

Fatigue in multiple sclerosis: modafinil

Evidence summary

Published: 2 April 2013

[nice.org.uk/guidance/esuom9](https://www.nice.org.uk/guidance/esuom9)

Key points from the evidence

The content of this evidence summary was up-to-date in April 2013. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Modafinil is an oral 'wakefulness-promoting' agent that is licensed in the UK for treating excessive sleepiness associated with narcolepsy with or without cataplexy.

Modafinil is not licensed for treating fatigue in multiple sclerosis (MS), and therefore this is an off-label use of this medication.

Two small placebo-controlled randomised controlled trials (RCTs) did not find any statistically significant evidence that modafinil (up to 200 mg or 400 mg daily in the respective trials) improved fatigue in adults with MS (of any disease pattern) at 8 weeks or 35 days respectively.

No serious adverse effects of modafinil were reported in either RCT; however, common adverse effects, including gastrointestinal complaints and restlessness, were observed in both.

The RCTs do not provide any evidence of the longer-term safety and efficacy of modafinil for treating fatigue in MS.

Modafinil can cause serious adverse effects including psychiatric disorders, cardiovascular symptoms, and serious skin and multi-organ hypersensitivity reactions. In January 2011, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP)

concluded that the benefits of modafinil could only be considered to outweigh the risks when used to treat narcolepsy. The UK Medicines and Healthcare products Regulatory Agency (MHRA) has issued further information and advice to support the safer use of modafinil in people with narcolepsy.

Modafinil is available as 100 mg tablets at a cost of £52.60 for a 30-tablet pack, and as 200 mg tablets at a cost of £105.21 for a 30-tablet pack. The standard dose (for treating narcolepsy) is between 200 mg and 400 mg daily.

No other drugs have marketing authorisation for MS-related fatigue, although off-label use amantadine may also be considered.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Overview for healthcare professionals

Modafinil is an oral wakefulness promoter. The precise mechanism of action of modafinil is unknown.

Regulatory status of modafinil

Modafinil is licensed in the UK for treating excessive sleepiness associated with narcolepsy with or without cataplexy. Modafinil is not licensed for treating fatigue in multiple sclerosis (MS), and therefore use for this indication is an off-label use of modafinil. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using modafinil outside of its authorised indications.

Evidence statements

- Two small double-blind, placebo-controlled randomised controlled trials (RCTs) that have evaluated modafinil for treating fatigue in MS provide the evidence for this summary.
- One RCT ([Möller et al. 2011](#)) (n=121) found that modafinil up to 200 mg daily did not statistically significantly improve the primary outcome of change in mean fatigue severity scale (FSS) score at 8 weeks, or improve secondary outcome measures of fatigue, sleepiness or quality of life compared with placebo. Effects on cognitive impairment were conflicting; modafinil statistically significantly improved performance on the symbol digit modalities test (SDMT) and placebo improved performance on the paced auditory serial addition test (PASAT).
- A second RCT ([Stankoff et al. 2005](#)) (n=115) found that modafinil up to 400 mg daily did not statistically significantly improve the primary outcome of change in mean modified fatigue impact scale (MFIS) score at 35 days, or improve secondary outcomes compared with placebo.
- Common adverse effects of modafinil, including restlessness, insomnia and gastrointestinal complaints such as diarrhoea and nausea, were reported in the 2 RCTs; no serious adverse effects were reported.
- The longer-term safety and efficacy of modafinil for treating fatigue in MS cannot be evaluated from these trials.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

Efficacy

Two small double-blind, placebo-controlled RCTs were identified that have evaluated modafinil for treating fatigue in adults with MS of any disease pattern.

The Hamburg Vigil Study ([Möller et al. 2011](#)) included 121 adults with an FSS mean score of 4 or more and an expanded disability status scale (EDSS) score of less than 7 and randomised them to 8 weeks' treatment with modafinil up to 200 mg daily or placebo. There was no statistically significant difference between the two treatment groups in improvement of mean FSS score at 8 weeks (mean score change 0.76 points for modafinil compared with 0.38 points for placebo; $p=0.07$). Neither was there a statistically significant difference between the two treatment groups for the secondary outcomes of change in MFIS, Epworth sleepiness scale (ESS), Pittsburgh sleep

quality index (PSQI) and the brief fatigue inventory (BFI) scores. Cognitive impairment was also assessed using the SDMT and the PASAT, which found conflicting results (improvement on SDMT with modafinil and improvement on PASAT with placebo).

