DRUGS FOR DEMENTIA: Galantamine
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 refer onto other services or may request that primary care assist in making onward referrals e.g., to occupational therapy, speech and language, Adult Social Care.

RAG List Status
Cholinesterase inhibitors are classified as GREEN (following specialist advice – see local guidance) drugs by the Greater Manchester Medicines Management Group.

Licensed Indications
Galantamine is licensed for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer type.

NICE Guidance
NICE TA217 recommends galantamine 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 states that galantamine can be considered for people with mild to moderate dementia with Lewy bodies if rivastigmine and donepezil are not well tolerated (off label use).

Preparations available
8mg, 16mg and 24mg prolonged release capsules; 4mg/ml oral solution

Dosage and Administration
For the Prolonged release capsules:

- The recommended starting dose is 8 mg/day for 4 weeks.
- The initial maintenance dose is 16 mg/day and patients should be maintained on this dose for at least 4 weeks.
- An increase to the maintenance dose of 24 mg/day should be considered on an individual basis after appropriate assessment including evaluation of clinical benefit and tolerability.
- In patients not showing an increased response or not tolerating 24 mg/day, a dose reduction to 16 mg/day should be considered.
- Galantamine prolonged-release capsules should be administered orally, once daily in the morning, preferably with food (to reduce the risk of cholinergic side effects). The capsules should be swallowed whole together with some liquid. The capsules must not be chewed or crushed.

For the liquid preparation

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- The recommended starting dose is 8 mg/day (4 mg twice a day) for 4 weeks.
- The initial maintenance dose is 16 mg/day (8 mg twice a day) and patients should be maintained on this dose for at least 4 weeks.
- An increase to the maintenance dose of 24 mg/day (12 mg twice a day) should be considered on an individual basis after appropriate assessment including evaluation of clinical benefit and tolerability.
- In individual patients not showing an increased response or not tolerating 24 mg/day, a dose reduction to 16 mg/day (8 mg twice a day) should be considered.
- Galantamine oral solution should be administered orally, twice a day, preferably with morning and evening meals (to reduce the risk of cholinergic side effects). Ensure adequate fluid intake during treatment.

To switch a patient to galantamine prolonged-release capsules from galantamine oral solution, it is recommended that the same total daily dose of galantamine is administered. Patients switching to the once-daily regimen should take their last dose of galantamine oral solution in the evening and start galantamine prolonged-release capsules the following morning.

Dose Modifications

Renal Impairment		**Hepatic Impairment**
eGFR >9ml/min	No dose adjustment	Mild Impairment – no dosage adjustment
eGFR <9ml/min	Contra-indicated	Moderate impairment (Child-Pugh score 7 – 9) begin with 4 mg once daily, preferably taken in the morning, for at least 1 week. Thereafter, patients should proceed with 4 mg twice daily for at least 4 weeks. In these patients, daily doses should not exceed 8 mg twice daily.
		Severe hepatic impairment – avoid.

Contraindications
Known hypersensitivity to galantamine or any excipient.
Severe hepatic or renal impairment

Cautions

- History of seizures
- Pre-existing cardiac disease
- Severe asthma or obstructive pulmonary disease or active pulmonary infections (e.g. pneumonia).
- History of peptic ulcers or recovering from gastrointestinal surgery.
- Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency as the capsules contain sucrose
- Urinary retention/bladder outflow obstruction

What are the main side-effects?
Patients should be advised to take the medicine with food to minimise side effects.
Very common side effects (may affect more than 1 in 10 people):

- Vomiting; Nausea

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

- Decreased appetite
- Hallucination
- Depression
- Syncope
- Dizziness
- Tremor
- Headache
- Somnolence
- Lethargy
- Bradycardia

- Hypertension
- Abdominal pain / discomfort
- Abdominal pain upper
- Diarrhoea
- Dyspepsia
- Muscle spasms
- Fatigue
- Asthenia
- Malaise
- Fall
- Laceration
- Weight decreased

Please refer to the BNF for further details.

Serious skin reactions (Stevens-Johnson syndrome and acute generalized exanthematous pustulosis) have been reported in patients receiving galantamine. It is recommended that patients be informed about the signs of serious skin reactions, and that use of galantamine be discontinued at the first appearance of skin rash.

Drug Interactions

- The risk of cardiac adverse effects, including bradycardia and Torsade de Pointes, may be increased if galantamine is given with amiodarone or other antihypertensive/antiarrhythmic drugs. Galantamine may antagonise effects of anticholinergic drugs and worsen Parkinsonian symptoms; this may induce or exacerbate extrapyramidal side effects.
- Potent inhibitors of CYP3A4 (including ritonavir, ketoconazole and erythromycin) may raise galantamine levels, paroxetine (a potent CYP2D6 inhibitor) has been shown to increase bioavailability by 40%. During initiation of treatment with potent inhibitors of CYP2D6 or CYP3A4 patients may experience an increased incidence of cholinergic adverse reactions, predominantly nausea and vomiting. Based on tolerability, a reduction of the galantamine maintenance dose can be considered.

Advice for patients having a general anaesthetic.
Galantamine can enhance the effects of suxamethonium and the duration of the block may be prolonged. Galantamine is expected to antagonise the effect of non-depolarising Neuromuscular Blocking Drugs (NMBDs); larger doses may be required to achieve satisfactory paralysis. Neostigmine may be ineffective as a reversal agent due to the pre-existing level of cholinesterase inhibition.
Potential deterioration in cognitive function if galantamine omitted.

Situation	Advice
Elective surgery	Stop 24 hours before operation
Emergency surgery	• If possible, delay surgery by 24 hours so that elective surgery advice can be followed • If delaying surgery is not possible, ideally avoid Neuromuscular Blocking Drugs (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. **Weight/BMI:** weight loss is associated with Alzheimer's disease but can also occur with galantamine.
3. **Concurrent medication:** Medication should be reviewed at each visit in order to identify potential drug interactions.
4. **Renal and hepatic function:** Baseline creatinine and LFTs should be measured; Patients with renal or hepatic impairment should have doses adjusted dependant on hepatic / renal function.
5. **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) for galantamine:

- in 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).

Galantamine 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.

There is no rebound effect after abrupt discontinuation of treatment.

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 GPs prescribing

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 galantamine 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.