Scottish Medicines Consortium

Re-Submission

modafinil 100mg and 200mg tablets (Provigil®)

Cephalon **No. 63/03**

Resubmission for new indication: excessive sleepiness associated with obstructive sleep apnoea / hypopnoea syndrome

10 February 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

modafinil (Provigil®) is not recommended for use within NHS Scotland for the treatment of excessive sleepiness associated with obstructive sleep apnoea / hypopnoea syndrome.

Modafinil demonstrated modest improvement in sleepiness and quality of life, the clinical significance of which is difficult to estimate. The economic case has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Modafinil 100mg and 200mg tablets (Provigil®)

Indication

Treatment of excessive sleepiness associated with obstructive sleep apnoea / hypopnoea syndrome

Dosing information

200mg to 400mg daily

UK launch date

December 2002

Comparator medications

No other medicines are licensed in the UK for treatment of excessive sleepiness associated with obstructive sleep apnoea / hypopnoea syndrome (OSA/HS). The Scottish Intercollegiate Guidelines Network (SIGN) advises that nasal continuous positive airways pressure (CPAP) is the treatment of choice for OSA/HS.

Cost of relevant comparators

The annual costs of modafinil 200mg and 400mg daily are £1460 and £2920, respectively, using costs from eVadis drug dictionary accessed on 15th November 2005.

Summary of evidence on comparative efficacy

Modafinil is a centrally acting sympathomimetic that promotes wakefulness by mechanisms which are not fully understood.

A double-blind 12-week trial randomised adults aged <70 years with OSA/HS and excessive daytime sleepiness, Epworth Sleepiness Scale (ESS) score ≥10 despite effective CPAP use, to placebo, modafinil 200mg or 400mg daily. Efficacy was evaluated in 291 patients who were at least partially compliant with CPAP, received at least one dose of study drug and had at least one post-baseline assessment of an efficacy variable. One of the primary endpoints was change from baseline to week 12 or final visit in mean sleep latency on the maintenance of wakefulness test (MWT), which averages time to sleep, measured by polysomnography, during four 20-minute nap opportunities each separated by two hours when the patient is asked to try to remain awake. The other primary endpoint was clinician-assessed clinical global impression of change (CGI-C) at week 12 or final visit. For both of these the primary analyses, which compared data from both modafinil groups combined to the placebo group, there were significant improvements with modafinil, with similar results for comparisons of each modafinil group to placebo. Mean changes from baseline in MWT sleep latency with modafinil 200mg, modafinil 400mg and placebo were 1.6, 1.5 and -1.1 minutes, respectively, with 61%, 68% and 37% of patients in the respective groups having some improvement on CGI-C. There were also significant improvements in the combined modafinil group compared with placebo for mean changes from baseline to week 12 or final visit in ESS; median reaction time and number of lapses on a psychomotor vigilance test (PVT); the functional

outcomes of sleep questionnaire (FOSQ) total score and vigilance, activity and general productivity domains; and the general health, vitality and composite physical scores of the short-form 36 (SF-36) questionnaire.

A double-blind 4-week trial recruited similar patients who were fully compliant with CPAP, defined as use for ≥4 hours per night on ≥70% of nights during a 21-day run-in period. They were randomised to placebo or modafinil 200mg daily for one week then 400mg daily. Efficacy was evaluated in 155 patients who received at least one dose of study drug and had a least one post-baseline assessment of an efficacy variable. The primary endpoint, mean change from baseline to week 4 or final visit in ESS, significantly improved with modafinil compared to placebo: -4.6 vs. -2.0. There were also significant improvements with modafinil compared to placebo in mean change from baseline to week 4 of final visit in sleep latency on multiple sleep latency test (MSLT), which provides an average time to sleep, measured by polysomnography, during four 20-minute opportunities to nap each separated by two hours; median reaction time and number of lapses transformed on a PVT; and total score, vigilance and activity domains of the FOSQ. Within the 73% of study patients who had CGI-C data, more patients had some improvement in the modafinil group compared with placebo: 66% vs. 34%.

Summary of evidence on comparative safety

The most common adverse effect associated with modafinil is headache, which is usually mild and transient. Other common adverse effects include nervousness, anxiety, insomnia, dizziness, depression, abnormal thinking, confusion, blurred vision, paraesthesia, asthesia, gastro-intestinal disturbances, abnormal liver function tests, tachycardia, palpitations and vasodilation.