Another RCT ([Stankoff et al. 2005](#)) included 115 adults with an MFIS score of 45 or more and an EDSS score between 0 and 6.5, and randomised them to 35 days' treatment with modafinil up to 400 mg daily or placebo. Compared with placebo, modafinil was not associated with a statistically significant improvement in the primary outcome, which in this study was change in MFIS score over 35 days (mean score change 10.8 points for modafinil compared with 14.1 points for placebo, $p=0.27$) Neither was modafinil associated with an improvement in the secondary outcomes of fatigue impact scale (FIS) and ESS scores, or fatigue on a visual impact scale compared to placebo.

Neither of the trials provides evidence of the longer-term efficacy of modafinil in MS.

Table 1 Summary of the trials

	Modafinil	Placebo	Analysis
Möller et al. (2011)			
Randomised	n=62	n=59	Modafinil up to 200 mg vs. placebo for 8 weeks
Efficacy	n=62	n=59	
Primary outcome: mean change from baseline to 8 weeks in 9-item FSS mean score	-0.76	-0.38	$p=0.07$
Safety	n=62	n=59	
Patients reporting serious adverse events	0%	0%	

Other adverse events	Restlessness, nausea, 'other' (including diarrhoea, and stomach pain) (figures not reported).		Modafinil group compared to placebo experienced: Non-significant increased restlessness at 4 weeks (p=0.07) Non-significant increased nausea at 8 weeks (p=0.08) Significant increased 'other' side effects at 4 weeks (p=0.01)
<u>Stankoff et al. (2005)</u>			
Randomised	n=56	n=59	Modafinil 200 to 400 mg vs. placebo for 35 days
Efficacy	n=56	n=59	
Primary outcome: change from baseline in MFIS mean score	-10.8	-14.1	p=0.27
Safety	n=56	n=59	
Patients reporting serious adverse events	0%	5.1% (3/59)	Serious adverse events in the placebo group not considered related to study medication
Selected adverse events:			
Nausea	9/56	1/59	Significance not given
Insomnia	8/56	2/59	
Abbreviations: FSS, fatigue severity scale; MFIS, modified fatigue impact scale; n, number of patients.			

Safety

No serious adverse effects of modafinil were reported in the RCTs by [Möller et al. \(2011\)](#) and [Stankoff et al. \(2005\)](#).

The [summary of product characteristics](#) for modafinil warns that it can cause serious adverse effects including psychiatric disorders (such as suicidal ideation, mania and hallucinations), cardiovascular symptoms (such as hypertension and irregular heart beat), and serious skin and multi-organ hypersensitivity reactions (including Stevens–Johnson syndrome and toxic epidermal necrolysis). The [European Medicines Agency](#) (EMA) has completed a review of the safety and effectiveness of modafinil. The EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of modafinil could only be considered to outweigh the risks when used to treat narcolepsy ([EMA 2011](#)). The CHMP recommended further changes to the product information to ensure modafinil is used appropriately, and asked manufacturers of modafinil to put in place risk-minimisation measures. As a result of the EMA's review, the [UK Medicines and Healthcare products Regulatory Agency](#) (MHRA) has issued further [information and advice](#) to support the safer use of modafinil in people with narcolepsy.

Cost effectiveness and cost

No studies of the cost effectiveness of modafinil for treating fatigue in MS were identified.

Modafinil is available as 100 mg tablets at a cost of £52.60 for a 30-tablet pack, and as 200 mg tablets at a cost of £105.21 for a 30-tablet pack (costs taken from the [Drug Tariff](#) March 2013). In the [summary of product characteristics](#) the standard dose (for treating excessive sleepiness in narcolepsy) is between 200 and 400 mg daily.

Relevance to NICE guidance programmes

Modafinil for treating fatigue in multiple sclerosis (MS) has not been appraised through the NICE technology appraisal work programme and is not currently planned into the technology appraisal or any other work programme. Unlicensed or off-label medicines are not considered for the NICE technology appraisal work programme.

NICE has published [Multiple sclerosis: management of multiple sclerosis in primary and secondary care](#) (NICE clinical guideline 8) which includes recommendations on managing fatigue in MS.

NICE has also published clinical guidelines containing recommendations on using modafinil, including:

- [Parkinson's disease: diagnosis and management in primary and secondary care](#) (NICE clinical guideline 35), which advises that modafinil may be considered for daytime hypersomnolence in people with Parkinson's disease.

- [Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults](#) (NICE clinical guideline 72), which includes modafinil as an unlicensed treatment option, only in the context of tertiary services after referral of children and young people whose ADHD is unresponsive to standard medications.

