Rivastigmine

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

Licensed Indications

Rivastigmine is indicated for the symptomatic treatment of mild to moderately severe dementia in Alzheimer's disease. Oral formulations are also indicated for the symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

Therapeutic Summary

According to NICE, rivastigmine is recommended as an option for managing mild to moderate Alzheimer's disease[1, 7]. Rivastigmine is an acetylcholinesterase inhibitor which works by increasing the concentration of acetylcholine at sites of neurotransmission.

Medicines Initiation and Continuation

Treatment with rivastigmine 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, 2, 3].

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

Products Available[4]

Immediate-release capsules: 1.5mg, 3mg, 4.5mg and 6mg
Transdermal patches: 4.6mg per 24 hour, 9.5mg per 24 hour and 13.3mg per 24 hour
Transdermal patches (Zeyzelf ®) twice-weekly application, Non Formulary, Grey
Oral solution: 2mg/mL sugar free (120ml bottle)

Dosages and Route of Administration[2,3,5]

Capsule / Oral Solution (for use in mild to moderate dementia in Alzheimer's disease and mild to moderate dementia in Parkinsons disease)

- Treatment should be initiated at 1.5mg twice a day, with morning and evening meals (to minimise cholinergic side effects). Swallow whole.
- If tolerated, after a minimum of 2 weeks of treatment, the dose maybe increased to 3mg twice daily. Further dosage increases to 4.5mg and then 6mg twice daily are again dependent on good tolerability of the current dose and may be considered after a minimum of 2 weeks treatment at that dose level.
- Maintenance dose is 3mg to 6mg twice a day.
- The minimum effective dose is 3mg twice daily.
- The MAXIMUM daily dose is 6mg twice daily.
- No dose adjustment is necessary for patients with mild to moderate renal or hepatic impairment. Rivastgmine may be employed for patients with severe hepatic impairment, but close monitoring is necessary – use has not been studied.
- **If treatment is interrupted for more than three days, it should be re-initiated at 1.5mg twice daily and then re-titrated as above (this is to reduce the possibility of adverse reactions e.g. vomiting).**
- The oral solution and the capsule preparations may be interchanged at equal doses.

Transdermal Patch (for use in mild to moderate dementia in Alzheimer's disease)

- Treatment should be initiated at 4.6mg / 24 hours.
- If tolerated, after a minimum of four weeks, the dose maybe increased to 9.5mg / 24 hour.
- The recommended maintenance dose is 9.5mg / 24 hour.

- The minimum effective dose is 4.6mg / 24 hours.
- If well tolerated, and only after a period of at least 6 months of treatment at 9.5mg / 24 hour, the specialist may consider increasing the dose to 13.3mg / 24 hour in patients who have demonstrated meaningful cognitive deterioration and/or functional decline whilst on the 9.5mg / 24 hour dose.

- Treatment should be temporarily interrupted if gastrointestinal adverse reactions are observed until these adverse reactions resolve. Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than three days. Otherwise treatment should be re-initiated with 4.6 mg /24 hour.

- Switches between the oral solution / capsules and the patches are as follows:

  - 3 mg/day to 6mg/day oral rivastigmine can be switched to 4.6 mg / 24 hour transdermal patches
  - 9 mg/day oral rivastigmine can be switched to 9.5 mg / 24 hour transdermal patches – only if 9mg/day oral dose has been tolerated. Otherwise a switch to 4.6 mg / 24 hour transdermal patches is recommended
  - 12 mg/day oral rivastigmine can be switched to 9.5 mg / 24 hour 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.

  It is recommended to apply the first transdermal patch on the day following the last oral dose.

- Transdermal patches should be applied once a day to clean, dry, hairless, intact healthy skin on the upper or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing. It is not recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine observed when the transdermal patch is applied to these areas of the body.

- The transdermal patch should not be applied to skin that is red, irritated or cut. Reapplication to the exact same skin location within 14 days should be avoided to minimise the potential risk of skin irritation.

  In 2010 the MHRA highlighted the risk of errors with rivastigmine patches[8]. They advised that patients and caregivers should told to replace the patch with a new one after 24 hours and the previous days patch must be removed before application of a new patch to a different skin location (same location should be avoided for 14 days). The patch should not be cut into pieces. In the case of suspected overdose, all patches should be removed immediately and no further patch should be applied for the next 24 hours. Symptoms of rivastigmine overdose include nausea, vomiting, diarrhoea, hypertension, hallucinations, bradycardia and/or syncope associated with malaise or falls.

  NB. Homecare workers employed by Nottinghamshire County Council (NCC) and independent providers commissioned by NCC to provide social care are not able to apply rivastigmine patches.

