Donepezil

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

Licensed Indications
Donepezil is indicated for the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease.

Therapeutic Summary
According to NICE, donepezil is recommended as an option for managing mild to moderate Alzheimer's disease[1].
Donepezil is an acetylcholinesterase inhibitor, which works by increasing the concentration of acetylcholine at sites of neurotransmission.

Medicines Initiation and Continuation
Treatment with donepezil must be initiated by specialists in the care of patients with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of older people) following a comprehensive assessment and diagnosis[1].

Once a decision has been made to start on donepezil, the first prescription may be made in primary care.

Products Available
Generic film coated tablets: 5mg and 10mg

Orodispersible tablets: 5mg and 10mg

Oral Solution (1mg/1mL) is non-formulary. For patients with swallowing difficulties, orodispersible tablets are the most cost effective product.[3]

Dosages and Route of Administration[2, 4]
- Treatment should be initiated at 5mg once a day, usually in the evenings. The orodispersible tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference.
- The 5mg once a day dose should be maintained for at least ONE month to allow steady-state concentrations of donepezil hydrochloride to be achieved and in order to allow the earliest clinical responses to treatment to be assessed. The dose may then be increased to 10mg once a day if appropriate.
- The minimum effective dose is 5mg daily.
- The MAXIMUM daily dose is 10mg daily.
- Upon discontinuation a gradual abatement of the beneficial effects of donepezil are seen.
- There is no evidence of a rebound effect after abrupt discontinuation of therapy.
- No dosage adjustments are required in renal impairment.
- In patients with mild to moderate hepatic impairment, dose escalation should be performed according to individual tolerability. There is no data for patients with severe hepatic impairment.

Duration of Treatment
Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms[1]. The prescriber would be required to discuss with the patient, carer and other professionals involved in the care of the patient before making the decision to stop treatment where there is no worthwhile effect. Gradual withdrawal over a 4-week period would be preferable to abrupt discontinuation[1].

Do not stop Acetylcholinesterase inhibitors in people with Alzheimer's disease because of disease severity alone. When assessing the severity of Alzheimer's disease and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so[1].

Primary Care Prescribers may refer back to the Specialist Service if changes or progress are cause for concern, or to discontinue donepezil treatment.

Monitoring Requirements and Responsibilities

Baseline screening/investigations to exclude other causes of cognitive impairment will have been carried out by the GP before initial referral to Specialist Service.

For patients with existing or suspected cardiac disease or bradycardia (including those with cardiac arrhythmias or valve problems, and patients with hypertension who are being treated with anti-hypertensives that have a rate-limiting effect e.g., beta-blockers), an ECG should be carried out by the GP, as part of the baseline investigations prior to referral. Other patients should be referred with the GP confirming the absence of these conditions.

No routine plasma monitoring is required during donepezil treatment.

The Primary Care Prescriber will carry out an annual patient review for all dementia patients[3].

For those prescribed pharmacological treatment, this will include a medication review as well as cognitive, global, functional and behavioural assessments, as per NICE guidance[1, 2].

Contraindications[2]

- Known hypersensitivity to the active substance, piperidine derivatives or any excipient.
- Pregnancy & breastfeeding.

Precautions[2]

- Cardiovascular conditions: donepezil may have vagotonic effects on heart rate e.g. bradycardia. The potential for this action may be particularly important to patients with “sick sinus syndrome” or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block.
- Gastrointestinal conditions: patients may be at increased risk for developing ulcers. Those with a history of ulcer disease or those receiving concurrent non-steroidal anti-inflammatory medication (NSAIDs) should be monitored for symptoms.
- Genitourinary: may cause bladder outflow obstruction.
- Neurological conditions: donepezil has the potential to cause generalised convulsions, however seizure activity may also be manifestation of Alzheimer’s disease. Donepezil also has the potential to exacerbate or induce extrapyramidal symptoms.
- Pulmonary conditions: prescribe with care to patients with a history of asthma or obstructive pulmonary disease due to cholinomimetic actions.
- Severe dementia in Alzheimer’s disease and other types of dementia - benefit has not been demonstrated.

Explicit Criteria for Review and Discontinuation of the Medicine[2]

ADVERSE EFFECT	ACTION
Very Common (≥ 1/10)	
Nausea Diarrhoea	• Advise patient to take with or after food. If severe, consider an antiemetic • Ensure patient takes plenty of fluids. • Please note if any symptoms are persistent and problematic consider a reduction in the dose of donepezil to a previously well tolerated dose.
Headache	• Treat with a simple analgesic e.g. paracetamol.
Common (≥ 1/100 to < 1/10)	
Vomiting Abdominal disturbance	• Ensure patient takes plenty of fluids. • Discuss with psychiatrist. • If severe dyspepsia, consider prescribing an antacid.
Anorexia	• Monitor weight on a regular basis.
Syncope / Dizziness	• Advise patient to take time to stand up. May subside during continued therapy.