Intervention and alternatives

Modafinil is a wakefulness-promoting agent that is available in 100 mg or 200 mg oral tablets. The precise mechanism of action of modafinil is unknown. The only licensed indication for modafinil is the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.

Condition

The NICE clinical guideline on [multiple sclerosis](#) (MS) describes MS as a neurological condition in which the white matter of the central nervous system becomes inflamed and destroyed. The disease usually starts in early adult life and there is no cure. The 3 recognised disease patterns are relapsing/remitting MS (which affects 80% of people at disease onset), primary progressive MS and secondary progressive MS. The prevalence of MS in England and Wales is around 100 to 120 people per 100,000 of the population. Fatigue is one of the commonest, most disabling and frustrating symptoms experienced by people with MS, affecting up to 80% of people with the disease.

Alternative treatment options

Fatigue in MS may be directly related to the disease, or be secondary to a number of non-disease factors. The NICE clinical guideline on [multiple sclerosis](#) advises that if fatigue is disrupting the individual's life then consideration should be given to the possibility of depression; the presence of other factors such as disturbed sleep, chronic pain or poor nutrition; and the need for review of medication. The NICE guideline recommends general advice and training on conservative techniques to manage fatigue, including encouragement to take aerobic exercise and using energy-conservation techniques. There are currently no medications recommended for the routine treatment of fatigue in MS, although the NICE guideline advises that a small clinical benefit might be gained from taking amantadine 200 mg daily. Amantadine is not licensed for treating fatigue in MS.

Evidence review: efficacy

Two small short double-blind, placebo-controlled randomised controlled trials (RCTs) that have evaluated modafinil for treating fatigue in multiple sclerosis (MS) provide the evidence for this summary.

Randomised controlled trial by Möller et al. (2011)

The Hamburg Vigil Study (Möller et al. 2011) included 121 adults (aged 18 to 65 years) who had MS diagnosed according to McDonald criteria, a baseline fatigue severity scale (FSS) mean score of 4 or more and an expanded disability status scale (EDSS) score of less than 7. Exclusion criteria included relapses or the need for steroid treatment in the past 4 weeks, mitoxantrone or other new medical treatments that may worsen fatigue started in the past 4 weeks, any psychiatric diagnosis, a severe neuropsychological deficit or contraindications to modafinil. Symptomatic treatments for fatigue had to have been discontinued at least 2 weeks before randomisation.

Participants were randomised to receive modafinil dosed up to 200 mg daily within 1 week (n=62) or placebo (n=59), with assessments at baseline, week 4 and week 8. The primary outcome was mean change in FSS mean score. FSS mean score was measured using a 9-item questionnaire assessing the effect of fatigue on daily activities using a 7-point Likert scale. A total score of between 9 and 63 could be gained with a mean score ranging from 1 to 7. Higher scores indicate a greater effect of fatigue on daily activities. The authors considered a reduction in mean score of 0.5 points to be clinically relevant. Secondary outcomes to assess different aspects of fatigue were the German versions of the modified fatigue impact scale (MFIS), the Epworth sleepiness scale (ESS), the Pittsburgh sleep quality index (PSQI) and the brief fatigue inventory (BFI). Participants were also asked to complete the Hamburg quality of life questionnaire in multiple sclerosis (HAQUAMS), the Rochester fatigue diary (RFD), and to rate overall daily fatigue on a visual analogue scale. Cognitive impairment was assessed using the oral version of the symbol digit modalities test (SDMT) and the paced auditory serial addition test (PASAT).

The placebo group contained significantly more women than the modafinil group (78% compared with 63%; $p=0.05$) but there were no other major baseline differences between the groups. Of all participants, 53% had relapsing-remitting MS, 21% primary progressive MS and 26% secondary progressive MS. Mean disease duration was 6.9 years and mean EDSS score at baseline was 3.3.

A total of 110 adults (91%) completed the 8-week study. Analysis was by intention-to-treat (ITT). Nine-item FSS mean score at baseline was 6.01 in the modafinil group, improving to 5.40 at 4 weeks and 5.25 at 8 weeks. In the placebo group, baseline FSS mean score was 5.80 improving to 5.43 at

4 weeks and 5.42 at 8 weeks. After 8 weeks, there was no statistically significant difference in improvement in FSS mean score from baseline between modafinil and placebo (mean score change 0.76 points for modafinil compared with 0.38 points for placebo; $p=0.07$). There was also no statistically significant difference between groups at 4 weeks ($p=0.26$).

