DRUGS FOR DEMENTIA: Donepezil
INFORMATION FOR PRIMARY CARE

Who will diagnose and decide who is suitable for which drug?
Specialists will diagnose and communicate to primary care the recommended dementia drug for the patient which may include instructions on any necessary titration. Specialists will counsel and inform patients of their diagnosis and treatment options.

Who will increase the dose?
Primary care may be asked to oversee the titration of medication to the recommended dose, whilst monitoring for any adverse effects or tolerability issues.

Who will follow up the patients?
Once the patient is stable on the maximum tolerated dose of medication, specialists usually discharge the patient back to primary care. During the assessment period, specialists will identify patients with complex needs and would be expected to refer onto other services or if they are not able to do so, may request that primary care assist in making onward referrals e.g., to occupational therapy, speech and language, Adult Social Care.

RAG List Status
Donepezil is classified as a GREEN (following specialist advice – see local guidance) drug by the Greater Manchester Medicines Management Group.

Licensed Indications
Donepezil is licensed for the symptomatic treatment of patients with mild to moderately severe Alzheimer's disease. Donepezil is the 1st choice acetylcholinesterase inhibitor in the GMMMG formulary.

NICE Guidance
NICE TA217 recommends donepezil as an option for managing mild to moderate Alzheimer's Disease.
"If prescribing an AChE inhibitor (donepezil, galantamine or rivastigmine), treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles."

NICE NG97 also recommends that donepezil be considered for people with dementia with Lewy bodies irrespective of severity.

Preparations available
5mg and 10mg film coated tablets OR 5mg and 10mg orodispersible tablets
1mg/ml oral solution

Dosage and Administration
It is given initially at 5 mg once daily. After 1 month the treatment should be assessed, and the dose increased to a maximum of 10 mg once daily if necessary. It is recommended that the dose is given at bedtime to minimise likelihood of gastrointestinal (GI) symptoms. However if sleep disturbances are noted, including abnormal dreams, nightmares or insomnia, then a shift to morning dosing can resolve this.

Dose Modifications

Renal Impairment	Hepatic Impairment
No dose adjustment required	Mild to moderate – dose escalation depending on individual tolerability. Severe – avoid.

Contraindications

Approved: May 2023
Review date: May 2026

Known hypersensitivity to donepezil, piperidine derivatives or any excipient.

Cautions

- History of seizures
- Pre-existing cardiac disease including cardiovascular conduction disorders such as sick-sinus syndrome or sinoatrial or atrioventricular block which may be susceptible to the vagotonic effects of donepezil
- Pre-existing or family history of QTc prolongation, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.
- Asthma or obstructive pulmonary disease.
- Urinary retention/bladder outflow obstruction
- Neuroleptic Malignant syndrome, especially in patients receiving concomitant antipsychotics
- May cause exacerbation or inducement of extrapyramidal symptoms
- Patients at increased risk for developing gastrointestinal ulcers, e.g. those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms.

What are the main side-effects?

Very common side effects (may affect more than 1 in 10 people):

- Diarrhoea
- Headache
- Nausea

Common side effects (may affect up to 1 in 10 people):

- Muscle cramp
- Anorexia
- Tiredness
- Difficulty in sleeping (insomnia)
- The common cold
- Hallucinations (seeing or hearing things that are not really there)
- Unusual dreams including nightmares
- Agitation
- Aggressive behaviour
- Fainting
- Dizziness
- Insomnia
- Vomiting
- Stomach feeling uncomfortable
- Rash/Pruritis
- Passing urine uncontrollably
- Pain
- Accidents (patients may be more prone to falls and accidental injury)

Please refer to the BNF for further details.

Drug Interactions

- Inhibitors of CYP3A4 and 2D6 such as itraconazole and erythromycin, ketoconazole and quinidine and fluoxetine could inhibit the metabolism of donepezil. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30%.
- Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care.
- Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity. There is also the potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists or beta blocking agents that have effects on cardiac conduction.
- Cases of QTc interval prolongation and Torsade de Pointes have been reported for donepezil. Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring (ECG) may be required. Examples include:

- Class IA antiarrhythmics (e.g. quinidine)
- Class III antiarrhythmics (e.g. amiodarone, sotalol)
- Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline)
- Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone)
- Certain antibiotics (e.g. clarithromycin, erythromycin, levofloxacin, moxifloxacin)

Advice for patients having a general anaesthetic

Donepezil is expected to prolong the effects of suxamethonium through the inhibition of acetylcholine metabolism. Donepezil potentially antagonises the effect of non-depolarising muscle relaxants such as atracurium, cisatracurium, mivacurium, pancuronium, rocuronium, vecuronium.
Potentially irreversible decline in cognitive function if donepezil stopped.

Situation	Advice
Planned & Emergency operations	Continue. Ensure Anaesthetist is aware of drug interactions. • If possible, avoid NMBDs • If NMBDs are required – monitor blockade • Consider use of rocuronium / sugammadex • Consider use of remifentanil infusion
Post-operative	Restart as soon as possible post-operatively.

Monitoring -

1. **Adverse effects:** Most common side effects are gastrointestinal disturbance (nausea, vomiting and diarrhoea).
2. **Concurrent medication:** Medication should be reviewed at each visit in order to identify potential drug interactions.
3. **Renal and hepatic function:** Baseline LFTs should be measured; patients with hepatic impairment should have doses titrated slowly and be monitored closely for adverse effects.
4. **Cognitive, global functional and behavioural assessment:** Patients who continue on treatment should be reviewed at least annually by the GP. A cognition test may be done but, especially in more advanced dementia where benefits of cholinesterase inhibitors may cease to outweigh risks of continued treatment, an assessment of well-being and functioning is more important. Carers' views on the patient's condition at follow-up should be sought.

When should the drug be stopped?

STOPP criteria:

- patients with a known history of persistent bradycardia (heart rate less than 60 beats per minute), heart block, recurrent unexplained syncope
- concurrent treatment with drugs that reduce heart rate (risk of cardiac conduction failure, syncope and injury).

Donepezil should be stopped if a patient is not apparently gaining any benefit from the drug, however in addition to treating the cognitive aspects of dementia, cholinesterase inhibitors and memantine have a role in behavioural and psychiatric changes in dementia and therefore, patients who are scoring low on cognitive testing may still benefit. Specialist advice should be sought on this decision from the locality memory treatment services.

What happens if my patient's needs change or become more complex following discharge?

They can be re-referred back to the appropriate memory service via the normal referral pathway.
You may wish to seek advice in the following circumstances:

- Emergent concerns regarding tolerability
- To consider whether to discontinue treatment

Guidance for Primary Care prescribing

Approved: May 2023
Review date: May 2026

The GP will monitor for ongoing side effects and discuss with Memory Service if any arise for advice on dose reduction, discontinuation etc. If a patient's cardiac health changes appropriateness of prescription will need to be discussed with the memory service and consideration for referral to cardiology.

- Provide regular prescriptions for donepezil as per local guidance.
- Be aware of side effects and common drug interactions as documented in this guideline.
- Provide regular health checks including where relevant the review of clients with vascular dementia or mixed dementia and provision of advice about lifestyle.
- Inform specialist services of any relevant physical health problems at the earliest opportunity for those still open to specialist services or re-refer if necessary.
- If patient suffers any adverse reaction, GP should liaise with secondary care/specialist services.

Approved: May 2023
Review date: May 2026