> ARMODAFINIL | 1.3 |
| DEXAMFETAMINE -> MODAFINIL -> ARMODAFINIL | 0.9 |
| MODAFINIL -> DEXAMFETAMINE -> ARMODAFINIL | 0.5 |
| OTHER | 0.5 |

Source: DHS PBS prescription database, extracted April 2019

The PBS clinical criteria for initiating treatment with modafinil or armodafinil restrict use to patients where therapy with dexamfetamine sulfate poses an unacceptable medical risk or when intolerance to dexamfetamine sulfate is of a severity to necessitate treatment withdrawal. Table 5 shows the drug initiating sequence for narcolepsy therapy with a look back period until 01 April 2005 when modafinil was PBS listed for narcolepsy. Armodafinil has less chance to appear in the data presented as it was listed on the PBS on 1 November 2016.

The majority of patients (83.9%) were only supplied one PBS listed therapy for narcolepsy in this period. 39.8% of patients were initiated treatment for narcolepsy with modafinil or armodafinil. 4.1% of patients were prescribed dexamfetamine after modafinil or armodafinil.

## Analysis of expenditure

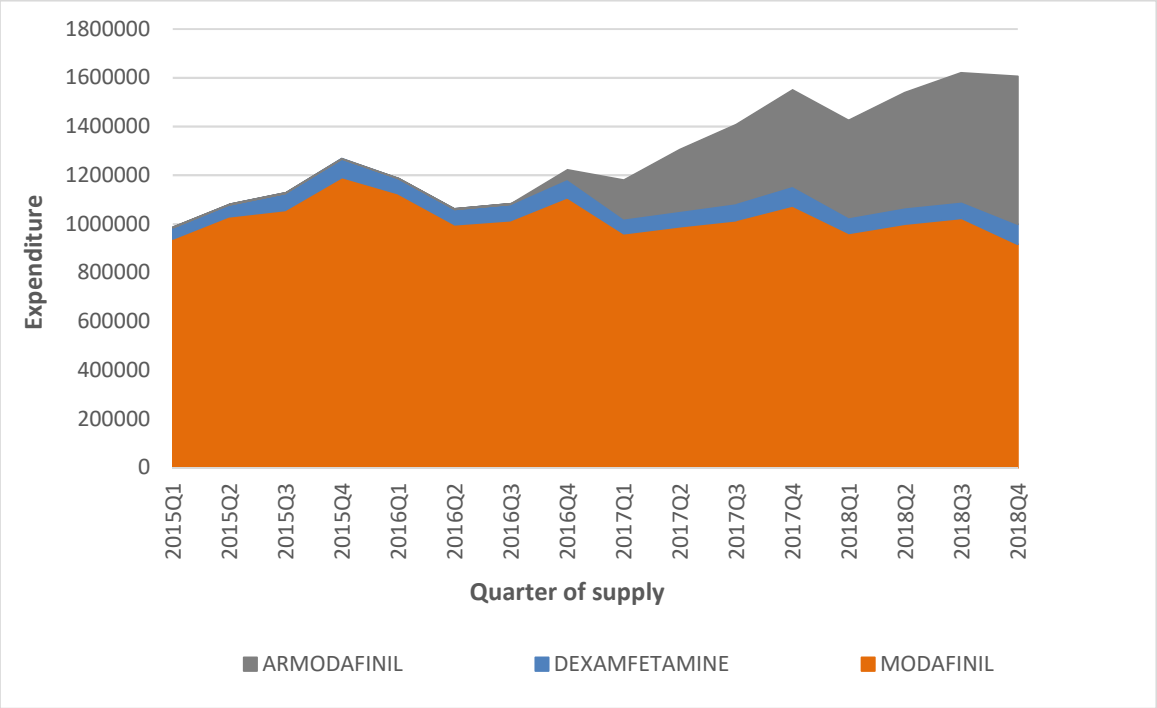


**Figure 9: PBS benefit by drug by quarter for PBS subsidised narcolepsy therapy**

Source: DHS PBS prescription database, extracted April 2019

Figure 9 presents PBS benefits for armodafinil, modafinil and dexamfetamine. The listing of armodafinil has increased the overall government expenditure for PBS-subsidised narcolepsy therapy.

