Modafinil

Traffic light classification - AMBER 2
Information sheet for Primary Care Prescribers

Licensed Indications[1]

Modafinil is indicated in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.

Therapeutic Summary

Modafinil is a wakefulness-promoting agent that acts on the CNS. It is an established first-line treatment for narcolepsy and, if effective and tolerated, is envisaged to be lifelong.

Medicines Initiation

Modafinil will be initiated by a Sleep Specialist and any decision to use it will be a joint decision made in the Neuro-respiratory Sleep Clinic at NUH.

Products available[2]

Modafinil is available generically as 100mg and 200mg tablets.
30 x 100mg tablets cost £2.72
30 x 200mg tablets cost £7.09

Dosages and route of administration[1,3]

The recommended starting daily dose is between 100mg and 200 mg. It is recommended that patients over 65 years of age commence therapy at 100 mg daily. Doses of up to 400mg can be used in patients with insufficient response to the initial modafinil dose. The total daily dose may be taken in one to four divided doses. Tablets should be swallowed whole.

Duration of treatment

Treatment should be continued for as long as it remains clinically effective and tolerated. Periodically re-evaluate the long-term use for the individual patients as the long-term efficacy of modafinil has not been evaluated (> 9 weeks).

Monitoring Requirements and Responsibilities

Pre-treatment/baseline* assessments will usually be performed by the specialist and will include: Medical history, measurements of height and weight (for BMI) and of heart rate and blood pressure (for cardiovascular status) and assessment for mental health illness. An ECG is recommended before starting modafinil to check for a normal QTc (<500ms).

***Baseline investigations are usually performed by specialists, however there are some cases where primary care maybe requested to carry out these

Ongoing monitoring

Ongoing monitoring[1]	Frequency[1]
Heart Rate and Blood Pressure	Baseline* then every 6 months. Also before and after each dose change**. Refer to NICE guidelines for hypertension in adults[4]
Weight	Baseline* then every 6 months. Consider BMI monitoring if weight has been affected
Development or worsening of psychiatric disorders	Baseline* then every 6 months. Also before and after each dose change**.
Medication related side-effects	At each visit.
Risk of diversion, misuse / abuse	At each visit.
ECG	A regular ECG is not recommended unless there is a clinical indication (e.g. family history of cardiomyopathy or cardiac illness or hypertension or concomitant treatment with a medication that may pose an increased cardiac risk)
Routine blood tests	Not recommended unless there is a clinical indication.

*****Baseline investigations are usually performed by specialists, however there are some cases where primary care maybe requested to carry out these

** After every change of dose: The specialist should determine the appropriate timing for this monitoring.

Explicit criteria for review and discontinuation of the medicine

Sustained resting tachycardia (>120bpm)	Withhold/reduce dose and discuss with specialist team. Timely cardiology input.
Arrhythmia	Withhold/reduce dose and discuss with specialist team. Timely cardiology input.
Systolic blood pressure greater than the 95th percentile (or a clinically significant increase) measured on two occasions	Withhold/reduce dose and discuss with specialist team. Timely cardiology input.
Patient fails to attend for physical monitoring	Arrange a further appointment in a timely manner. If follow up appointments are not attended, do not provide further prescriptions and inform specialist team.
Insomnia	May respond to dose reduction or timing adjustment. Discuss with specialist team.
Reduced appetite and / or clinically significant weight change	May respond to dose reduction. Discuss with specialist team.
Development or worsening of psychiatric disorders (anxiety, depression, psychotic symptoms, mania, behavioural changes, suicide related behaviour)	Withhold and discuss with specialist team in a timely manner.
Suspected drug misuse and diversion	Discuss with specialist team.
Serious skin rash or hypersensitivity reaction	Withhold and discuss with specialist team.

	Modafinil should be discontinued at the first sign of rash and not re-started Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalization or be life-threatening. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions associated with modafinil. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included myocarditis, hepatitis, liver function test abnormalities, haematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia. Because multi-organ hypersensitivity is variable in its expression, other organ system symptoms and signs, not noted here, may occur.

IF YOU ARE IN ANY DOUBT ABOUT ANY POTENTIAL ADVERSE REACTION, PLEASE CONTACT THE SPECIALIST TEAM.

Contraindications[1,3,5]

1. Cardiac - uncontrolled moderate or severe hypertension, cardiac arrhythmias, history of clinically significant signs of CNS stimulant-induced mitral valve prolapse (including ischaemic ECG changes, chest pain and arrhythmias), cor pulmonale, left ventricular hypertrophy.
2. Endocrine - hyperthyroidism or thyrotoxicosis, phaeochromocytoma,
3. Psychiatric - anorexia, agitated states, psychosis, uncontrolled bipolar disorder, schizophrenia, suicidal tendencies, glaucoma, history of alcohol or drug abuse
4. Hypersensitivity to the active substance or to any of the excipients listed in the SPC.

Precautions[1,3,5]

Caution should be exercised in giving modafinil to patients with a history of psychiatric disorders including psychosis, depression, mania, major anxiety, agitation, insomnia, co-morbid bipolar disorder or a history of alcohol, drug or illicit substance abuse

The dosage of modafinil should be reduced by half in severe hepatic impairment.
There is inadequate information to determine safety and efficacy of dosing in renal impairment.

Pregnancy and Breastfeeding[1,3,6,7]

Modafinil should not be used during pregnancy. Post-marketing reports show that the use of modafinil in pregnancy is associated with a higher rate of congenital malformations such as heart defects, hypospadias, and orofacial clefts.

