

## 5.01 ARMODAFINIL tablets, 50mg, 150mg and 250mg, Nuvigil<sup>®</sup>, TEVA Pharma Australia Pty Ltd

### 1 Purpose of Application

- 1.1 The submission sought an Authority Required listing on the General Schedule for armodafinil for treatment of excessive daytime sleepiness associated with narcolepsy.

### 2 Requested listing

- 2.1 The restrictions have been reformatted by the Secretariat to comply with requirements for entry into the PBS database. The requested listings are:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ARMODAFINIL 30 ORAL TABLETS 50MG,	2	5	\$ [REDACTED] (revised: \$ [REDACTED])	Nuvigil <sup>®</sup> TEVA
ARMODAFINIL 30 ORAL TABLETS 150MG	1	5	\$ [REDACTED] <sup>a</sup> (revised: \$ [REDACTED] <sup>b</sup> )	
ARMODAFINIL 30 ORAL TABLETS 250MG	1	5	\$ [REDACTED] <sup>a</sup> (revised: \$ [REDACTED] <sup>b</sup> )	

<sup>a</sup> Based on June 2015 mark-ups and dispensing fees

<sup>b</sup> Based on the updated mark-ups and dispensing fees (effective in July 2015)

Similar details were presented for maintenance/continuation in the submission

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



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<b>Administrative Advice 1</b>	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). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a> Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001
<b>Administrative Advice 2</b>	This drug is not PBS-subsidised when used in combination with PBS-subsidised dexamphetamine sulfate.

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	-
<b>Condition:</b>	Narcolepsy
<b>PBS Indication:</b>	Narcolepsy
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<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
<b>Clinical criteria:</b>	Patient must have previously been issued with an authority prescription for this drug.
<b>Administrative Advice 1</b>	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).
<b>Administrative Advice 2</b>	Written applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001
<b>Administrative Advice 3</b>	This drug is not PBS-subsidised when used in combination with PBS-subsidised dexamphetamine sulfate.

2.2 The wording of the proposed PBS restriction for armodafinil was identical to that of the current listing for modafinil, the main comparator. The current modafinil restriction was largely based upon the International Classification of Sleep Disorders, 2<sup>nd</sup> edition

(ICSD-2)<sup>1</sup>, with less strict diagnostic criteria<sup>2</sup> to reflect clinical experience in the diagnosis of narcolepsy and the clinical need for modafinil, as per request from the Australasian Sleep Association (ASA) and the Australian New Zealand Association of Neurologists (ANZAN) (March 2009 PBAC Outcomes – Positive Recommendations). The nomenclature, classification and diagnosis of narcolepsy have been revised according to the International Classification of Sleep Disorders, 3<sup>rd</sup> edition (ICSD-3) (published in 2014)<sup>3</sup>. The submission indicated that the sponsor is willing to discuss changes to the listing, should the PBAC consider this necessary.

- 2.3 Listing was sought on a cost-minimisation basis to modafinil. However, there were concerns regarding the claimed equi-effective doses between armodafinil and modafinil (see below).

### **3 Background**

- 3.1 The submission was made under Therapeutic Goods Administration (TGA)/PBAC Parallel Process. An application for marketing authorisation was submitted to the TGA in August 2014. In a request for the Advisory Committee on Prescription Medicines (ACPM) advice, which became available during the evaluation, the Delegate recommended the registration of armodafinil for the following indications: 1) to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy; 2) to treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where non-pharmacological interventions are unsuccessful or inappropriate; and 3) as an adjunct to continuous positive airways pressure in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness. The application was considered at the ACPM meeting on 2<sup>nd</sup> October 2015.
- 3.2 This was the first submission to the PBAC for armodafinil for the treatment of excessive daytime sleepiness associated with narcolepsy.

### **4 Clinical place for the proposed therapy**

- 4.1 Narcolepsy is a debilitating lifelong sleep disorder, interfering with every aspect of life, in work and social settings. Excessive daytime sleepiness is the main symptom of narcolepsy and is a lifelong condition, although it diminishes with age. The current PBS reimbursed treatment for excessive daytime sleepiness associated with narcolepsy is dexamphetamine sulphate and modafinil when dexamphetamine sulphate is unsuitable due to contraindications or side-effects.
- 4.2 The submission proposed that armodafinil is an alternative to modafinil in the treatment of excessive daytime sleepiness associated with narcolepsy, based on a

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<sup>1</sup> Billiard M. Diagnosis of narcolepsy and idiopathic hypersomnia. An update based on the International classification of sleep disorders, 2nd edition. *Sleep medicine reviews*. 2007 Oct;11(5):377-88.

<sup>2</sup> For example, the removal of the need for a multiple sleep latency test in patients with cataplexy and the omission of the requirement of the number of sleep onset rapid movement periods in patients without cataplexy.

<sup>3</sup> American Academy of Sleep Medicine. *International Classification of Sleep Disorders - Third Edition (ICSD-3)*: American Academy of Sleep Medicine. 2014.

claim that armodafinil is non-inferior to modafinil in terms of comparative effectiveness and safety. The ESC considered that there was currently no unmet clinical need for armodafinil.