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 rivastigmine 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 the 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 affect 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 rivastigmine treatment.

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

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[2,3,5]

- Known hypersensitivity to the active substance rivastigmine, to other carbamate derivatives or to any of the excipients.
- Pregnancy and breastfeeding – no clinical evidence, should not be used.

Precautions[2,3,5]

- Cardiovascular conditions: rivastigmine 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: rivastigmine may cause increased gastric acid secretions. Thus those with a history of ulcer disease / active ulcer disease / those that are predisposed to these conditions, or receiving concurrent non-steroidal anti-inflammatory medication (NSAIDs) should be monitored for symptoms.
- Genitourinary: rivastigmine may induce or exacerbate urinary obstruction.
- Neurological conditions: rivastigmine has the potential to cause generalised convulsions, however seizure activity may also be manifestation of Alzheimer's disease. Rivastigmine 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.
- Skin application site reactions may occur with rivastigmine patch and are usually mild or moderate in intensity. These reactions are not in themselves an indication of sensitisation. However, use of rivastigmine patch may lead to allergic contact dermatitis. Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued.

Explicit Criteria for Review and Discontinuation of the Medicine

ADVERSE EFFECT	ACTION
Very Common (≥ 1/10)[2,3]	
Nausea and diarrhoea / vomiting	• 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 & problematic consider a reduction in the dose of rivastigmine to a previously well tolerated dose.
Weight decrease / anorexia	• Monitor weight on a regular basis.
Dizziness	• Advise patient to take time to stand up. May subside during continued therapy.
Application site skin reactions (e.g. erythema, pruritus, oedema, dermatitis, irritation) – patch only.	• Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, stop treatment.
Common (≥ 1/100 to < 1/10)[3]	
Abdominal pain Dyspepsia	• Ensure patient takes plenty of fluids. • Discuss with psychiatrist. • If severe consider prescribing an antacid.
Headache	• Treat with a simple analgesic e.g. paracetamol.
Tremor	• Discuss with psychiatrist.
Somnolence	• Consider a dose reduction.
Confusion Agitation / anxiety	• Consider a dose reduction. • Discuss with psychiatrist.
Hyperhydrosis	• Discuss with psychiatrist.
Muscle Cramps	• Consider a dose reduction.
Fatigue and Asthenia, Malaise	• Consider a dose reduction.
Uncommon (≥ 1/1000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000) or other[3]	

Uncommon - insomnia, depression, syncope, elevated liver function tests, falls.
Rare – seizures (discontinue unless taking anticonvulsants, d/w psychiatrist), angina pectoris, gastric and duodenal ulcers, rash.
Very rare – hallucinations, extrapyramidal symptoms, cardiac arrhythmias (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia), gastrointestinal haemorrhage, pancreatitis, urinary tract infections, hypertension.
Unknown – dehydration, aggression, restlessness, sick sinus syndrome, oesophageal rupture (associated with severe vomiting), hepatitis, pruritis, disseminated allergic dermatitis (oral, transdermal).

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, 3]

- Rivastigmine may antagonise the effect of anticholinergic medication (e.g. procyclidine)
- Caution when used in combination with other medications that significantly reduce the heart rate e.g. digoxin, beta-blockers, certain calcium-channel blocking agents and amiodarone due to synergistic effects.
- Caution with medications that have the potential to cause torsades de pointes – consider an ECG in these cases.
- Rivastigmine is not to be used with other cholinergic agonists / cholinomimetics (e.g. donepezil, galantamine, neostigmine, pyridostigmine, ambenonium) due to synergistic effects.
- Caution with Succinylcholine and other muscle relaxants-. Rivastigmine is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.
- Rivastigmine has the potential to increase the risk for developing ulcers when co-prescribed with non-steroidal anti-inflammatory medication (NSAIDs).

No pharmacokinetic interaction is expected with medicinal products metabolised by the following cytochromes isoemzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6.

Information Given To Patient

The patient/carer should be instructed how to safely remove and replace rivastigmine patches, to wash hands with soap and water after removing the patch and to avoid contact with the eyes after handling the patch.

All skin application site reactions should be reported to a healthcare professional.

If treatment (oral and transdermal) is interrupted for more than three days this should be reported to a healthcare professional before it is restarted.

Further written information sheets on rivastigmine can be accessed via the following site:
- http://www.choiceandmedication.org/nottinghamshirehealthcare/
-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 / carer will report any suspected adverse reactions to the GP for assessment.
- The patient / carer will report to their GP or specialist signs of clinical worsening.
- The patient / 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

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

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8. MHRA Drug Safety Update. Rivastigmine (Exelon) transdermal patch: risk of medication errors. June 2010, Vol3,Issue11.(Link)