PUBLIC SUMMARY DOCUMENT
Product: Modafinil, tablet, 100 mg, Modavigil®
Sponsor: CSL Limited
Date of PBAC Consideration: November 2008

1. Purpose of Application

The Australasian Sleep Association (ASA) and the Australian New Zealand Association of Neurologists (ANZAN) joint working party, together with the sponsor requested an amendment to the PBS listing of modafinil to allow use as first line therapy for the treatment of narcolepsy. The Working Party also requested changes to the diagnostic criteria for narcolepsy included in the current restriction for modafinil.

2. Background

A submission for modafinil was rejected by the PBAC at its June 2002 meeting, as was a re-submission to the March 2003 PBAC meeting. The March 2003 application was rejected because of the uncertain clinical benefit and uncertain cost-effectiveness.

At the November 2004 meeting, the PBAC recommended listing on the basis of acceptable cost-effectiveness in the patient group proposed. The PBAC considered that a continuation rule should not be required partly because patients would have to pay the full cost of the polysomnography test for continuing treatment, and that there may be problems with access to sleep laboratories in the time-frames specified for assessment of response. Modafinil was PBS listed 1 August 2005.

In March 2008 a joint working party between the ASA and ANZAN was established to review the current availability of modafinil for the treatment of narcolepsy in Australia. The stated impetus for the review was twofold: (i) increasing knowledge on the potential harms of dexamphetamine related to risk of sudden death, long term cardiovascular risk, psychiatric problems, potential for misuse and abuse which the submission noted has led to a detailed regulatory update in 2006 and 2007 and re-assessment of the implications for chronic lifetime therapy from early adulthood and (ii) clinical experience with the application of the diagnostic criteria for narcolepsy which finds they are too restrictive and are unnecessarily excluding patients from treatment.

3. Registration Status

Modafinil was TGA registered on 2 July 2002 for the improvement of wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.

Two additional indications were TGA registered in April 2007:

- Treatment of excessive sleepiness associated with moderate to severe chronic shift work sleep disorder.
- Adjunct to continuous positive airways pressure in obstructive sleep apnoea/ hypopnoea syndrome in order to improve wakefulness.

4. Listing Requested and PBAC's View

Authority required

Initial treatment, by a qualified sleep medicine practitioner or neurologist, of patients with narcolepsy who meet the following definition:

i) Excessive daytime sleepiness, recurrent naps or lapses into sleep occurring almost daily for at least 3 months; and

ii) 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

iii) Absence of any medical or psychiatric disorder that could otherwise account for the hypersomnia.

Authority required

Continuing treatment of narcolepsy, where the patient has previously been issued with an authority prescription for this drug.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Narcolepsy is a rare, chronic condition first affecting patients in their late teens and early twenties and then remaining for life. The defining and most debilitating symptom is excessive daytime sleepiness manifested by both continuous sleepiness and uncontrolled sleep attacks. This has a profound effect on the individual's social, academic and work performance and may expose them to higher levels of risk from accidents.

Traditionally, stimulants such as methylphenidate and dexamphetamine have been the only treatment options for excessive daytime sleepiness in narcolepsy. The ASA/ANZAN Working Party claimed there is an argument for instatement of modafinil as first line therapy for narcolepsy due to its favourable benefit/risk profile to dexamphetamine, and lack of addictive potential.

6. Comparator

The submission nominated "no treatment" as the main comparator. The ASA/ANZAN working party believed that after recent re-assessment of dexamphetamine safety, and considering narcolepsy treatment was life-long, that from a legal and medical perspective dexamphetamine could no longer be considered the standard of care for narcolepsy, and as such was not an appropriate comparator for modafinil.

For PBAC's view see Recommendation and Reasons.

7. Clinical Trials

The basis of the submission is three direct randomised comparative trials comparing modafinil and placebo (two of which have been previously considered and Black (2006)) and four supplementary studies – three cross-over studies comparing modafinil and placebo and one non-comparative study in which patients switched from stimulant to modafinil therapy for narcolepsy (all previously considered by the PBAC). The trial by Black (2006) differed in design to the trials previously considered by the PBAC as patient eligibility criteria included

that patients be on stable doses of modafinil (i.e., a responder population) and the dose of modafinil used ranged between 200 and 600 mg/day (the TGA approved doses were 200-400 mg/day).

The published trial changed from previous submissions was:

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial – modafinil versus placebo		
Black J et al	Sodium oxybate improves excessive daytime sleepiness in narcolepsy.	Black J et al. Sleep 2006; 29:939-946

8. Results of Trials

The key results of the trial reported by Black (2006) are summarised in the table below. The primary outcome of the Black (2006) trial was the 20 minute Maintenance of Wakefulness Test (MWT), which was performed at visits 2, 3, 4 and 5 according to validated standards.

