East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, North East Hampshire & Farnham CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence Review for Prescribing Clinical Network

Treatment: Modafinil

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Summary page

- How strong is the evidence for claimed efficacy?
  (Grade A = > 1 RCT or meta-analysis; Grade B = 1 RCT or descriptive study;
  Grade C = expert committee report/opinion)

Limited evidence for use off label in MS fatigue / other sleep disorders.
Licensed indication narcolepsy

- Is the drug licensed / licensed for this indication in the United Kingdom?

Yes – for narcolepsy No – for MS fatigue / other sleep disorders

- Is monitoring for efficacy required

Yes

- Is monitoring for toxicity required?

Yes

- Is dose titration required?

Yes

- Recommended traffic light status (i.e. who will prescribe the drug and any restrictions required)?

Black – for unlicensed indications MS fatigue / other sleep disorders
Amber for narcolepsy

- Role of the specialist (if applicable)

Initiation / shared care for narcolepsy

- Role of GP (if applicable)?

Shared care for narcolepsy

- National Guidance available

NICE ESUOM9 for modafinil MS in fatigue
MHRA alert: Modafinil information to support safer use: now restricted to narcolepsy

1. Purpose of the Review

No information about modafinil is currently available on the Prescribing Advisory Database. A number of queries have come up recently and therefore it seemed appropriate for modafinil to be considered by the Prescribing Clinical Network

2. Background

Modafinil is licensed in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy. Excessive sleepiness is defined as difficulty maintaining wakefulness and an increased likelihood of falling asleep in inappropriate situations. Modafinil should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of narcolepsy, has been made in accordance with ICSD diagnostic criteria. Such an evaluation usually consists, in addition to the patient's history, sleep measurements testing (for example an Epworth Sleepiness Scale score of 11 or more) in a laboratory setting and exclusion of other possible causes of the observed hypersomnia. The precise mechanism(s) through which modafinil promotes wakefulness is unknown (please refer to the SPC for full information http://www.medicines.org.uk/emc/medicine/28918).

Diagnosis: Narcolepsy / other sleep disorders including MS fatigue

The Intervention: Modafinil

How does it work:
Modafinil is a CNS stimulant, psychoanaleptic centrally acting sympathomimetic, that promotes wakefulness in a variety of species, including man. The precise mechanism(s) through which modafinil promotes wakefulness is unknown (please refer to the SPC for full information http://www.medicines.org.uk/emc/medicine/28918).

Care setting:
Outpatient Setting

3. Effectiveness

Expected benefits
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. The CHMP also concluded that modafinil should no longer be used to treat:

- Obstructive sleep apnoea; (including in patients with excessive sleepiness despite correctly using a Continuous Positive Airway Pressure machine)
- Shift work sleep disorder;
- Idiopathic hypersomnia.

http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON111502

Modafinil is contraindicated in those with:
1. Hypersensitivity to the active substance or to any of the excipients.
2. Uncontrolled moderate to severe hypertension
3. cardiac arrhythmias

Special Warnings/Precautions

• Patients with major anxiety should only receive treatment with modafinil in a specialist unit.
• Sexually active women of child bearing potential should be established on a contraceptive programme before taking modafinil. Since the effectiveness of oral contraceptives may be reduced with modafinil, alternative/concomitant methods of contraception are recommended (and for 2 months after discontinuation). For women not wishing to use either a barrier method or nonmedicated IUD, alternatives are; increasing the dose of oestrogen in a combined pill, injections of some progestogens or a medicated IUD such as Mirena.
• It is recommended that modafinil tablets not be used in patients with a history of left ventricular hypertrophy or cor pulmonale. Modafinil should not be used in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants. This syndrome may present with ischaemic ECG changes, chest pain or arrhythmia.
• Patients should be advised that modafinil is not a replacement for sleep and good sleep hygiene should be maintained. Steps to ensure good sleep hygiene may include a review of caffeine intake.

Serious skin reactions

Stevens Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis have been reported in association with modafinil. These conditions usually occurred within the first 5 weeks of treatment, although there have been isolated cases after more than 3 months' treatment. In clinical trials, the risk of rash resulting in discontinuation of modafinil treatment was higher in children than adults (0·8% vs no cases). Modafinil is not authorised for use in children.

Psychiatric symptoms

Suicidal ideation, hallucinations, delusion, aggression, psychosis, and mania have been reported in association with modafinil. These reactions have occurred mainly, but not exclusively, in patients with a history of psychosis, depression, or mania.

Advice for healthcare professionals:

• Modafinil should be discontinued at the first sign of rash and not restarted
• Modafinil should be discontinued in patients who experience any psychiatric symptoms and not restarted
• Modafinil should be used with caution in patients with a history of psychosis, depression, or mania
• Modafinil should be used with caution in patients with a history of alcohol, drug, or illicit substance abuse

In the USA modafinil is increasingly being diverted for nonmedical use by healthy individuals in the expectation that it will improve cognitive performance.

Review of evidence

As mentioned previously the EMA concluded that the benefits of modafinil could only be considered to outweigh the risks when used to treat narcolepsy.

NICE ESUOM9 (Evidence summary: unlicensed or off-label medicine): Fatigue in multiple sclerosis: modafinil
http://www.nice.org.uk/advice/esuom9/resources/non-guidance-fatigue-in-multiple-sclerosis-modafinil-pdf

Key points:

- 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.

4. Summary of Key Points for Consideration

National guidance:

- EMA guidance recommends restricting the use of modafinil: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/07/news_detail_001061.jsp&mid=WC0b01ac058004d5c1
- **NICE ESUOM9** (Evidence summary: unlicensed or off-label medicine): Fatigue in multiple sclerosis: modafinil

Efficacy Limited evidence for the use of modafinil for fatigue in MS.

4.5 Budgetary Impact

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.

Prescriber Name	Total Items 13/14	Total Act Cost 13/14
EAST SURREY CCG	280	£33K
GUILDFORD AND WAVERLEY CCG	234	£34K
SURREY DOWNS CCG	263	£39K
SURREY HEATH CCG	145	£14K
NW SURREY CCG	498	£76K
CRAWLEY CCG	203	£32K
HORSHAM & MID SUSSEX CCG	197	£30K

5. Conclusions and Recommendations

- Modafiil should be considered as amber on the traffic light system for the licensed indication narcolepsy. A local shared care protocol will be produced based on the example shared care embedded MODAFINIL-ABHBsharedCareProtocolFIN
- Modafinil should be considered as black for all other unlicensed indications:
  - Obstructive sleep apnoea; (including in patients with excessive sleepiness despite correctly using a Continuous Positive Airway Pressure machine)
  - Shift work sleep disorder
  - Idiopathic hypersomnia
  - Fatigue in multiple sclerosis

Appendix 1: Evidence search

Search terms used:

Resource	Used in this review?
National Library for Health (NHL) http://www.library.nhs.uk/Default.aspx A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.	✓
National Institute of Health and Clinical Excellence (NICE) http://www.nice.org.uk/ NICE produces national guidance in three areas of health: 1. Public health - guidance on the promotion of good health and the prevention of ill health 2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS 3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.	✓ (through NHL)
Bandolier http://www.medicine.ox.ac.uk/bandolier/index.html Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.	✓(through NHL)
Centre for Reviews and Dissemination http://www.york.ac.uk/inst/crd/ CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database	✓(through NHL)
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/ Scottish equivalent of NICE	✓
Medical Services Advisory Committee (Australia) http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-1 The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.	✓
Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.	✓