There was no statistically significant difference between modafinil and placebo at 8 weeks for any of the secondary outcomes, with the exception of SDMT and PASAT. Modafinil improved performance on the SDMT (mean score change 0.32 standard deviations improvement with modafinil compared with 0.09 standard deviations improvement with placebo; $p=0.045$), and placebo improved cognition on the PASAT (mean score change 0.21 standard deviations improvement with modafinil compared with 0.51 standard deviations improvement with placebo; $p=0.04$).

Subgroup analyses according to age, sex, disease course, disease-modifying treatment, MS duration, and EDSS score had no significant effect on differences between the modafinil and placebo groups.

Randomised controlled trial by Stankoff et al. (2005)

Another RCT (Stankoff et al. 2005) included 115 adults (aged 18 to 65 years) who had MS diagnosed according to Poser criteria, chronic fatigue for at least 6 months with an MFIS score of 45 or more and an EDSS score between 0 and 6.5. Exclusion criteria included relapses or the need for steroid treatment in the past 2 months, pregnancy or breastfeeding, uncontrolled depression, anxiety or dementia. Symptomatic treatments for fatigue had to have been discontinued at least 2 weeks before randomisation, and people on disease-modifying therapies had to have been at a stable dose for at least 6 months.

Randomisation to modafinil ($n=56$) or placebo ($n=59$) was stratified according to EDSS. Modafinil was started at 100 mg twice daily for the first week, and if tolerated increased by 100 mg each week during the first 3 weeks to a maximum dose of 400 mg daily. Assessments were at baseline and day 35. The primary outcome was fatigue measured using the French version of the global MFIS (21 items; score range 0 to 84 with lower scores indicating less fatigue). This is a validated shortened version of the fatigue impact scale (FIS) recommended by the Fatigue Guidelines Development Panel of the MS Council for Clinical Practical Guidelines. Secondary outcomes were FIS score, ESS score and fatigue on a visual analogue scale. Other assessments were depression on the French-validated Montgomery/Asberg depression rating scale (MADRS), anxiety on the Covi anxiety scale (CAS), neurologic disability on the EDSS and psychomotor speed and mental flexibility

on the trail making test. There were no statistically significant baseline differences between groups.

A total of 105 adults (91%) completed the 35-day study and analysis was by ITT. In the modafinil group, 91% reached at least a 300 mg study dose, and 70% reached 400 mg. In the modafinil group, the mean global MFIS score at baseline was 63.1 which improved to 52.3 at day 35, and in the placebo group the respective scores were 63.3 at baseline and 49.2 at day 35. Modafinil did not statistically significantly improve MFIS compared with placebo: mean score change 10.8 points with modafinil compared with 14.1 points with placebo ($p=0.27$). There was no statistically significant difference between modafinil and placebo at 35 days for any of the secondary outcomes.

Subgroup analyses revealed no effect of EDSS stratification or disease-modifying therapy.

Evidence review: safety

Adverse effects in randomised controlled trials

In the Hamburg Vigil Study by (Möller et al. 2011), Modafinil was reported to cause no severe adverse events or previously unobserved effects. Study medication was withdrawn by 7 people in the modafinil group and 4 in the placebo group; 6 of these 11 withdrawals were due to adverse events (the number in each group is not reported). There was a non-significant increase in uneasiness/restlessness with modafinil at 4 weeks ($p=0.07$), and in nausea at 8 weeks with modafinil ($p=0.08$) compared with placebo. 'Other side effects' were reported more often with modafinil at 4 weeks ($p=0.01$), including diarrhoea, nausea and stomach pains.

In the trial by Stankoff et al. (2005), 60.7% of people randomised to modafinil (34 out of 56) and 47.5% of people randomised to placebo (28 out of 59) experienced at least 1 adverse effect. These effects were considered by a physician to be treatment-related in 29 out of 34 people in the modafinil group and in 20 out of 28 people in the placebo group. There were 8 discontinuations because of adverse effects: 6 in the modafinil group and 2 in the placebo group. The most common adverse effects were neurological, gastrointestinal or psychiatric in nature, with gastrointestinal complaints and insomnia more common with modafinil. Three people in the placebo group experienced serious adverse events, not related to study medication (2 MS relapses and 1 lumbar peritoneal shunt review). There was no significant change in mood in either group (mean change in MADRS: +0.32 in the modafinil group and -0.8 in the placebo group).

