

7.13 ARMODAFINIL

Tablets, 50 mg, 150 mg and 250 mg Nuvigil®, TEVA Pharma Australia Pty Ltd

1 Purpose of Application

- 1.1 The resubmission requested an Authority Required listing for armodafinil for the treatment of narcolepsy.

2 Requested listing

- 2.1 The resubmission requested the following new listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ARMODAFINIL 50 mg tablet, 30	2	5	\$ [REDACTED]	Nuvigil® TEVA
ARMODAFINIL 150 mg tablet, 30	1	5	\$ [REDACTED]	
ARMODAFINIL 250 mg tablet, 30	1	5	\$ [REDACTED]	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Narcolepsy
PBS Indication:	Narcolepsy
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a qualified sleep medicine practitioner or neurologist

Public Summary Document – March 2016 PBAC Meeting

<p>Clinical criteria:</p>	<p>Patients must meet the following definition of narcolepsy: Excessive daytime sleepiness, recurrent naps or lapses into sleep occurring almost daily for at least 3 months, AND A definite history of cataplexy; or A mean sleep latency less than or equal to 10 minutes on a Multiple Sleep Latency Test (MSLT). The MSLT must be preceded by nocturnal polysomnography. Sleep prior to the MSLT must be at least 6 hours in duration; or an electroencephalographic (EEG) recording showing the pathologically rapid development of REM sleep, AND Absence of any medical or psychiatric disorder that could otherwise account for the hypersomnia.</p>
<p>Prescriber Instruction</p>	<p>The authority application must be made in writing and must include the following: (a) a completed authority prescription form; and (b) a completed Narcolepsy Initial PBS authority application and Supporting information form; and (c) details of the contraindication or intolerance to dexamphetamine sulfate; and (d) either: (i) the result and date of the polysomnography test and Multiple Sleep Latency Test (MSLT) conducted by, or under the supervision of, a qualified sleep medicine practitioner; or (ii) the result and date of the electroencephalograph (EEG), conducted by, or under the supervision of, a neurologist.</p> <p>The presence of any one of the following indicates treatment with dexamphetamine 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 dexamphetamine sulfate as specified in the TGA-approved Product Information.</p> <p>The MSLT must be preceded by nocturnal polysomnography. Sleep prior to the MSLT must be at least 6 hours in duration.</p> <p>The polysomnography, MSLT or EEG test reports must be provided with the authority application.</p>

Public Summary Document – March 2016 PBAC Meeting

Administrative Advice	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>This drug is not PBS-subsidised when used in combination with PBS-subsidised dexamphetamine sulfate.</p>
------------------------------	--

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Excessive daytime sleepiness
Severity:	-
Condition:	Narcolepsy
PBS Indication:	Narcolepsy
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug.
Administrative Advice	<p>Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Written applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>This drug is not PBS-subsidised when used in combination with PBS-subsidised dexamphetamine sulfate.</p>

2.2 In the previous submission, the sponsor indicated it would offer a ■■■% price reduction upon the listing of the first generic version of modafinil. In the resubmission, the sponsor proposed a further price reduction of approximately ■■■% based on the revised therapeutic relativity presented in the resubmission.

3 Background

- 3.1 Armodafinil is TGA registered 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; as an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness.
- 3.2 A submission for armodafinil was previously considered and rejected by the PBAC at its November 2015 meeting.
- 3.3 In November 2015, the PBAC considered that there was no apparent unmet clinical need for armodafinil, and that the estimation of the equi-effective doses remained uncertain in the cost-minimisation analysis.

4 Clinical place for the proposed therapy

- 4.1 The resubmission stated that rates of withdrawal from modafinil therapy indicates that there is a clinical need for more than one medication in the therapeutic area, with armodafinil having been shown in long-term studies to provide an effective and tolerable option for some patients.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 The previous major submission considered by the PBAC in November 2015 nominated modafinil as the comparator. This remained unchanged. The PBAC previously agreed that modafinil was the appropriate comparator, but considered that a comparison against the split dose regimen of modafinil was also relevant.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (4) via the Consumer Comments facility on the PBS website. The comments described some of the perceived benefits of treatment with armodafinil including better symptom control and convenience of single dose treatment.

Clinical trials

- 6.3 As a minor submission, no new clinical trials were presented in the resubmission.

- 6.4 The previous November 2015 submission was based on an indirect comparison between one placebo controlled armodafinil trial (Trial 3020, published as Harsh et al 2006) and a meta-analysis of two modafinil placebo controlled trials (Fry 1998 and Gross 2000), using the placebo arms as the common reference.