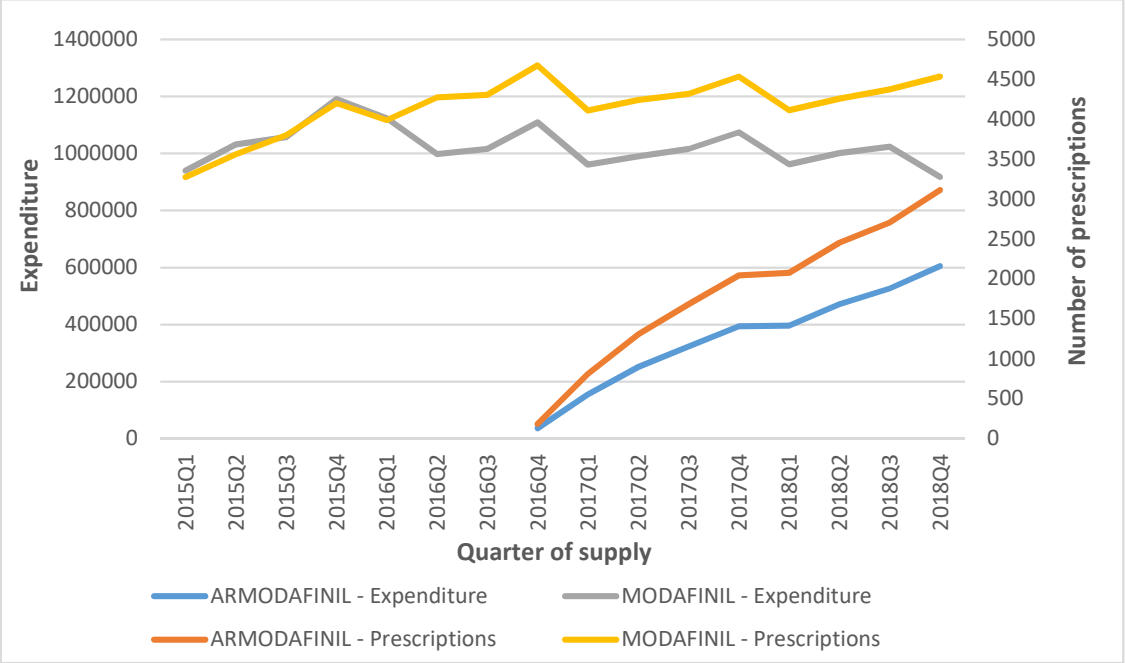


**Figure 10: Total number of prescriptions and PBS benefit for PBS subsidised modafinil and armodafinil**

Source: DHS PBS prescription database, extracted April 2019

Modafinil was listed on the PBS for narcolepsy on 1 April 2005. Modafinil received a 16% statutory price reduction (SPR) on the 1 April 2016 (beginning of second quarter) with a listing of a new brand and a price disclosure reduction of 13.5% on 1 October 2018 (beginning of fourth quarter). Armodafinil was listed on the 1 November 2016, on a cost-minimisation basis to the modafinil price after the 16% SPR. Armodafinil has not received any price reductions since listing.

The number of prescriptions for modafinil has remained moderately stable and the benefit paid for PBS subsidised modafinil for narcolepsy has decreased from 2016-2018 due to the above-mentioned price reductions. The number of prescriptions and PBS benefits paid for armodafinil have increased since its listing on the PBS (Figure 10).

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available DHS Medicare date of processing data.

## Analysis of actual versus predicted utilisation

A comparison of the predicted utilisation of armodafinil versus actual use is presented in Table 6.

**Table 6: Armodafinil: actual versus predicted utilisation**

| | | Year 1 | Year 2 |
|---|---|---|---|
| **patients** | Predicted | [redacted] | [redacted] |
| | Actual | 883 | 1430 |
| | %Difference | [redacted] | [redacted] |
| **prescriptions** | Predicted | [redacted] | [redacted] |
| | Actual | 4,622 | 9,658 |
| | %Difference | [redacted] | [redacted] |
| Rx 50 mg | Predicted | [redacted] | [redacted] |
| | Actual | 161 | 379 |
| | %Difference | [redacted] | [redacted] |
| Rx 150 mg | Predicted | [redacted] | [redacted] |
| | Actual | 1163 | 2321 |
| | %Difference | [redacted] | [redacted] |
| Rx 250 mg | Predicted | [redacted] | [redacted] |
| | Actual | 3,298 | 6,958 |
| | %Difference | [redacted] | [redacted] |
| **Expenditure** | Predicted | [redacted] | [redacted] |
| | Actual | $887,399 | $1,863,483 |
| | %Difference | [redacted] | [redacted] |

Source: Armodafinil Final Estimates (predicted), DHS prescription database (actual), extracted April 2019

In the first two years of listing, the total number of patients and prescriptions were underestimated resulting in a higher government expenditure than predicted in the submission.