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

## **5 Comparator**

- 5.1 The submission nominated modafinil as the comparator. However, the key modafinil trials included for the indirect comparison only assessed modafinil dosed once daily (OD) and evidence was lacking regarding the potentially more effective split dosing regimen. Modafinil Product Information (PI) states that modafinil should be given at 200 mg to 400 mg/day as a single dose in the morning or as two divided doses in the morning and at noon. In Section A of the submission, it was noted that split-dosing (twice daily (BD)) of modafinil prolongs wakefulness throughout the day compared to OD dosing and may be more appropriate than OD dosing for patients who experience late-afternoon or evening sleepiness. This was evidenced in a study comparing the effectiveness of modafinil 400 mg split dose with 400 mg OD, which showed that the split-dose regimen improved wakefulness significantly in the evening compared to OD ( $P < 0.05$ ) (Schwartz JRL, Feldman NT et al. 2005) (pp16-7, Section A of the submission).
- 5.2 The Pre-Sub-Committee Response (PSCR) argued that it could not be concluded that suboptimal dosing of modafinil has been used – “The population reported in Schwartz 2005 comprised only patients with narcolepsy experiencing residual late-afternoon/evening sleepiness following satisfactory responses earlier in the day. Hence, this group represents only a subset of the narcolepsy population. Moreover, it was only a 3-week study and it was not a placebo-controlled study...” The ESC considered that this did not exclude the possibility that split dose modafinil could also be an appropriate comparator dosing regimen, particularly considering that armodafinil has a longer half-life than modafinil, which results in a more prolonged effect during the day and potential improvement in wakefulness in the late-afternoon in patients with narcolepsy.
- 5.3 Armodafinil and modafinil belong to the same pharmacological class, and are indicated for treatment of the same populations for which PBS reimbursement is requested. The main differences between armodafinil and modafinil are likely to be their pharmacokinetic profiles. Armodafinil is the (R)-enantiomer of modafinil, which is a 50%:50% mixture of the (R)- and (S)-enantiomers. The submission indicated that the (R)- and (S)-enantiomers of modafinil appear to be identical with respect to the mechanism of action but with different pharmacokinetics, e.g. the half-life of (R)-enantiomer is about three times that of the (S)-enantiomer in adult humans (15 hours vs 4 hours). At steady state, total exposure to (R)-modafinil is approximately three times that of (S)-modafinil. The trough concentration of circulating modafinil after OD dosing consists of 90% (R)-modafinil and 10% (S)-modafinil (modafinil Product Information). The data indicate that R-modafinil is the predominant enantiomer following administration of the racemate. The ESC noted armodafinil and modafinil being in the same pharmacological class and essentially the same drug after

metabolism highlights the potential for split dosing of modafinil to be a relevant comparator.

## **6 Consideration of the evidence**

### **Sponsor hearing**

6.1 There was no hearing for this item.

### **Consumer comments**

6.2 The PBAC noted that no consumer comments were received for this item.

### **Clinical trials**

6.3 The 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”:

- Trial 3020 was a randomised parallel group placebo-controlled trial examining the efficacy and safety of OD armodafinil 150 mg/day and 250 mg/day, versus placebo, in adult patients with excessive daytime sleepiness associated with narcolepsy, over a 12-week period;
- Fry 1998 and Gross 2000 were two randomised parallel group placebo-controlled trials, both examining the efficacy and safety of modafinil 200 mg/day (OD) and 400 mg/day (OD) versus placebo, over a 9-week period.

6.4 The submission also included two additional modafinil studies for sensitivity analyses:

- Besset 1993 – randomised, double-blind, cross-over study comparing modafinil 300 mg/day (morning: 200 mg; noon:100 mg) versus placebo (n=16) and
- Broughton 1997 – randomised, double-blind, cross-over study comparing two doses of modafinil (200 mg/day and 400 mg/day, both in divided doses morning and noon) versus placebo (n=75).

Although these cross-over studies assessed split dosing of modafinil, the indirect sensitivity analyses presented in the submission using these studies are difficult to interpret. Change in maintenance wakefulness test (MWT) and Epworth sleepiness scale (ESS) from baseline data were not reported in the cross-over studies. Differences in mean scores at the final visit between modafinil and placebo were used instead and “pooled” with change from baseline data from the Fry (1998) and Gross (2000) trials.