Summary of clinical effectiveness issues

It is difficult to determine the clinical significance of changes in objective assessments of sleepiness (MWT and MSLT) and vigilance (PVT) and subjective assessment of sleepiness (ESS), which appear to be modest. The FOSQ and SF-36 provide a better estimate of the potential benefits to be expected in practice. The placebo-corrected statistically significant effects on the FOSQ scale appear modest, being less than 2% of the score range. The largest placebo-corrected difference was observed in the SF-36 vitality score, approximately 10 to 15 points on a 100-point scale in the 12-week study, with smaller differences of less than 10 points in SF-36 general health and composite physical scores.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis compared to an option of “no treatment”. The analysis was carried out by extrapolating data from clinical trials and allowing the dose to be increased or treatment to be discontinued. The cost per QALY was estimated to be £25,000. The study was designed to an acceptable standard, with key assumptions being tested in a sensitivity analysis.

Resource use and costing was generally straightforward with the exception of the estimate of the additional medical costs of excessive sleepiness. This was taken from an American study, so there are concerns about its generalisability. It is also assumed the excess cost is entirely eradicated when modafinil is successful, in contrast to the utility gain estimated by the manufacturer, which is modest.

The results were clearly presented and the sensitivity analysis was helpful. However, it highlights that the results are sensitive to the utility gain from modafinil and the savings on additional medical costs of excessive sleepiness, both of which are based on data around which there is considerable uncertainty. In particular if the savings on the excess medical costs of sleepiness fall much below £500 then the cost per QALY exceeds £30k and, given the small change in utility values demonstrated, this seems to be a real possibility.

Patient and public involvement

A Patient Interest Group submission was not made.

Budget impact

To reflect the initial number of prevalent patients being treated, followed by incident cases, the manufacturer estimated that in year 1 there would be 41 eligible patients and in year 5 there would be 38 new patients. On this basis, modafinil would cost £60K in year 1 and £163K in year 5. There are no predicted medicines budget savings. There are some savings from avoiding medical costs of excessive sleepiness: when these are taken into account the net economic cost would be £29K in year 1 rising to £68K in year 5.

Guidelines and protocols

The June 2003 SIGN publication number 73: management of obstructive sleep apnoea / hypopnoea syndrome in adults notes that there is some evidence to suggest that alerting drugs, such as modafinil, may have a small beneficial effect on sleepiness in some patients who remain sleepy despite good CPAP compliance. However, they may decrease CPAP use and longer-term studies of their value and risks are needed. There is no evidence to suggest that they could be used as an alternative to CPAP and they are not a substitute for careful attention to improving CPAP comfort and efficacy. Pharmacological therapy is not recommended as first-line treatment for OSA/HS.

Additional information

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 13th October 2003 that modafinil is not recommended for use within NHS Scotland [for treatment of excessive sleepiness associated with OSA/HS. Modafinil may have a small beneficial effect on daytime sleepiness suffered by patients with obstructive sleep apnoea / hypopnoea syndrome and thus improves some quality of life assessments, particularly measures of ability to perform daily tasks, vigilance, general health and vitality. However, the economic case for its use within NHS Scotland was not demonstrated in the data submitted. The licence holder has indicated their decision to resubmit.

After review of a resubmission, SMC issued advice on 6th May 2005 that modafinil (Provigil®) is not recommended for use within NHS Scotland for the treatment of excessive sleepiness associated with obstructive sleep apnoea / hypopnoea syndrome. Modafinil demonstrated improvements in sleepiness and quality of life, the clinical significance of which is difficult to estimate. The submitted health economic case had some uncertainties and failed to demonstrate cost-effectiveness.

After review of a full submission, SMC issued advice on 6th May 2005 that modafinil (Provigil®) is not recommended for use within NHS Scotland for the treatment of excessive sleepiness associated with moderate to severe shift work sleep disorder. Modafinil demonstrated a modest improvement in sleepiness and quality of life, the clinical significance of which is difficult to estimate. The submitted health economics case does not demonstrate cost-effectiveness of the therapy.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 16 January 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The under noted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Black JE, Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated Obstructive Sleep Apnea/Hypopnea Syndrome. Sleep 2005; 28: 464-71.

Pack AI, Black JE, Schwartz JRL, et al. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. Am J Respir Crit Care Med 2001; 164: 1675-81.

Scottish Intercollegiate Guidelines Network (SIGN). Publication number 73: management of obstructive sleep apnoea / hypopnoea syndrome in adults. June 2003