## DUSC consideration

The number of patients on therapy for narcolepsy has increased over the last four-year period. There was also a 35.9% increase in patients new to therapy between 2017 and 2018. DUSC noted that there has been market growth in PBS subsidised therapy for narcolepsy.

The listing of armodafinil has increased the total narcolepsy market, with number of people starting PBS subsidised armodafinil being higher than the number of patients starting modafinil since its listing in 2016. The number of patients starting initial therapy for narcolepsy with armodafinil surpassed that for modafinil in the fourth quarter of 2018, but did not appear to affect the number of people initiating therapy for narcolepsy with dexamfetamine and modafinil. DUSC noted the listing of armodafinil has increased the total narcolepsy market to a greater extent than predicted. In the Pre-Sub Committee Response (PSCR), the Sponsor superimposed a line onto Figure 2 (number of PBS/RPBS dexamfetamine, modafinil and armodafinil prescriptions supplied per quarter) of the DUSC report to demonstrate market growth. Based on this, the sponsor considered that the data presented in Figure 2 for the number of prescriptions supplied indicates that growth in the overall narcolepsy market has only been marginally impacted by the listing of armodafinil. DUSC acknowledged the Sponsor's comments but noted no statistical analyses were provided to demonstrate the linear fit shown in the graph. DUSC also discussed that armodafinil is a more expensive drug than modafinil and has increased the market at a higher rate than predicted.

Dexamfetamine remains the most supplied drug for narcolepsy by prescription volume and number of prevalent patients. DUSC was concerned with the increased use of dexamfetamine from the second quarter of 2018. DUSC discussed whether this is due to an increase in the overall narcolepsy market or if there was potential diversion of dexamfetamine. DUSC noted that more general practitioners were initiating dexamfetamine compared to armodafinil or modafinil.

DUSC noted a substantial number of patients were initiated treatment for narcolepsy with modafinil or armodafinil. DUSC discussed possible reasons as to why dexamfetamine may not be used as first line therapy and questioned whether the difference in the treatment algorithm between the PBS restriction (dexamfetamine first line) and clinical guidelines (modafinil and armodafinil as first line) may be contributing to this. DUSC also noted generic brands of modafinil are now available in the market, possibly making it more affordable for patients than previously. DUSC noted dexamfetamine is a Schedule 8 medicine and as such has additional state and territory restrictions in prescribing compared to modafinil or armodafinil. DUSC considered if this could be contributing to the increase use of modafinil and armodafinil in narcolepsy. DUSC discussed the PBS restriction in which psychiatric disorders are considered a potential unacceptable medical risk for initiating therapy with dexamfetamine but noted that people with narcolepsy often have comorbid psychiatric conditions.

In the PSCR, the Sponsor considered it difficult to reconcile the visual presentation of the data in Figure 1 (number of incident and prevalent patients to narcolepsy therapy by quarter) and 2 (number of prescriptions supplied per quarter) with Table 4 of the DUSC report as there were inconsistencies. DUSC discussed that in the report, the number of patients per each time period (quarter or year) were calculated separately. It is not accurate to add the number of patients per each quarter (from Figure 1) to calculate the total number of patients per calendar year (Table 4) because there is potential to double count a patient if they appear in multiple quarters as they continue treatment. Table 4 is the total number of patients counted for the whole calendar year. Each patient is only counted once for the whole year even if they had received treatment across more than one quarter. Figure 2 illustrates the number of prescriptions supplied per quarter and not the number of patients (Table 4). Therefore, the numbers from Figure 1 and Figure 2 are not intended to be comparable with Table 4.

DUSC acknowledged the error on page 22 of the report identified in the PSCR. The listing date of modafinil was 1 April 2005 not 1 August 2015.

In summary, the results of the 24 month predicted versus actual analysis show the total number of patients and prescriptions of armodafinil were underestimated, resulting in a higher government expenditure than predicted. DUSC considered that future reports of narcolepsy medicine use could attempt PBS/MBS linkage data analysis to compare utilisation of PBS/RPBS subsidised narcolepsy treatment with MBS reimbursement for sleep studies.

## DUSC Actions

DUSC requested that the report be provided to the PBAC.

## Context for analysis

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

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

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

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

## Sponsor's comment

Teva Pharma Australia Pty Limited: The Sponsor notes the DUSC commentary that "according to the Australian therapeutic guidelines, modafinil and armodafinil are first line drugs for the treatment of increasing alertness in narcolepsy." Despite this, most initiating occurs via dexamfetamine. Although the use of armodafinil is growing, it is still the least used of the three available medications.

## 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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