Primary outcome: Maintenance of Wakefulness Test in the randomised trial Black (2006)

	Modafinil Mean minutes (SD)	Placebo Mean minutes (SD)
Visit 3 (randomisation)	N=63, 10.48 (6.03)	N=55, 9.74 (6.57)
Visit 5 (8 weeks)	N=62, 9.86 (5.89)	N=53, 6.87 (6.14)
Difference	-0.53 (4.36)	-2.72 (4.54)
p value	p=0.006	

The re-submission presented new toxicity data as a summary of the changes made to the modafinil and dexamphetamine product information (PI) documents. The re-submission argued that due to the safety concerns associated with the use of dexamphetamine that dexamphetamine should no longer be considered as a first-line option for the treatment of narcolepsy.

9. Clinical Claim

Although not explicitly stated, it was assumed that the re-submission would describe modafinil as superior in terms of comparative effectiveness but associated with greater toxicity than placebo. Based on the supporting data, this description was reasonable. However, as noted by the PBAC in its considerations of the previous submissions, given the outcomes reported in the trials, the patient relevance and magnitude of clinical benefit of modafinil remained uncertain. The clinical importance of each outcome measure was unclear and 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 and/or able to drive.

10. Economic Analysis

The submission did not present an economic analysis. The PBAC considered that the omission of economic analyses was inappropriate. It was noted that modafinil and dexamphetamine 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.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year were estimated to be < 10,000, while the financial cost/year to the PBS (excluding co-payments) minus any savings in use of other drugs was

estimated to be < $ 10 million using the lower prevalence estimate and > $10 million in Year 5 using a higher prevalence estimate.

12. Recommendation and Reasons

The PBAC welcomed the submission from the Australian Sleep Association (ASA) and the Australian New Zealand Association of Neurologists (ANZAN) joint working party and indicated its empathy with the position put forward by this group. However, as noted during the hearing the Committee must make its recommendations in accordance with the National Health Act (1953) which requires it to be satisfied that any new therapy (and by extension any change to the PBS availability of an existing therapy) "where therapy involving the use of a particular drug …is substantially more costly than an alternative therapy …the Committee shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits …unless the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies."

The PBAC did not accept the premise of the submission that from a medical and legal view, dexamphetamine can no longer be considered the standard of care for treatment of this life-long condition, and was not an appropriate comparator for modafinil in the first-line setting. The Committee 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 the hearing that not all patients currently on dexamphetamine will switch to modafinil appeared to contradict the first statement. Although it was acknowledged that the decision to switch therapies in prevalent patients may be somewhat confounded by other factors (e.g. the "high" offered by dexamphetamine), and may differ from the decision on which therapy to initiate new patients, the Committee considered that overall there was insufficient basis for it to change its previous finding that dexamphetamine is the appropriate comparator (alternative therapy) for first-line modafinil.

The PBAC also recalled that the incremental benefit (efficacy and safety) of modafinil over dexamphetamine 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. The PBAC further considered that the omission of economic analyses was inappropriate. It was noted that modafinil and dexamphetamine 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.

With respect to the requested changes to the current restriction's diagnostic criteria for narcolepsy, the PBAC acknowledged the pre-Sub-Committee response argument that "the MSLT is neither perfectly sensitive nor specific for the diagnosis of narcolepsy", and as such patients may be misdiagnosed and denied treatment, and that as the MSLT was only available in major centres it was an inappropriate requirement for the restriction. The Pre-Sub-Committee response also argued that the requirement for 2 or more sleep onset REM periods on MSLT was inappropriate as it would exclude up to 30 % of patients with narcolepsy. The pre-Sub-Committee response acknowledged that a mean sleep latency of 8 minutes was supported in the literature around narcolepsy diagnosis, but argued that this too could act to exclude excessively sleepy narcolepsy patients. The PBAC acknowledged the letter provided

with the submission from the Australasian Sleep Association 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.

The PBAC therefore rejected the application because of insufficient evidence to support the claim that placebo rather than dexamphetamine 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. The Committee indicated its willingness to hold further dialogue with the working party and other relevant stakeholders on the restriction's diagnostic criteria.

Recommendation:
Reject

13. 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.

14. Sponsor's Comment

The Australian Sleep Association (ASA) and the Australian New Zealand Association of Neurologists (ANZAN) joint working party is disappointed by the PBAC rejection. The working party will work with the PBAC on the restriction's diagnostic criteria to ensure that they do not unnecessarily exclude narcolepsy patients from treatment.