6.5 Details of the trials presented in the submission are provided in the table below.

**Table 1: Trials and associated reports presented in the submission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
3020	<p>Clinical study report No: TEVA, C10953/3020/NA/MN: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of CEP-10953 (150 and 250 mg/day) as treatment for Adults With Excessive Sleepiness Associated With Narcolepsy.</p> <p>Clinical study report No: Cephalon - Teva Pharmaceutical Industries NCT00078377: Safety and Efficacy Study of armodafinil (CEP-10953) in the Treatment of Excessive Sleepiness Associated With Narcolepsy (C10953/3020/NA/MN).</p> <p>Harsh, J. R, R. Hayduk, R. Rosenberg, K. A. Wesnes, J. K. Walsh, S. Arora, G. E. Niebler and T. Roth (2006). "The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy."</p>	<p>9 March 2005</p> <p><i>Current Medical Research and Opinion</i> 2006; 22(4): 761-774.</p>
Fry 1998	<p>Fry, J. M. Treatment modalities for narcolepsy."</p> <p>Emsellem, H. Efficacy and safety profiles of modafinil maintained during long-term (40 and 88 weeks) treatment of excessive daytime sleepiness associated with narcolepsy."</p> <p>Cephalon Inc. Provigil® (modafinil) Tablets (C-IV): Supplemental NDA: Briefing Document For Peripheral and Central Nervous System Drugs Advisory Committee Meeting.</p>	<p><i>Neurology</i> 1998; 50(Suppl 1): S43-S48.</p> <p><i>Neurology</i> 2000; 7(Suppl 3): A29-A30.</p> <p>2003</p>
Gross 2000	Gross, P. T., on behalf of US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy.	<i>Neurology</i> 2000; 54(5): 1166-1175.
Supplementary modafinil studies included in the submission for sensitivity analyses		
Besset 1993	Besset, A., Tafti, M., Villemin, E and Billiard, M. The effects of modafinil (300 mg) on sleep, sleepiness and arousal in narcoleptic patients.	<i>Neurophysiol Clin</i> 1993; 23: 47-60.
Broughton 1997	Broughton, R. J., Fleming, J. A. E., George C. F. P., J. D. Hill, Kryger, M. H., Moldofsky, H., Montplaisir, J. Y, Morehouse, R. L., Moscovitch, A. and Murphy, W. F.. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy.	<i>Neurology</i> 1997; 49(2): 444-451.

CEP-10953 = armodafinil; NDA = new drug application.

Sources: Table B.2.1, page B.14 of the submission

6.6 The key features of the randomised trials used for the indirect comparison are summarised in the table below.

**Table 2: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>armodafinil vs. placebo</b>					
Trial 3020	194	R, DB 12 weeks	High <sup>a</sup>	Patients with excessive daytime sleepiness associated with narcolepsy	MWT, ESS, CGI-C
<b>modafinil vs. placebo</b>					
Fry 1998	273	R DB 9 weeks	Unclear <sup>b</sup>	Patients with excessive daytime sleepiness associated with narcolepsy	MWT, ESS, CGI-C
Gross 2000	257	R, DB 9 weeks	Unclear <sup>b</sup>	Patients with excessive daytime sleepiness associated with narcolepsy	MWT, ESS, CGI-C
Meta-analysis	530	Included Fry 1998 and Gross 2000	Unclear <sup>b</sup>	Patients with excessive daytime sleepiness associated with narcolepsy	MWT, ESS, CGI-C

DB=double blind; R = randomised; MWT = Maintenance of Wakefulness Test; ESS = Epworth Sleepiness Scale; CGI-C = Clinical Global Impression of Change, a subjective measure of the patient's global health.

<sup>a</sup> Although double blinded, potential for unmasking from side effects of active drugs cannot be ruled out. In addition, there is a high risk of attrition bias. Only 75% of randomised patients in the 150mg/day arm completed the study (84% and 86% in the 250mg/day and placebo arms, respectively). The full analysis set of the combined armodafinil arms was 89% with the last observation carried forward (LOCF) approach used.

<sup>b</sup> Although double blinded, potential for unmasking from side effects of active drugs cannot be ruled out. No details provided on blinding of outcome assessment. There is a low risk of attrition bias.

Source: compiled during the evaluation

- 6.7 There was a high risk of bias in the indirect comparison presented in the submission. There were differences in baseline disease characteristics between treatment arms within the trials and across the trials such as disease severity, MWT and Clinical Global Impression of Severity of Illness (CGI-S). For the armodafinil Trial 3020, in terms of CGI-S, there was a higher proportion of patients who were considered markedly or severely ill in the placebo arm (71%) versus the armodafinil 250mg arm (63%); there was a similar trend observed in the modafinil Gross trial (placebo 38% vs modafinil 200mg/day 28%) whereas the reverse was true for the modafinil Fry trial (placebo 34% vs modafinil 200/400mg/day 44%). This also implies that across the trials, disease severity, as measured in terms of CGI-S, may have been substantially different casting doubt on the exchangeability of these trials. Whilst the indirect comparisons were adjusted for the common reference, the exchangeability of these trials and the validity of the indirect comparative estimates remain uncertain.
- 6.8 The efficacy outcomes assessed in the included trials were primarily MWT sleep latency and Clinical Global Impression of Change (CGI-C). However, as noted by the PBAC in previous considerations of modafinil, the patient relevance, and MCID, of these endpoints remain uncertain (Modafinil Public Summary Document, PBAC consideration, November 2008). The PBAC noted that it was difficult to extrapolate from the surrogate outcomes to clinically important endpoints. Unambiguously patient relevant endpoints included being completely free of drop attacks or achieving a level of reduction in sleep attacks that would allow a patient to return to work. These outcomes were not measured in the trials included in the indirect comparison.
- 6.9 In Trial 3020, assessments were conducted at weeks 4, 8, and 12 of the double-blind treatment phase and in Fry and Gross at Week 9. The indirect analyses only included data from week 8 and 12 for Study 3020, with a Last Observation Carried Forward

(LOCF) analysis for week 12 (no LOCF was done for Week 8 given the limited loss to follow up at that period) and LOCF for week 9 for Fry and Gross. The use of LOCF to handle missing data for the armodafinil Week 12 and modafinil Week 9 comparison is not recommended as it is based on the unrealistic assumption that the outcomes of participants do not change after they have dropped out, leading to biased treatment effects<sup>4</sup>. The extent of missing data and the impact of bias that could arise from the LOCF approach were not discussed in either the submission or the accompanying statistical report (Attachment 7 to the main submission). The PSCR acknowledged that use of LOCF is generally not recommended but claimed that “the sensitivity analysis based on the 8 week data was presented in the submission not only to examine whether shorter follow-up had any impact on estimated differences, but also to partially evaluate the potential impact of missing data at week 12 (given that the impact of missing data on outcome at week 8 is unlikely to be substantial).”