Hence, women of childbearing potential must use reliable and effective contraception during treatment with, and for two months after stopping, modafinil.
NB: As modafinil may reduce the effectiveness of some hormonal contraceptives (the combined oral contraceptive pill, the progesterone-only pill and the contraceptive implant), additional methods

of contraception are required, or else the woman should first switch to an alternative: the coil (Mirena, copper IUD), depot progestogen-only injectables, or sterilisation.

For further information regarding the risks of modafinil use during pregnancy see MHRA alert.

Modafinil is excreted in breast milk and should not be used in those who are breastfeeding.

Driving[8]
Patients must tell the DVLA of their narcolepsy diagnosis. Please refer to government advice on driving and narcolepsy.

Clinically relevant medicine interactions and their management[1,3]

- Anticonvulsants: Co-administration of potent inducers of CYP activity, such as carbamazepine and phenobarbital, could reduce levels of modafinil. Modafinil may decrease the clearance of phenytoin - monitor for signs of phenytoin toxicity and consider monitoring plasma levels upon initiation or discontinuation of modafinil.
- Steroidal contraceptives: The effectiveness of steroidal contraceptives may be impaired due to induction of CYP3A4/5 by modafinil. Alternative or concomitant methods of contraception are recommended. Adequate contraception will require continuation of these methods for two months after stopping modafinil. (See above for specifics).
- Antidepressants: modafinil may inhibit CYP2C19 mediated metabolism of tricyclic antidepressants and SSRIs, which may be the dominant metabolism pathway in some patients. Lower doses of antidepressants may be required in such patients.
- Anticoagulants: Modafinil may inhibit warfarin metabolism- monitor INR regularly during the first 2 months of modafinil use and after changes in modafinil dosage.
- Other medicinal products: Substances that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol and omeprazole may have reduced clearance upon coadministration of modafinil and may thus require dosage reduction.
- Modafinil may induce CYP1A2, CYP2B6 and CYP3A4/5 activities. The largest effects may be on substrates of CYP3A4/5 that undergo significant pre-systemic elimination, particularly via CYP3A enzymes in the gastrointestinal tract. Examples include ciclosporin, HIV-protease inhibitors, buspirone, triazolam, midazolam and most of the calcium channel blockers and statins.

For a full list of contraindications, precautions and drug interactions refer to the BNF/ product SPC.

Information Given to Patient

- The specialist will provide, where relevant, written information to people with narcolepsy and their families and carers about diagnosis, assessment, support groups, self-help, psychological treatment, medicine treatment and possible side-effects.
- The patient must be warned to report any suspected adverse reactions to the GP for assessment and to report to their GP or specialist any heart palpitations, psychiatric symptoms or skin rash.
- Female patients of childbearing potential should be fully informed of the potential risks to a foetus if modafinil is used during pregnancy and of the need to use effective contraception during treatment with, and for two months after stopping, modafinil. The patient must be warned to inform the GP or specialist of any planned pregnancy before stopping contraception.

The patient should be warned not to stop medication suddenly, but discuss withdrawal with their specialist first.

ACCESS AND CONTACT POINTS

In working hours:
Telephone: 0115 924 9924 extension 84777 (Dr Singhal's secretary)
Email: sumeet.singhal@nuh.nhs.uk

Pharmacy Medicines Information
Nottingham University Hospitals - Tel: 0115 970 9200 (patient line)
0115 924 9924 Extension 84185/81200 (**Healthcare professionals only**)

Out of Hours
Neurologist on-call contact via QMC Switchboard 0115 924 9924 **(GPs only)**
Email: sumeet.singhal@nuh.nhs.uk

References

1. Modafinil 100mg tablets – Aurobindo Pharma - Milpharm Ltd. Summary of product characteristics [11/2022] available at https://www.medicines.org.uk/emc/product/4319/smpc [accessed 03/07/2023].
2. The Electronic Drug Tariff. Accessed via dm+d browser (nhsbsa.nhs.uk) on 03/07/2023
3. BNF, accessed via BNF (British National Formulary) | NICE on 03/07/2023
4. Hypertension in adults: diagnosis and management. NICE Clinical Guideline 136 (March 2022). Available: https://www.nice.org.uk/guidance/ng136
5. MHRA: Drug Safety Update March 2011, vol 4 issue 8: A1. Modafinil (Provigil): now restricted to narcolepsy
6. Direct Healthcare Professional Communication (DHPC) Modafinil: potential risk of congenital malformations during pregnancy, Jan 2020. Accessed at: https://assets.publishing.service.gov.uk/media/5e43e03fe5274a6d34ddad60/Modafinil-Jan-2020.pdf
7. MHRA Drug Safety Update 2020. Modafinil (Provigil): increased risk of congenital malformations if used during pregnancy.
8. DVLA. Narcolepsy and driving [accessed 03/07/2023]. Available from: https://www.gov.uk/narcolepsy-and-driving

Version Control- Modafinil in Narcolepsy Amber 2 Information Sheet			
Version	Author(s)	Date	Changes
2.0	Vimbayi Mushayi, Specialist Interface Medicine Optimisation Pharmacist. Nottingham and Nottinghamshire ICB in consultation with Dr Sumeet Singhal, Consultant Neurologist, Nottingham University Hospitals	July 2023	• Header and version control • Updated prices • Added administration instructions • Added information about regarding treatment r/v • Additional information on adverse effects management requirements added • Additional information regarding interaction with contraceptive added as per SPC • Updated contact details • Updated references
1.1	Dr Sumeet Singhal, Consultant Neurologist, Nottingham University Hospitals, Professor Jill Baker, Respiratory Consultant, Nottingham University Hospitals, Lynne Kennell, Interface and Formulary Pharmacist, Nottinghamshire APC	January 2021	