Comparative effectiveness

- 6.5 The resubmission presented data to indicate the differences between armodafinil and modafinil (see table below). The resubmission proposed that these differences are substantive enough to have a clinical impact and that patients not responding to one drug may respond to the other therapy. It was suggested that even though the change between the two medications might be conceived as minimal, they are substantive enough to impact clinically.

Table 1: 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 <u>Narcolepsy</u> : 150 mg or 250 mg given once daily in the morning.	Starting Dose: 200mg ¹ <u>Narcolepsy</u> : 200 to 400 mg/day, given as a single dose in the morning, or as two divided doses, in the morning and at noon. 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 split into 200mg in the morning and 200mg at noon. ^{1,2} 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
C_{max}	2.99 µg/mL after a 100 mg dose ³ 5.9 µg/mL after a 250 mg dose ³	3.3 mg/mL after a 200 mg dose

¹ Adenuga, O. and H. Attarian (2014). "Treatment of disorders of hypersomnolence." *Curr Treat Options Neurol* **16**(9): 302.

² Schwartz, J. R. L., N. T. Feldman, R. K. Bogan, M. T. Nelson and R. J. Hughes (2003). "Dosing regimen effects of modafinil for improving daytime wakefulness in patients with narcolepsy." *Clinical Neuropharmacology* **26**(5): 252-257.

³ Garnock-Jones KP, Dhillon S and Scott LJ (2009). "Armodafinil." *CNS Drugs* **23**(9): 703-803.

	Armodafinil	Modafinil
T _{max}	2 hours ⁴	2-4 hours ⁵

Source: submission, Table 2 p.7

- 6.6 The resubmission highlighted differences in plasma concentrations (plasma concentration following armodafinil administration is higher late in the day than that following modafinil administration) and dose response (armodafinil exhibits linear pharmacokinetics while modafinil pharmacokinetics are dose-independent).

Clinical claim

- 6.7 At its November 2015 meeting, the PBAC considered that the data presented in the submission suggested that armodafinil may be non-inferior to modafinil in terms of comparative efficacy and safety.

Economic analysis

- 6.8 In the previous major submission considered by the PBAC in November 2015, the submission presented a cost-minimisation analysis against modafinil.
- 6.9 The previous submission estimated the equi-effective doses as armodafinil 216.39 mg and modafinil 349.65 mg, and a dose relativity of 5:8 (armodafinil vs modafinil) was used to determine the requested price for armodafinil. The resubmission proposed that the maximum dose (250 mg daily) be utilised 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.
- 6.10 In the previous submission, the sponsor indicated it would offer a ■■■% price reduction upon the listing of the first generic version of modafinil. In the resubmission, the sponsor proposed a further price reduction of approximately ■■■■% based on the revised therapeutic relativity presented in the resubmission.

Estimated PBS usage & financial implications

- 6.11 The submission used a market-share approach to estimate the use and costs of listing armodafinil on the PBS.

⁴ Darwish, M., M. Kirby, E. T. Hellriegel, R. Yang and P. Robertson, Jr. (2009). "Pharmacokinetic profile of armodafinil in healthy subjects: pooled analysis of data from three randomized studies." *Clin Drug Investig* **29**(2): 87-100.

⁵ Dell'Osso, B., C. Dobrea, L. Cremaschi, C. Arici and A. C. Altamura (2014). "Wake-promoting pharmacotherapy for psychiatric disorders." *Curr Psychiatry Rep* **16**(12): 524.

Table 2: Estimated use and financial implications

	2016	2017	2018	2019	2020	2021
Total number of patients treated per year (i.e. armodafinil and modafinil combined)						
Total number of patients treated per year with Nuvigil						
Total number of prescriptions (i.e. Armodafinil and modafinil combined)						
Total number of prescriptions (of Nuvigil)						
Total cost of Nuvigil	\$	\$	\$	\$	\$	\$
Net cost to Government of Nuvigil	\$	\$	\$	\$	\$	\$
Savings from displacement of modafinil (1 April 2016 pricing)	-\$	\$	-\$	-\$	-\$	-\$
Net cost (saving) to Government of proposed listing (1 April 2016 pricing)	-\$	-\$	-\$	-\$	-\$	-\$

Source: Section E Excel spreadsheet of the resubmission

The redacted table shows that at year 5, the estimated number of patients was less than 10, 000 per year and the net saving to the PBS would be less than \$10 million per year.