- 6.10 The submission derived the non-inferiority margin for the indirect comparison between armodafinil versus modafinil from the treatment effect, relative to placebo, that the included trials were powered to detect in the sample size calculations. These margins were sourced directly from the armodafinil and modafinil placebo controlled trials and thus represent the entire anticipated treatment effect compared to placebo for power calculations. Thus the margins specified in the trials, versus placebo, may not inform the non-inferiority margin for the indirect comparison between armodafinil and an active comparator (i.e. modafinil).
- 6.11 The PSCR contended that non-inferiority was determined with reference to superiority margins used in the trials, due to the absence of published non-inferiority margins. The ESC noted the following table provided in the PSCR.

**Table 3: Assessment of data that can inform non-inferiority of armodafinil and modafinil**

Outcome	Trial	Pre-specified differences versus placebo in the individual trials	Indirect comparison		Percent of superiority margin accounted for by 95% CI
			Effect size (95% CIs)	95% CI for effect size in the indirect comparison	
MWT	Study 3020	2.5 minute difference	0.9 (-1.35, 3.16)	-1.35	1.35/2.5 = 54%
	Fry 1998	4.0 minute difference			1.35/4 = 34%
	Gross 2000	4.0 minute difference			
ESS	Study 3020	-	0.91 (-0.63, 2.45)	2.45*	2.45/3 = 82%
	Fry 1998	-			
	Gross 2000	-			
	Dauvilliers 2013 <sup>b</sup>	3 point difference			
CGI-S	Study 3020	25% difference	-	-	-
	Fry 1998	1 point difference	MD: 0.11 (-0.05, 0.28)	-0.05	0.05/1 = 5%
	Gross 2000	1 point difference			

\* a negative value shows a favourable response, therefore upper 95% CI is used to determine NI.

RR = relative risk, MD = mean difference.

Source: PSCR, Table 1 p.3

<sup>4</sup> Little RJ, D'Agostino R, et al. The prevention and treatment of missing data in clinical trials. *New England Journal of Medicine*. 2012;367(14):1355-60.

## Comparative effectiveness

6.12 The comparative results for armodafinil/modafinil versus placebo and the indirect comparisons between armodafinil and modafinil (via placebo as the common reference) are summarised below.

**Table 4: Comparative benefit (MWT, ESS and CGI-C) versus placebo in the individual trials and indirect comparisons between armodafinil and modafinil**

Outcome	Analysis method	Trial 3020 (combined armodafinil 250mg and 150mg) vs. Placebo	Pooled Fry and Gross (combined modafinil 200mg and 400mg vs. Placebo)	Armodafinil vs Modafinil (indirect comparison)	
		Effect size (SE) [95% CI]	Pooled effect (SE) [95% CI]	Effect Size (SE) [95% CI]	p-value
MWT <sup>a</sup>	Primary <sup>a</sup> Final visit, LOCF	3.80 (1.07) [1.70, 5.90]	2.90 (0.41) [2.09, 3.71]	0.90 (1.15) [-1.35, 3.16]	0.4310
ESS <sup>a</sup>	Primary <sup>a</sup> Final visit LOCF	-2.00 (0.68) [-3.34, -0.66]	-2.91 (0.38) [-3.66, -2.15]	0.91 (0.78) [-0.63, 2.45]	0.2463
CGI-C <sup>b</sup>	RR	2.17 (0.20) [1.48, 3.20]	1.71 (0.10) [1.39, 2.10]	1.27 <sup>c</sup> (0.23) [0.82, 1.98]	0.2903
CGI-C <sup>b</sup>	ARD	0.38 (0.07) [0.24, 0.53]	0.27 (0.05) [0.17, 0.36]	0.11 (0.08) [-0.05, 0.28]	0.1725

<sup>a</sup> Primary analysis for the submission. Final visit = week 12 (for trial 3020)/week 9 (Fry 1998 and Gross 2010) or last post-baseline visit. Both MWT and ESS were measured as the mean difference in change from baseline between treatment arms.

<sup>b</sup> Measured as the proportion of patients with at least minimal improvement in the CGI-C rating at the final visit. The CGI-C represents a subjective measure of the patient's global health (i.e., a clinician's rating of disease severity as compared with a pre-treatment evaluation as assessed by the use of the CGI-S). The clinician assessed the change from baseline in the patient's condition in response to treatment. The CGI-C uses the following categories and scoring assignments: 1=Very much improved; 2=Much improved; 3=Minimally improved; 4=No change; 5=Minimally worse; 6=Much worse; and 7=Very much worse.

