DRUGS FOR DEMENTIA: Rivastigmine
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
Rivastigmine is classified as a GREEN (following specialist initiation – see local guidance) drug by the Greater Manchester Medicines Management Group.

Licensed Indications
Rivastigmine is licensed for:

- the symptomatic treatment of mild to moderately severe Alzheimer's dementia.
- The symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease (capsules only).

NICE Guidance
NICE TA217 recommended rivastigmine 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 recommends that rivastigmine be considered for people with dementia with Lewy bodies irrespective of severity.

NICE NG71 recommends that a cholinesterase inhibitor be offered to people with mild or moderate Parkinson's disease dementia.
NB As of March 2023, rivastigmine capsules are the only treatment with a UK marketing authorisation for this indication. Use of donepezil, galantamine and rivastigmine patches was off-label.

NICE NG71 recommends that a cholinesterase inhibitor be offered to people with severe Parkinson's disease dementia.
NB As of March 2023, this was an off-label use of cholinesterase inhibitors.

Preparations available
1.5mg, 3mg, 4.5mg and 6mg capsules; 2mg/ml oral solution; 4.6mg/24hour, 9.5mg/24 hour and 13.3mg/24 hour patches.

Dosage and Administration
Oral dosage:

- The dose is initially 1.5 mg twice daily

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- Depending on tolerance, this can be increased in steps of 1.5 mg twice daily at intervals of at least 2 weeks up to a maximum dose of 6 mg twice daily.
- To achieve maximum therapeutic benefit patients should be maintained on their highest well tolerated dose.

Rivastigmine increases gastric acid secretion and should be taken with food to minimise the effects of this. If treatment is interrupted for more than three days, it should be re-initiated at 1.5 mg twice daily. Dose titration should then be carried out as previously described.

Transdermal dosage:

- Treatment is started with a 4.6 mg/24 h patch.
- After a minimum of four weeks of treatment and if well tolerated, the dose of 4.6 mg/24 h should be increased to 9.5 mg/24 h, the daily recommended effective dose
- If, after a further 6 months of 9.5mg/24 hr treatment, the patient has demonstrated a meaningful cognitive deterioration (e.g. decrease in the MMSE) and/or functional decline, the dose may be increased to 13.3mg/24 hr.

Switching from oral to transdermal administration:

- It is recommended to apply the first transdermal patch on the day following the last oral dose.
- A patient on a dose of 3 mg/day oral rivastigmine can be switched to 4.6 mg/24 h transdermal patches.
- A patient on a dose of 6 mg/day oral rivastigmine can be switched to 4.6 mg/24 h transdermal patches.
- A patient on a stable and well tolerated dose of 9 mg/day oral rivastigmine can be switched to 9.5 mg/24 h transdermal patches. If the oral dose of 9 mg/day has not been stable and well tolerated, a switch to 4.6 mg/24 h transdermal patches is recommended.
- A patient on a dose of 12 mg/day oral rivastigmine can be switched to 9.5 mg/24 h transdermal patches.

After switching to 4.6 mg/24 h transdermal patches, provided these are well tolerated after a minimum of four weeks of treatment, the dose of 4.6 mg/24 h should be increased to 9.5 mg/24 h, which is the recommended effective dose.
If transdermal treatment is interrupted for more than three days, it should be re-initiated with 4.6 mg/24 h.

See specific SPC's for further information on using patches.

Dose Modifications

Renal Impairment / Hepatic Impairment	**Body Weight <50kg**
No dose adjustment is necessary for patients with mild to moderate renal or hepatic impairment. Patients with clinically significant renal or hepatic impairment might experience more adverse reactions. Dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant renal or hepatic impairment might experience more dose-dependent adverse reactions.	Patients with body weight below 50 kg may experience more adverse reactions and may be more likely to discontinue due to adverse reactions. Carefully titrate and monitor these patients for adverse reactions (e.g. excessive nausea or vomiting)

Contraindications

Known hypersensitivity to rivastigmine, other carbamate derivatives, or to any of the excipients used in the formulation. Previous history of application site reactions suggestive of allergic contact dermatitis with the rivastigmine patch.

Cautions

- History of seizures

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- 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 rivastigmine
- 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 COPD
- History of peptic ulcers or recovering from gastrointestinal surgery.
- Urinary retention/bladder outflow obstruction
- Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

What are the main side-effects?

