Modafinil for the treatment of adult patients with excessive sleepiness associated with narcolepsy with or without cataplexy, and for the treatment of daytime sleepiness in adult patients with Parkinson's Disease.
INFORMATION FOR PRIMARY CARE

RAG List Status

Modafinil is classified as a Green (following specialist Initiation) medicine by GMMMG for the indication of: treatment of adults with excessive sleepiness associated with narcolepsy with or without cataplexy, for the treatment of daytime sleepiness in adult patients with Parkinson's Disease in adults. Patients should remain under specialist oversight and be subject to appropriate specialist follow-up.

All Indications

Treatment of excessive sleepiness associated with narcolepsy with or without cataplexy, in adults (licensed indication).
Treatment of fatigue in patients with multiple sclerosis (unlicensed, as per NICE guideline NG220).
Treatment of daytime sleepiness in patients with Parkinson's Disease (unlicensed, as per NICE guideline NG71).

Preparations available

Modafinil is available as 100mg and 200mg tablets.

Dosage and Administration

The recommended starting daily dose is 200 mg taken as a single dose in the morning or 100mg twice daily, morning and at noon.
In the elderly (age >65) a starting dose of 100mg in the morning is advised.
The total daily dose may be increased by 100mg every 2-4 weeks if there has been an inadequate response and if tolerated. An inadequate response would be where a patient continues to experience rapid onset of involuntary sleep during the day. A good response would be one where sleep is mainly restricted to night time.
The licensed maximum is 400mg daily in one or two divided doses.
Full dosing instructions should be provided by the specialist on transfer of prescribing.

Dose Modifications

Renal Impairment	Hepatic Impairment
There is inadequate data to determine safety and efficacy of dosing in patients with renal impairment.	In patients with severe hepatic impairment the dose should be halved.

Contraindications

- Hypersensitivity to modafinil or any of the excipients in the product
- Uncontrolled moderate to severe hypertension
- Cardiac arrythmias
- Patients with hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption
- Patients with a history of left ventricular hypertrophy or cor pulmonale, or with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants.
- Pregnancy & Breastfeeding

Use with caution in:

- Patients with a history of psychiatric disorders including psychosis, depression, mania, major anxiety, agitation, insomnia or substance abuse. If psychiatric symptoms develop whilst receiving treatment with modafinil, modafinil should be discontinued and not restarted without specialist review
- patients with a history of alcohol, drug or illicit substance abuse, and be alert to the possibility of dependence

- those using steroidal contraceptives as effectiveness of them may be reduced when used with modafinil
- people of childbearing potential – discuss teratogenic risk, and ensure effective contraception during treatment and for 2 months after discontinuation, noting interaction with steroidal hormonal contraception

What are the main side-effects?

- Cardiovascular - Tachycardia, hypertension, palpitations. An ECG is recommended in all patients before modafinil treatment is initiated. Blood pressure and heart rate should be regularly monitored (see "Disease and drug monitoring" below). **Modafinil should be discontinued in patients who develop arrhythmia or moderate to severe hypertension and not restarted until the condition has been adequately evaluated and treated.**
- Headache – Common affecting ~20% of patients. Treat symptomatically, typically resolves within a few days
- Gastrointestinal - GI disturbances e.g. reduced appetite, nausea, gastric discomfort – minimise by taking dose with food. Diarrhoea, constipation and dry mouth.
- Hepatic – Liver function tests are found to be abnormal in 1-10% of patients (dose related increases in alkaline phosphatase and gamma GT have been observed) Monitor LFTs if there are signs of hepatotoxicity. Dose related increases in alkaline phosphatase and gamma glutamyl transferase have been observed. If levels >3 times the upper limit of normal occurs, the specialist should be contacted. **If levels >5 times the upper limit of normal, treatment should be discontinued.**
- Skin reactions - Serious rashes (including Stevens - Johnson syndrome, Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms) have been reported early on in treatment (1-5 weeks) but occasionally after prolonged treatment. **Modafinil should be discontinued and not restarted in cases of skin or hypersensitivity reaction.**
- Psychiatric symptoms such as psychosis, suicide related behaviour - mainly but not exclusively in those with a history of psychosis, depression, mania. Patients should be monitored for the appearance of psychiatric symptoms. **Should these emerge whilst on therapy, modafinil should be discontinued and not restarted.**
- Hypersensitivity reactions - Multi organ hypersensitivity reactions have been reported. Typically, although not exclusively, this presents as 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. **If symptoms are suspected, modafinil should be discontinued.**
- Dependence and abuse potential - the possibility of dependence with longterm use cannot be entirely excluded.
- Other reactions - dizziness, somnolence, paraesthesia, blurred vision.

For a full list see SPC at www.medicines.org.uk/EMC

Drug Interactions

- Modafinil is a hepatic enzyme inducer and has the potential to increase hepatic metabolism of a number of drugs.
- Steroidal contraceptives - The effectiveness of steroidal contraceptives may be impaired by modafinil and this may impair effectiveness. Effective, alternative and/or concomitant methods of contraception are recommended and should be continued for two months after stopping modafinil.
- Anti-seizure medications - Care should be observed when used in combination with anti-seizure medications. Modafinil levels may be reduced by carbamazepine, and phenobarbitone and phenytoin levels may be increased by modafinil. Measurement of phenytoin plasma levels may be appropriate on initiation or discontinuation of treatment with modafinil.

- Antidepressants - Serotonin syndrome has been reported when MAOIs have been used concurrently with modafinil and should be used together with caution. Metabolism of some TCADs (amitriptyline, clomipramine, imipramine, fluvoxamine) and SSRIs (citalopram) may be inhibited by modafinil and lower doses of these antidepressants may be required.
- Warfarin - modafinil may increase the anticoagulant effect of warfarin. The INR should be monitored regularly during the first 2 months of modafinil use and after changes in modafinil dosage.
- Ciclosporin – modafinil may reduce plasma concentrations of ciclosporin. Advice may need to be sought from the specialist as to the significance of this interaction and ciclosporin levels rechecked as necessary.

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Pregnancy & breastfeeding
Modafinil is contraindicated during pregnancy and breastfeeding. Modafinil potentially increases the risk of congenital malformations. **If a patient falls pregnant modafinil must be discontinued immediately urgent specialist advice should be sought. Similarly if a patient is planning a pregnancy, the primary care prescriber must seek specialist advice, however, the patient may continue treatment with advice to not attempt to conceive before specialist review.**

People of childbearing potential must use effective contraception during treatment and for two months after stopping modafinil. See MHRA drug safety update

The effectiveness of steroidal contraceptives may be impaired by modafinil and this may impair effectiveness. Effective, alternative and/or concomitant methods of contraception are recommended and should be continued for two months after stopping modafinil.

Monitoring
Blood pressure & heart rate should be monitored every 6 months for 2 years then annually. Modafinil should be discontinued in patients who develop arrythmia or moderate to severe hypertension. An ECG should be performed if there are concerns of arrythmias.

When to seek specialist advice / review
- Patient is pregnant or planning pregnancy – URGENTLY SEEK SPECIALIST ADVICE
- In event of treatment discontinuation for any reason
- Lack of efficacy on maximum or maximum tolerated dose