<sup>c</sup> Derived from inverting the log of the difference between log 2.17 and 1.71.

MWT = maintenance of wakefulness test; ESS = Epworth Sleepiness Scale; CGI-C = Clinical Global Impression of Change; LOCF = last observation carried forward; SE = standard error; CI = confidence interval; RR = relative risk; ARD = absolute risk difference.

Source: Modified from Table B.6.1, p74 of Section B of the submission

6.13 The results from Trial 3020 for armodafinil (both 250mg/day and 150mg/day armodafinil doses combined) and the pooled results for modafinil (both 200mg/day and 400mg/day doses of modafinil combined) from the Fry and Gross trials were compared. The lower 95% confidence limit of the point estimate of the indirect treatment effect, for all three endpoints (MWT, ESS and CGI-C), satisfied the respective "non-inferiority margins" chosen in the submission. The submission noted that sensitivity analyses of the indirect comparisons were consistent with results from the primary indirect comparison.

6.14 For the outcome of MWT, the baseline values and change from baseline in the placebo arms varied across the armodafinil and modafinil trials. The placebo arm decreased wakefulness (MWT) from baseline by approximately 2 minutes in the armodafinil 3020 trial and by only 0.7 minutes in either of the modafinil Fry or Gross trials. The baseline point-estimate of the MWT in the placebo arm was also higher in the armodafinil trial (12.5 minutes) compared to the modafinil trials (6 minutes). This

casts doubt on the exchangeability of the trials and thus the validity of the indirect comparison. The PSCR argued that in undertaking this indirect analysis, the best available data were utilised, and that with respect to variation in baseline MWT values between the trials, “the MWT deterioration seen in the placebo groups was consistent when considered as % deterioration/baseline, being 15% in the armodafinil study and 12% in the modafinil studies. Considering the improvement/deterioration in the context of the baseline measured in the study provides a more reasonable method to compare the results in the placebo arms across the different studies than looking at the absolute values.

**Table 5: Change from baseline in MWT (20 minutes<sup>s</sup>) in the randomised arms of the individual armodafinil and modafinil trials**

	Study 3020				Fry 1998			Gross 2000		
	Armodafinil 250 mg	Armodafinil 150 mg	Armodafinil (both doses combined)	Placebo	Modafinil 400 mg	Modafinil 200 mg	Placebo	Modafinil 400 mg	Modafinil 200 mg	Placebo
N	60	58	118	58	86	95	92	86	83	88
Baseline MWT, mean (SD), mins	9.5 (6.1)	12.1 (6.6)	10.8 (6.4)	12.5 (6.6)	6.6 (5.2)	5.8 (5.0)	5.8 (4.7)	5.9 (4.4)	6.1 (4.9)	6.0 (5.0)
Endpoint MWT, mean (SD), mins	12.1 (6.3)	13.3 (6.3)	12.7 (6.3)	10.7 (6.6)	8.9 (6.3)	8.2 (6.2)	5.1 (4.7)	7.9 (5.3)	8.3 (5.9)	5.3 (4.5)
Change from baseline to endpoint, mean (SD), mins	2.6 (6.2)	1.3 (6.3)	1.9 (6.28)	-1.9 (6.9)	2.3 (4.9)	2.3 (4.7)	-0.7 (4.6)	2.0 (4.8)	2.2 (4.5)	-0.7 (4.2)
p-value vs. placebo	0.0099	0.0068	0.0024		<0.001	<0.001		<0.001	<0.001	

<sup>s</sup> Armodafinil - average of 4 naps at 09:00, 11:00, 13:00 and 15:00. Modafinil – average of 4 naps at 08.00, 10.00, 12.00, 14.00. MWT = maintenance of wakefulness test; mins = minutes; SD = standard deviation  
Source: Table B.6.2, p77 of Section B of the submission.

- 6.15 As noted earlier, there is uncertainty regarding the clinical meaningfulness of the “non-inferiority margins” used in the submission in the context of the indirect comparison.
- 6.16 There were concerns regarding the applicability of the indirect comparisons and their interpretation:
- The indirect comparisons were conducted for the combined strengths of armodafinil and modafinil, which made the results difficult to apply to the individual dose strengths; and;
  - The modafinil trials assessed a potentially suboptimal dosing regimen of OD rather than split dosing. As noted earlier, split dosing is expected to result in longer wakefulness during the latter parts of the day.

### Comparative harms

- 6.17 The submission conducted indirect statistical comparisons for each adverse event (AE). For the majority of these AEs, these analyses lacked adequate statistical

power with very wide 95% confidence intervals, which limited meaningful conclusions. The indirect comparison of safety between armodafinil and modafinil is presented below. There was a 1.4% increased risk of at least one AE in the armodafinil treatment arms compared with the modafinil treatment arms, which was statistically significant. These AEs were not necessarily treatment related. All other results lacked precision and are difficult to interpret. These results should be viewed with caution given the indirect nature of the comparisons across trials of unconvincing exchangeability.