- 6.12 In November 2015, the PBAC agreed that given the submission’s claim of non-inferiority of armodafinil to modafinil and the cost-minimisation approach taken, listing of armodafinil should be cost-neutral. The revised financial estimates provided in the resubmission estimated a net cost saving to Government of \$ in Year 1 increasing to \$ in Year 5.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

- 7.1 The PBAC recommended an Authority Required listing for armodafinil for the treatment of narcolepsy on a cost-minimisation basis with modafinil. The PBAC considered the equi-effective doses to be armodafinil 250 mg and modafinil 348.55 mg, resulting in a dose relativity of 5:7 as proposed by the resubmission.
- 7.2 In making its recommendation, the PBAC considered that the revised equi-effective doses presented in the re-submission were reasonable. The PBAC also noted that it

had previously considered that armodafinil was very likely to be non-inferior in effectiveness and safety compared with modafinil.

- 7.3 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 were not convinced that these differences would result in armodafinil having any appreciable clinical advantage over modafinil.
- 7.4 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.
- 7.5 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.
- 7.6 The PBAC recommended under Section 101(3BA) of the National Health Act, that armodafinil should be treated as interchangeable on an individual patient basis with modafinil.
- 7.7 The PBAC recommended that the Early Supply Rule should apply.
- 7.8 The PBAC advised that armodafinil is not suitable for prescribing by nurse practitioners.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
ARMODAFINIL 50 mg tablet, 30	2	5	Nuvigil®	TEVA
ARMODAFINIL 150 mg tablet, 30	1	5		
ARMODAFINIL 250 mg tablet, 30	1	5		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives

Public Summary Document – March 2016 PBAC Meeting

Episodicity:	-
Severity:	-
Condition:	Narcolepsy
PBS Indication:	Narcolepsy
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a qualified sleep medicine practitioner or neurologist
Clinical criteria:	<p>Patients must meet the following definition of narcolepsy:</p> <p>Excessive daytime sleepiness, recurrent naps or lapses into sleep occurring almost daily for at least 3 months,</p> <p>AND</p> <p>A definite history of cataplexy;</p> <p>or</p> <p>A mean sleep latency less than or equal to 10 minutes on a Multiple Sleep Latency Test (MSLT). The MSLT must be preceded by nocturnal polysomnography. Sleep prior to the MSLT must be at least 6 hours in duration;</p> <p>or</p> <p>an electroencephalographic (EEG) recording showing the pathologically rapid development of REM sleep,</p> <p>AND</p> <p>Absence of any medical or psychiatric disorder that could otherwise account for the hypersomnia.</p>

Public Summary Document – March 2016 PBAC Meeting

Prescriber Instruction	<p>The authority application must be made in writing and must include the following:</p> <ul style="list-style-type: none"> (a) a completed authority prescription form; and (b) a completed Narcolepsy Initial PBS authority application and Supporting information form; and (c) details of the contraindication or intolerance to dexamphetamine sulfate; and (d) either: <ul style="list-style-type: none"> (i) the result and date of the polysomnography test and Multiple Sleep Latency Test (MSLT) conducted by, or under the supervision of, a qualified sleep medicine practitioner; or (ii) the result and date of the electroencephalograph (EEG), conducted by, or under the supervision of, a neurologist. <p>The presence of any one of the following indicates treatment with dexamphetamine sulfate poses an unacceptable medical risk:</p> <ul style="list-style-type: none"> (a) a psychiatric disorder; (b) a cardiovascular disorder; (c) a history of substance abuse; (d) glaucoma; (e) any other absolute contraindication to dexamphetamine sulfate as specified in the TGA-approved Product Information. <p>The MSLT must be preceded by nocturnal polysomnography. Sleep prior to the MSLT must be at least 6 hours in duration.</p> <p>The polysomnography, MSLT or EEG test reports must be provided with the authority application.</p>
Administrative Advice	<p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>This drug is not PBS-subsidised when used in combination with PBS-subsidised dexamphetamine sulfate.</p>

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Excessive daytime sleepiness
Severity:	-
Condition:	Narcolepsy
PBS Indication:	Narcolepsy
Treatment phase:	Continuing treatment

Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug.
Administrative Advice	<p>Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Written applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>This drug is not PBS-subsidised when used in combination with PBS-subsidised dexamphetamine sulfate.</p>

9 Context for Decision

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

10 Sponsor's Comment

TEVA welcomed the PBAC recommendation and has worked with the department to progress the listing of Nuvigil onto the PBS