Warning of potential serious adverse effects

The [summary of product characteristics](#) for modafinil warns that it can cause serious adverse effects including psychiatric disorders (such as suicidal ideation, mania and hallucinations), cardiovascular symptoms (such as hypertension and irregular heart beat), and serious skin and multi-organ hypersensitivity reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis). Common adverse effects include decreased appetite, diarrhoea, nausea, anxiety/nervousness, back pain, headache, dizziness and insomnia. The use of modafinil in children is not recommended by the manufacturer for any medical condition because of the risk of serious adverse events and lack of safety and efficacy data.

In 2007, the Pharmacovigilance Working Party (PhVWP) of the [Committee for Medicinal Products for Human Use](#) (CHMP) reviewed the safety of modafinil because of the concerns over the associations with serious psychiatric disorders and severe allergic reactions. This led to the update of product information to strengthen the warnings about these risks. Further to this, in 2009 the CHMP conducted a review of all data from the clinical trials of modafinil in narcolepsy, obstructive sleep apnoea, shift-work sleep disorder and idiopathic hypersomnia. In January 2011, the European Medicine Agency published a [statement](#) to say that as the result of the review, the CHMP had concluded that the benefits of modafinil continue to outweigh their risks only when used for treating narcolepsy. The CHMP recommended further changes to the product information to ensure modafinil is used appropriately, and asked manufacturers of modafinil to put in place risk-minimisation measures.

As a result of the EMA's review, the UK [Medicines and Healthcare products Regulatory Agency](#) (MHRA) has issued [further information](#) and advice to support the safer use of modafinil in people with narcolepsy.

Evidence review: economic issues

Cost effectiveness

No studies of the cost effectiveness of modafinil for treating fatigue in multiple sclerosis (MS) were identified.

Cost

Modafinil is available as 100 mg tablets at a cost of £52.60 for a 30-tablet pack, and as 200 mg tablets at a cost of £105.21 for a 30-tablet pack (costs taken from the [Drug Tariff](#) February 2013).

In the [summary of product characteristics](#) the standard dose (for treating narcolepsy) is between 200 and 400 mg daily.

Amantadine is not licensed for treating fatigue in MS, but it is suggested in the NICE clinical guideline on [MS](#) that a small clinical benefit may be gained from 200 mg daily. Amantadine hydrochloride (Symmetrel, Alliance Pharmaceuticals) is available as 100 mg capsules at a cost of £9.90 for a 56-capsule pack, and is also available in a 50 mg per 5 ml syrup at a cost of £5.33 for 150 ml pack (costs taken from the [Drug Tariff](#) March 2013).

Current drug usage

The Prescription Cost Analysis for the NHS in England reported that 68,981 community prescriptions for modafinil were dispensed in 2012, costing approximately £9.8 million (net ingredient cost [NIC]). Information on the indications for which these medications were prescribed is not available. (NHS Business Services Authority: personal communication February 2013).

Evidence strengths and limitations

Both trials considered in this evidence summary were small and of short duration (up to 8 weeks). They were double blind, placebo controlled trials; neither compared modafinil with an active comparator, this may be because there is no treatment licensed for this indication. Allocation concealment was unclear in both studies. A high follow-up of more than 90% was achieved in both studies, and their results were analysed using [intention to treat](#) (ITT) analysis.

The short treatment periods may have prevented the detection of any longer term treatment effects; [Möller et al. \(2011\)](#) noted the possibility of an initial placebo effect, with improvements in the primary outcome in the second half of the study period in the modafinil group. The length of the studies also restricted assessment of safety and adverse events to a 5- or 8-week treatment period, so longer-term adverse events may be missed.

The 2 trials identified had relatively small patient numbers, and people with different disease patterns of MS were all assessed together. As a result only large differences in treatment effects would be detected; smaller, but clinically significant, differences, or differences in specific patient populations may have been missed.

The trials used various scales to measure fatigue; it is difficult to establish their ability to differentiate different types of fatigue in MS (which may respond differently to drug treatment).

Whilst the statistical significance of changes in the rating scales are reported, the clinical significance of these scales is not clear.

Summary for patients

A [summary written for patients](#) is available on the NICE website.