**Table 6: Overall adverse events in the individual trials and results from the indirect comparison**

Outcome	Armodafinil (both 150mg and 250mg) vs. Placebo		Modafinil (both 200mg and 400mg OD doses combined) vs. Placebo Pooled across Fry and Gross		Armodafinil vs Modafinil (Indirect comparison)	
	RR (95% CI)	ARD (95% CI)	RR (95% CI)	ARD (95% CI)	RR (95% CI)	ARD (95% CI)
≥ 1 AE	1.49 (1.12, 2.00)	0.23 (0.08, 0.37)	1.06 (0.98, 1.14)	0.05 (-0.02, 0.11)	1.41 (1.04, 1.91)	0.18 (0.03, 0.33)
≥ 1 treatment related AE	1.75 (1.05, 2.92)	0.17 (0.03, 0.30)	2.85 (1.37, 5.90)	0.08 (0.02, 0.13)	0.61 (0.25, 1.50)	0.09 (-0.05, 0.24)
≥ 1 SAE	1.45 (0.06, 35.21)	0.01 (-0.02, 0.04)	0.91 (0.31, 2.68)	0.00 (-0.03, 0.02)	1.59 (0.05, 46.40)	0.01 (-0.02, 0.05)
Treatment withdrawals	3.37 (0.42, 26.78)	0.04 (-0.01, 0.09)	2.89 (0.26, 32.05)	0.04 (-0.02, 0.09)	1.17 (0.05, 28.08)	0.00 (-0.08, 0.08)

RR = relative risk; ARD = absolute risk difference; CI = confidence interval; AE = adverse event; SAE = serious adverse event.  
Source: Tables 3 and 4, statistical report for armodafinil (7 July 2015) accompanying the main submission.

### Clinical claim

- 6.18 The submission described armodafinil as non-inferior to modafinil in terms of comparative efficacy and safety.
- 6.19 The indirect comparison in the submission was conducted using trials that were not convincingly exchangeable with uncertainties regarding choice of the non-inferiority margins. Furthermore, the evidence for modafinil was limited to OD dosing. However, the TGA Clinical Evaluator has concluded that the benefits of armodafinil treatment are similar to those of modafinil (Request for ACPM advice).
- 6.20 The ESC noted the exchangeability issues raised in the commentary but considered that Trial 3020, Fry (1998) and Gross (2000) studies showed acceptable efficacy across sleep latency, ESS and CGI-C outcome measures.
- 6.21 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, however the estimated equi-effective doses remained relatively uncertain.

### Economic analysis

- 6.22 The submission argued that the randomised trials which were included for the indirect comparison of armodafinil with modafinil to inform the clinical claim were

fixed dose trials and could not reflect the use of the armodafinil and modafinil in Australian clinical practice, where the doses of the two drugs would be adjusted at the discretion of clinicians. The draft armodafinil PI recommends an armodafinil dose of 150 mg or 250 mg OD; whereas the modafinil PI indicates that the recommended dose of modafinil is 200 mg/day (as a single dose or as two divided doses) and that, 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.

6.23 The submission determined the dose relativity between armodafinil and modafinil on the basis of three armodafinil and two modafinil single-arm studies.

- Study 3023 (armodafinil): a 12-month open-label, flexible-dosage study, followed by an open-ended extension period in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnoea/hypopnoea syndrome or shift work sleep disorder. Armodafinil was titrated from an initial dose of 100 mg/day to 150 mg/day on Day 4. Increments of 50 mg could be made every third day to a maximum dose of 250 mg/day, based on tolerability. The dosage could be decreased to a minimum of 100 mg/day;
- Study 3024 (armodafinil): a 12-month, open-label, flexible-dosage extension study which included patients who completed Trial 3020 (patients with narcolepsy), Trial 3022 (patients with shift work sleep disorders) or Trial 3025 (patients with obstructive sleep apnoea/hypopnoea syndrome). Armodafinil was titrated from a starting dose of 100 mg/day to 150 mg/day on Day 4. Increments of 50 mg could be made every third day to a maximum dosage of 250 mg/day, based on tolerability. The dosage may be decreased to a minimum of 100 mg/day;
- Study 3046: (armodafinil): an 8-week, open-label study, followed by a long-term evaluation in patients with excessive sleepiness associated with narcolepsy or obstructive sleep apnoea/hypopnoea syndrome. Armodafinil was titrated from a starting dose of 50 mg/day to 150 mg/day on Day 4. The dose could be increased at a 50 mg increment every third day to a maximum dosage of 250 mg/day during an 8-week short-term evaluation period, based on tolerability. In the long-term evaluation period, patients continued treatment with armodafinil at the optimal dose determined in the short-term evaluation period. If a patient was unable to tolerate the current dosage due to recurrent or persistent AEs, the dose of armodafinil could be decreased by one dosage level, to a minimum of 100 mg/day;
- Hirshkowitz 2001 (modafinil): a long-term, open-label, extension study of two randomised controlled trials assessing the safety and efficacy of modafinil for treatment of excessive daytime sleepiness in patients with narcolepsy. During the extension period, patients from one trial received modafinil at a dose of 200 mg/day. Thereafter, the daily dose of modafinil could be increased or decreased in 100 mg increments at the discretion of the investigator, depending on efficacy and tolerability. The range of daily doses permitted was 200 to 400 mg. Other patients in this extension study were assigned to treatment with modafinil at a dose of 200 mg for 1 week, followed by treatment with modafinil 400 mg daily for 1 week. At the end of the 2-week treatment period, the study investigator determined the optimum dose of modafinil (i.e. 200 or 400 mg) based on efficacy and tolerability and assigned the patient to receive the optimum dose thereafter; and