Insomnia	• Should subside after one week.
Hallucinations Agitation Aggressive behaviour Abnormal dreams and nightmares	• Symptoms have resolved after a dose reduction or discontinuation of treatment. • Discuss with psychiatrist.
Rash, Pruritis	• Consider a dose reduction.
Muscle Cramps	• Consider a dose reduction.
Fatigue	• Consider a dose reduction.
Pain	• Treat with a simple analgesic e.g. paracetamol.
Common cold	• Treat as appropriate
Accidents including falls	• Consider a dose reduction
Urinary Incontinence	• Consider a dose reduction. • Consider other causes.
Uncommon (≥ 1/1000 to < 1/100) or Rare (≥ 1/10,000 to < 1/1,000)	
Seizures (discontinue unless on anticonvulsants & discuss with specialist), bradycardia, gastrointestinal haemorrhage, gastric and duodenal ulcers, minor Increase in serum concentration of muscle Creatinine Kinase, extrapyramidal symptoms, sino-atrial block, atrioventricular block (action: withhold and discuss with psychiatrist), liver dysfunction including Hepatitis (in cases of unexplained liver dysfunction, consider withdrawal of donepezil).	

Report suspected adverse drug reactions via the Yellow Card Scheme, either online at https://yellowcard.mhra.gov.uk/ or by using the yellow forms at the back of a current BNF.

Clinically Relevant Medicine Interactions and Their Management[2]

- CYP450 inhibitors such as ketoconazole, itraconazole and erythromycin, and CYP2D6 inhibitors such as quinidine and fluoxetine may inhibit donepezil metabolism thus leading to increased donepezil plasma levels (in vitro studies). The dose of donepezil may need to be reduced.
- Enzyme inducers such as rifampicin, phenytoin, carbamazepine and alcohol may reduce donepezil levels.
- Donepezil may antagonise the effect of anticholinergic medication (e.g. procyclidine).
- Beta-blockers that have effects on cardiac conduction. Co-prescribing with donepezil should be avoided as this may induce bradycardias. If possible, switch to another antihypertensive.
- Donepezil is not to be used with other cholinergic agonists / cholinomimetics (e.g. galantamine, rivastigmine, neostigmine, pyridostigmine, ambenonium) due to synergistic effects.
- Caution with Succinylcholine and other muscle relaxants, donepezil is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.
- Non-steroidal anti-inflammatory medications (NSAIDs) – donepezil has the potential to increase the risk of developing ulcers as well as NSAIDs.

Information Given To Patient

Further written information sheets on donepezil can be accessed via the following sites:

- https://www.nhs.uk/medicines/donepezil/
- https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/alzheimers-drug-treatments
- https://www.alzheimers.org.uk/about-dementia/treatments/dementia-medication/medication-dementia-symptoms

Patient / Carer's Role

The following should be discussed with the patient on initiation or during review/consultation:

- The patient (if appropriate) / carer will report any suspected adverse reactions to the GP for assessment.
- The patient (if appropriate) / carer will report to their GP or specialist signs of clinical worsening.
- The patient (if appropriate) / carer will attend all follow-up appointments with GP and specialist. If they are unable to attend any appointments they should inform the relevant practitioner as soon as possible and arrange an alternative appointment.

Pharmacy Contacts - Nottinghamshire Healthcare NHS Foundation Trust
Wells Road Centre Pharmacy 01159 555 357
Nottinghamshire Healthcare Pharmacy Advisory Line 0300 303 5808
Email MI@nottshc.nhs.uk

References

1. National Institute for Health and Care Excellence (NICE). *Dementia: assessment, management and support for people living with dementia and their carers [NG97].* 2018. Available from: https://www.nice.org.uk/guidance/ng97 [Accessed 23rd November 2023].

2. Electronic Medicines Compendium (EMC). *Donepezil hydrochloride 10mg film-coated tablets SmPC.* Available from https://www.medicines.org.uk/emc/product/5319/smpc [Accessed 23rd November 2023].

3. The Electronic Drug Tariff. http://www.drugtariff.nhsbsa.nhs.uk/#/00786378-DD/DD00786373/Home [Accessed 23rd November 2023].

4. Joint Formulary Committee. *British National Formulary*. 2023. Available at: http://www.medicinescomplete.com [Accessed: 23rd November 2023]

5. Nottinghamshire Area Prescribing Committee (NAPC). *Managing Behaviour and Psychological Problems in Patients with Diagnosed or Suspected Dementia in Primary and Secondary care.* (2018). Available from: https://www.nottsapc.nhs.uk/media/p0jlee5o/bpsd-guideline.pdf?UNLID=913286040202311231242 2 [Accessed 23rd November 2023].

6. National Institute for Health and Care Excellence (NICE). *Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease [TA217].* 2011. Available from: https://www.nice.org.uk/guidance/ta217 [Accessed 23rd November 2023].

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