References

Aurobindo Pharma - Milpharm Ltd (2012) [Modafinil 100 mg tablets summary or product characteristics](#) [online; accessed 07 February 2013]

Aurobindo Pharma - Milpharm Ltd (2012) [Modafinil 200 mg tablets summary of product characteristics](#) [online; accessed 07 February 2013]

Cephalon (UK) Limited (2012) [Provigil 100 mg and 200 mg tablets summary of product characteristics](#) [online; accessed 07 February 2013]

European Medicines Agency (2011) [Questions and answers on the review of medicines containing modafinil](#) [online; accessed 07 February 2013]

Medicines and Healthcare products Regulatory Agency (MHRA) (2011) [Modafinil \(Provigil\): information to support safer use; now restricted to narcolepsy](#) [online; accessed 07 February 2013]

Medicines and Healthcare products Regulatory Agency (MHRA) (2012) [Public assessment report decentralised procedure: Modafinil 100 mg tablets, Modafinil 200 mg tablets](#) [online; accessed 07 February 2013]

Möller F, Poettgen J, Broemel F et al. (2011) [HAGIL \(Hamburg Vigil Study\): a randomized placebo-controlled double-blind study with modafinil for treatment of fatigue in patients with multiple sclerosis](#). *Multiple Sclerosis* 17: 1002–9

National Institute for Health and Clinical Excellence (2008) [Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults](#). NICE clinical guideline 72

National Institute for Health and Clinical Excellence (2006) [Parkinson's disease: diagnosis and management in primary and secondary care](#). NICE clinical guideline 35

National Institute for Health and Clinical Excellence (2003) [Multiple sclerosis: management of multiple sclerosis in primary and secondary care](#). NICE clinical guideline 8

Stankoff B, Waubant E, Confavreux C et al. (2005) [Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study](#). *Neurology* 64: 1139–43

Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [interim process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

Project team

Bazian Ltd

Medicines and Prescribing Centre, NICE

Peer reviewers and contributors

Lizzie Amis, Senior Public Involvement Adviser, Public Involvement Programme, National Institute for Health and Clinical Excellence

Teva UK Limited and Teva Pharmaceuticals Ireland

Expert advisers

Amy Bowen, Director of Service Development, MS Trust

Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

- [NHS Evidence](#)
- [NICE](#)
- [Euroscan](#)
- Broad internet search: [Google](#), for example, allintitle: modafinil "multiple sclerosis" filetype:pdf
- [Scirus](#)

Medline (via Ovid)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 modafinil.tw. (998)

2 provigil.tw. (34)

3 Modiodal.tw. (7)

4 Vigil.tw. (205)

5 Modasomil.tw. (0)

6 68693-11-8.rn. (864)

7 or/1-6 (1347)

8 exp Multiple Sclerosis/ (41186)

9 multiple sclerosis.tw. (44483)

10 8 or 9 (51760)

11 7 and 10 (52)

12 limit 11 to english language (42)

Embase (via Ovid)

Database: Embase <1988 to 2013 January 04>

Search Strategy:

1 modafinil.tw. (1393)

2 provigil.tw. (383)

3 Modiodal.tw. (72)

4 Vigil.tw. (236)

5 Modasomil.tw. (12)

6 68693-11-8.rn. (3260)

7 or/1-6 (3713)

8 exp Multiple Sclerosis/ (57465)

9 multiple sclerosis.tw. (49314)

10 8 or 9 (62896)

11 7 and 10 (259)

12 limit 11 to english language (218)

13 limit 12 to exclude medline journals (44)

Cochrane Central Register of Controlled Trials (CENTRAL)

modafinil and multiple sclerosis (in title abstract keywords)

CRD HTA, DARE and EED database

1 (modafinil) OR (provigil) 16

2 MeSH DESCRIPTOR multiple sclerosis EXPLODE ALL TREES 169

3 (multiple sclerosis) 302

4 #2 OR #3 303

5 #1 AND #4 3

Grey literature and ongoing trials

- [FDA](#)
- [EMA](#)
- [MHRA](#)
- [Scottish Medicines Consortium](#)
- [All Wales Medicine Strategy Group](#)
- [metaRegister of Controlled Trials \(mRCT\)](#)
- [ClinicalTrials.gov](#)

Manufacturers' websites

[Aurobindo](#)

Milpharm (a subsidiary of Aurobindo)

Cephalon

Dawa Limited

Evidence selection

Studies were included based on predetermined criteria for relevance to the question set at scoping. The highest quality research was selected as the basis for answering the questions set on efficacy, safety and cost. Only randomised controlled trials were included for the assessment of efficacy.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

Copyright

© Bazian Ltd 2013. All rights reserved. This material may be freely reproduced for educational and not-for-profit purposes. If you wish to reproduce this information for use by commercial organisations or for commercial purposes, please email nice@nice.org.uk.

Contact NICE

National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT

www.nice.org.uk; nice@nice.org.uk; 0845 033 7780