- Becker 2004 (modafinil): a 6-week, open-label, flexible-dosage study in patients with narcolepsy. During the first week of treatment, all patients received 200 mg modafinil OD. At the end of Week 1, the dose of modafinil could be increased to 400 mg at the discretion of the investigator, depending on efficacy and tolerability. At the end of the second week of treatment, the investigator determined the optimal daily dose of modafinil (either 200 or 400 mg), which was given for the remainder of the study.
- 6.24 The dose relativity was calculated based on the proportion of patients with narcolepsy who have been stabilised on each dose of armodafinil or modafinil in Studies 3023, 3024, Hirshkowitz 2001 and Becker 2004 and the mean dose reported in Study 3046 (dose distribution not reported in this study). The equi-effective doses were estimated as armodafinil [REDACTED] mg and modafinil [REDACTED] mg. The ex-manufacturer price/mg for modafinil and the dose relativity of [REDACTED] (armodafinil vs modafinil) were used to determine the requested price for armodafinil.
- 6.25 The submission's approach to determining the dose relativity between armodafinil and modafinil was not considered to be reliable on a number of grounds:
- The dose relativity was determined without considering health outcomes to form the basis of a judgement about equi-effectiveness. A meaningful indirect comparison between armodafinil and modafinil cannot be constructed from these long term observational data, because: 1) limited data on patient baseline characteristics are available for Studies 3023, 3024 and Hirshkowitz 2001; 2) all three studies were single-arm studies (the lack of a common reference group makes it impossible to assess exchangeability assumption, or conduct a common reference-based [adjusted] indirect comparison); 3) the published paper on study Hirshkowitz 2001 only presented the mean ESS scores at different time points during the study, without reporting results of variability measures (therefore, 95% confidence intervals of the indirect point estimates cannot be calculated for non-inferiority testing);
  - It is unclear whether the dose distribution of modafinil, i.e. a vast majority of patients receiving a higher dose of 400 mg, as observed in the two modafinil studies (Hirshkowitz 2001 and Becker 2004), reflect Australian clinical practice. Although a maximum dose of 400 mg daily is recommended, both the Australian Medicines Handbook and the modafinil PI suggest that "there is no statistically significant evidence that doses of 400 mg daily give greater benefit than 200 mg daily"; and
  - The submission did not consider alternative modafinil dosing regimens. The BD dosing was not used in the two modafinil studies. As noted earlier, a split dose of modafinil improves wakefulness in the later afternoon or evening compared to a single dose;
  - The dose of armodafinil was titrated according to tolerability in all three armodafinil studies, at an increment or decrement of 50 mg. It is uncertain whether the dose distribution of armodafinil following this manner of titration would best reflect those in clinical practice. The proposed armodafinil PI recommends a dosage regimen of either 150 mg or 250 mg OD; and
  - Some dose regimens in the five studies used to estimate the dose relativity are not recommended by PI documents, e.g. modafinil 800 mg, armodafinil 50 mg, 100 mg and 200 mg.

- 6.26 The ESC noted that similar effects were observed between modafinil 200 mg and 400 mg vs armodafinil 150 mg and 250 mg, however no dose response data was provided.
- 6.27 The comparative costs of armodafinil and modafinil treatment per day were calculated during the evaluation and presented below. The daily dose distributions for armodafinil and modafinil were based on a weighted average of the strength distributions from Studies 3024 and 3023 and on the strength distribution from Study Hirshkowitz 2001, as the proportion of narcoleptic patients receiving each dose of armodafinil was not reported in Study 3046 and some patients in Becker 2004 were treated with a modafinil dose which is not recommended, i.e. 800 mg. However, the dose of 800 mg/day in Becker 2004 was used in the submission's calculation of the dose relativity between armodafinil and modafinil.

**Table 7: Costs for armodafinil and modafinil per day**

	Dose distribution	Number of tablets/day	Dispensed price/day	Weighted dispensed price/day
<b>Armodafinil</b>				
250mg	66.1%	1 x 250mg tablet	\$ [REDACTED]	\$ [REDACTED]
200mg	10.5%	1 x 150mg tablet + 1 x 50mg tablet	\$ [REDACTED]	
150mg	14.6%	1 x 150mg tablet	\$ [REDACTED]	
100mg	7.5%	2 x 50mg tablets	\$ [REDACTED]	
50mg	1.3%	2 x 50mg tablets	\$ [REDACTED]	
<b>Modafinil</b>				
400mg	74.0%	4 x 100mg tablets	\$11.27	\$9.80
200mg	26.0%	2 x 100mg tablets	\$5.63	