The following adverse reactions have been reported in patients with Alzheimer's dementia treated with rivastigmine.

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

- Anorexia
- Dizziness
- Nausea
- Vomiting
- Diarrhoea

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

- Decreased appetite
- Nightmares
- Agitation
- Confusion
- Anxiety
- Headache
- Somnolence
- Tremor
- Abdominal pain and dyspepsia
- Hyperhydrosis
- Fatigue and asthenia
- Malaise
- Weight loss
- Delirium*
- Pyrexia*
- decreased appetite*
- urinary incontinence*

* additional adverse reactions observed with rivastigmine transdermal patches

The following adverse reactions have been reported in patients with dementia associated with Parkinson's disease treated with rivastigmine.

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

- Tremor
- Nausea
- Vomiting
- Fall

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

- Decreased appetite
- Dehydration
- Insomnia
- Anxiety
- Restlessness
- Hallucination, visual
- Depression
- Dizziness
- Somnolence
- Headache
- Worsening of Parkinson's disease
- Bradykinesia
- Dyskinesia
- Hypokinesia
- Cogwheel rigidity
- Bradycardia
- Hypertension
- Diarrhoea
- Abdominal pain and dyspepsia
- Salivary hypersecretion
- Sweating increased
- Fatigue and asthenia
- Gait abnormality
- Parkinson gait
- Agitation*

* additional adverse reactions observed with rivastigmine transdermal patches

Please refer to the BNF for further details.

Patients should be advised to take the oral formulation with food to minimise side effects, however transdermal administration is less likely to cause side-effects.

There have been rare post-marketing reports of patients experiencing allergic dermatitis (disseminated) when administered rivastigmine irrespective of the route of administration (oral, transdermal). In these cases, treatment should be discontinued.
Treatment should be interrupted if dehydration resulting from prolonged vomiting or diarrhoea occurs and withheld until resolution—retitrate dose if necessary.

Drug Interactions
There are no specific dose changes which need to be made in relation to rivastigmine however it would be useful for prescribers to be aware of the following:

- Smoking tobacco increases the clearance of rivastigmine.
- The risk of adverse effects, including bradycardia, may be increased if an acetylcholinesterase inhibitor is given with amiodarone or other antihypertensive/antiarrhythmic drugs.
- Rivastigmine may antagonise effects of anticholinergic drugs and worsen Parkinsonian symptoms; this may induce or exacerbate extrapyramidal side effects.
- Since bradycardia constitutes a risk factor in the occurrence of torsades de pointes, the combination of rivastigmine with torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, amisulpride), pimozide, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacine should be observed with caution and clinical monitoring (ECG) may also be required.

Advice for patients having a general anaesthetic
Rivastigmine is expected to prolong the effects of suxamethonium through their inhibition of acetylcholine metabolism. Rivastigmine 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 rivastigmine omitted.

Situation	Advice
Planned Operations	Stop 24 hours before operation
Emergency operations	• If possible, delay surgery by 24 hours so that elective surgery advice can be followed • If delaying surgery is not possible, ideally avoid NMBDs • If NMBDs are required – monitor blockade • Consider use of rocuronium / sugammadex1 • Consider use of remifentanil infusion
Post-operative	Restart as soon as possible post-operatively. If recovering from gastrointestinal or bladder surgery seek specialist advice before restarting

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 rivastigmine.
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 titrated according to the individuals tolerability and be monitored closely for adverse effects.
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?
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Drugs should be stopped if a patient develops an allergy or contra-indication to the medication.
The clinical benefit of rivastigmine should be reassessed on a regular basis, especially for patients treated at doses less than 3 mg twice a day. If after 3 months of maintenance dose treatment the patient's rate of decline in dementia symptoms is not altered favourably, the treatment should be discontinued and the patient be re-referred.

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 rivastigmine 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.

Important advice for patients and caregivers where transdermal patches are used:

- The previous day's patch must be removed before applying a new one every day
- The patch should be replaced by a new one after 24 hours. Only one patch should be worn at a time
- The patch should be pressed down firmly for at least 30 seconds using the palm of the hand until the edges stick well.
- If the patch falls off, a new one should be applied for the rest of the day, then it should be replaced at the same time as usual the next day.
- The patch can be used in everyday situations, including bathing and during hot weather.
- The patch should not be exposed to any external heat sources (e.g., excessive sunlight, saunas, solarium) for long periods of time.
- The patch should not be cut into pieces.

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