Source: Analysis performed during the evaluation

- 6.28 Armodafinil, at its requested PBS price, is cost-minimising relative to modafinil only if the PBAC accepts the equi-effective doses proposed in the submission ([REDACTED] mg armodafinil vs [REDACTED] mg modafinil) and the claim of non-inferiority in terms of safety. The dose relativity between armodafinil and modafinil was determined without consideration of equi-effectiveness. The ESC considered that it could not be confident about the equi-effective doses in the absence of good quality direct dose response comparison studies.
- 6.29 It was noted that the US Patent No. RE37516 which covers pharmaceutical compositions and methods of treatment with the form of modafinil contained in Provigil® (brand name of modafinil in the US) expired on 6<sup>th</sup> October 2014 (with paediatric exclusivity, this patent expired on 6<sup>th</sup> April 2015) and a generic version of modafinil has been approved by the US Food and Drug Administration (FDA). If generic modafinil was available at a lower price in Australia, this would have implications for the relative price/outcome or cost-minimisation claim for armodafinil.
- 6.30 The Pre-PBAC Response proposed that the price of armodafinil be reduced by [REDACTED]% upon the generic entry of modafinil.

### Drug cost/patient/month

6.31 \$█/patient/month at 150 mg/day or \$█/patient/month at 250 mg/day. This is compared to modafinil of \$171/patient/month at 200 mg/day or \$343/patient/month at 400 mg/day, based on the updated Dispensed Price for Maximum Quantity (DPMQ) for each drug. The treatment should be ongoing.

### Estimated PBS usage & financial implications

6.32 This submission was not considered by DUSC. The submission used a market-share approach to estimate the use and costs of listing armodafinil on the PBS. The average dose that is expected to be prescribed to patients was based on a weighted average of the strengths used by participants in Studies 3024 and 3023. This was inappropriate and introduced substantial uncertainty, given that the equivalence of effectiveness of armodafinil to modafinil has not been established from these studies.

6.33 Given the submission's claim of non-inferiority of armodafinil to modafinil and the cost-minimisation approach taken, cost-neutrality to government health budget should be achieved from the listing of armodafinil. The submission's estimates of financial implications from listing of armodafinil are summarised below.

**Table 8: Estimated use and financial implications**

	2016	2017	2018	2019	2020
<b>the extent of use of armodafinil</b>					
Total patients eligible for treatment	█	█	█	█	█
% uptake armodafinil	█	█	█	█	█
Total patients treated with armodafinil	█	█	█	█	█
Total cost of armodafinil	\$█	\$█	\$█	\$█	\$█
Less patient contributions	\$█	\$█	\$█	\$█	\$█
Net cost for armodafinil	\$█	\$█	\$█	\$█	\$█
<b>Reduction in use of modafinil</b>					
Total cost of modafinil	-\$█	-\$█	-\$█	-\$█	-\$█
Less patient contributions	-\$█	-\$█	-\$█	-\$█	-\$█
Net cost of modafinil	-\$█	-\$█	-\$█	-\$█	-\$█
<b>Net cost to the PBS/RPBS</b>	<b>\$█</b>	<b>\$█</b>	<b>\$█</b>	<b>\$█</b>	<b>\$█</b>

Source: compiled during the evaluation, based on information presented in 'Nuvigil Section E Final'

*The redacted table above shows that the number of patients treated with armodafinil is estimated to be less than 10,000 per year at a net cost to PBS of less than \$10 million per year.*

### Quality Use of Medicines

6.34 Modafinil is associated with significant 'off-label' use and this presents some safety concerns<sup>5</sup>. The potential for similar use and the associated concerns are likely to apply to armodafinil as well.

<sup>5</sup> Peñaloza RA, et al. Trends in on-label and off-label modafinil use in a nationally representative sample. JAMA internal medicine. 2013;173(8):704-6.

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

## 7 PBAC Outcome

- 7.1 The PBAC decided not to recommend the listing of armodafinil on the PBS for excessive daytime sleepiness associated with narcolepsy. In making its recommendation, the PBAC considered that there was no apparent unmet clinical need for armodafinil and the estimation of the equi-effective doses remained uncertain in the cost-minimisation analysis.
- 7.2 The PBAC considered that while the pharmacokinetic properties of armodafinil differed from modafinil, i.e. armodafinil has a greater half-life than modafinil, the pharmacodynamic effects of the drug were likely similar, and it was not necessarily expected that armodafinil would offer any appreciable clinical advantage over modafinil.
- 7.3 The PBAC noted the submission had estimated the equi-effective doses 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.
- 7.4 The PBAC agreed that modafinil was the appropriate comparator, but considered that a comparison against the split dose regimen of modafinil was also relevant.
- 7.5 The PBAC noted the ESC's concerns regarding the comparability of the trials, risk of bias, the clinical importance of the trial outcomes, and the basis of the inferiority margin for the indirect comparison. The PBAC acknowledged these issues but considered that the data presented in the submission, and the fact that armodafinil is the R-enantiomer of modafinil, suggested that armodafinil is very likely to be non-inferior in terms of comparative effectiveness and safety compared to modafinil.
- 7.6 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.
- 7.7 The PBAC considered that while the issue of the equi-effective doses may be adjusted to address the PBAC's concerns, the overall question of the clinical need for patients would not be resolved by greater confidence in the equi-effective doses.
- 7.8 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**  
Rejected

**8 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.

**9 Sponsor's Comment**

TEVA will work to resolve the concerns raised by the PBAC.