Rotigotine Patch *(Neupro®)*

SCG: For the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults in whom first, second and third line treatments have failed following a sustained therapeutic trial or are contraindicated or not tolerated **and** who present with uncontrolled, breakthrough daytime symptoms.

This guideline provides information relating to Rotigotine and outlines the responsibilities of the general practitioner and the Consultant Specialists based at the Respiratory Support and Sleep Centre at Papworth Hospital NHS Foundation Trust, in the prescribing and the overall management of patients stabilised on this medicine.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

Introduction:

Restless legs syndrome (RLS) is a neurological disorder characterized by unpleasant sensations (dysaesthesias) in the legs accompanied by an often irresistible urge to move them. Symptoms typically occur at night when a person is relaxing and can increase in severity during the night. Moving the legs temporarily relieves the discomfort. Severity ranges from mild and infrequent to daily, prolonged and even painful.

The most distinctive or unusual aspect of this condition is that lying down and trying to relax often precipitates or exacerbates the symptoms. Most people with RLS have difficulty initiating and maintaining sleep. Symptoms can adversely impact quality of life by causing disabling tiredness. Many people with RLS report that their job, personal relations, and activities of daily living are strongly affected as a result of their sleep deprivation. They are often unable to concentrate, have impaired memory, or fail to accomplish daily tasks. Travelling can become difficult and depression has been associated with RLS.

Moderate to severe RLS affects approximately 2-3 percent of adults and occurs in both men and women, although the incidence is about twice as high in women. It may develop at any time but symptoms typically become more frequent and prolonged with age. Many of the more severely affected individuals are middle-aged or older.

In most cases the cause of RLS is not clear. There is evidence to suggest that dysfunctional dopaminergic pathways in the basal ganglia underlie RLS. Individuals with Parkinson's disease, another disorder of the basal ganglia, often have RLS. There are familial cases of RLS, when the onset of symptoms is often earlier, and specific gene variants have been found. Low levels of iron in the brain also seem to have a mechanistic role.

RLS has been associated with several other factors or conditions, although we do not yet know if these relationships are causal:

- Chronic diseases such as kidney failure, diabetes, and peripheral neuropathy. Treating the underlying condition may relieve RLS symptoms.
- Certain medications may aggravate symptoms. These include antinausea drugs (prochlorperazine or metoclopramide), antipsychotic drugs (haloperidol or

phenothiazine derivatives), antidepressants that increase serotonin, and some cold and allergy medications that contain sedating antihistamines.

- Pregnancy, especially in the last trimester. In most cases, symptoms usually disappear within 4 weeks of delivery.

Alcohol, caffeine and sleep deprivation aggravate or trigger symptoms in some individuals. Reducing or completely eliminating these factors may relieve symptoms.

If a diagnosis of RLS is unclear, please refer your patient to a specialist sleep centre for further investigation.

Dopamine agonists are recognised as first-line treatment for RLS. Ropinirole, Pramipexole and Rotigotine are licensed for this indication. Rotigotine is a non-ergoline dopamine agonist with selectivity for D1, D2 and D3 receptors. It is administered via transdermal patches which release rotigotine for 24 hours. The continuous delivery makes it particularly useful for cases where daytime symptoms are prolonged, and for those patients who develop augmentation syndrome after treatment with other dopamine agonists. Augmentation syndrome involves the development of RLS symptoms earlier in the day, before the scheduled time that a dopamine agonist is being taken.

Rotigotine Patches (Neupro®) are licensed for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults. At Papworth Hospital NHS Foundation Trust, Rotigotine will be reserved for those patients who:

- have been given a formal diagnosis of RLS by one of our specialist Sleep Consultants. This will be on the basis of thorough clinical assessment, with recourse to investigations including complex sleep studies as appropriate. Patients will have been assessed for serum ferritin, pregnancy, renal failure, muscle cramps, arthritis, neuropathy or drug-induced akathisia **before** a diagnosis of primary RLS is considered.
- will have an International RLS Rating Scale (IRLS) score of 15 points or more (indicating at least moderate symptom severity). This is in line with trial evidence and recommendations by the Scottish Medicines Consortium (see references).
- have already tried other licensed dopamine agonists but not experienced a benefit due to: persistent/recurrent RLS symptoms, drug tolerance, augmentation and/or intolerable side effects.

The recommendation to start Rotigotine Patch treatment will be made by Consultant only, after all other therapeutic options have been considered.

RESPONSIBILITIES and ROLES

Specialist Responsibilities (Respiratory Support and Sleep Centre (RSSC)):

The patients will be assessed by one of the consultants (Dr I E Smith, Dr T Quinnell, Dr M Davies and Dr N Oscroft) and the hospital will undertake to:

1. Provide information to the patient regarding the medicine.
2. Provide an initial six week supply of Rotigotine.
3. Recommend an initial dose and how this may be titrated according to the response to treatment.

4. Review the patient's progress toward the end of the initial 6 week treatment period. If the patient has failed to respond to treatment then Rotigotine Patch therapy will be discontinued.
5. Be available for advice to the general practitioner.
6. Answer patient enquiries on any aspect of this therapy.
7. Review all treatment responders at an out-patient clinic 4 months after initiation of therapy and again at an out-patient clinic 6 months later. The need for treatment continuation will be reconsidered every 6 months. If the patient is receiving no benefit from treatment with Rotigotine Patches then treatment will be discontinued.
8. Communicate all relevant information regarding treatment to the general practitioner, outlining when therapy may be reduced and stopped assuming no relapse in the patient's condition.

General Practitioner's responsibilities:

1. Continue to prescribe Rotigotine Patches once this has been initiated by the Respiratory Support and Sleep Centre consultant specialists.
2. Communicate any adverse events or other problems with the medicine to the supervising consultant at Papworth Hospital.

Patient's role:

1. Report any adverse effects to their Consultant or G.P. whilst taking Rotigotine Patches.
2. Share any concerns they have in relation to treatment with Rotigotine Patches.
3. Report to the Consultant or G.P. if they do not have a clear understanding of their treatment.
4. Obtain their prescription from the same dedicated pharmacy of their choice.

BACK-UP ADVICE AND SUPPORT

- Papworth Hospital Main Switchboard 01480 830541
- Respiratory Support and Sleep Centre 01480 364260 (direct line)
- Secretary to Dr Smith 01480 364164 (direct line)
- Secretary to Dr Quinnell 01480 364174 (direct line)
- Secretary to Dr Davies 01480 364542 (direct line)
- Secretary to Dr Oscroft 01480 364164
- Pharmacy Medicines Information Service 01480 364179 (direct line)
- Pharmacy Medicines Helpline (answerphone) 01480 364739

SUPPORTING INFORMATION

Indications and Usage

- Rotigotine Patches (Neupro®) are licensed for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults in whom first, second and third line treatments have failed following a sustained therapeutic trial or are contraindicated or not tolerated **and** who present with uncontrolled, daytime symptoms.

Dosage and Administration

- A single daily dose should be initiated at 1 mg/24 h. Depending on the individual patient response; the dose may be increased in weekly increments of 1 mg/24 h to a maximum dose of 3 mg/24 h.
- The patch should be applied to clean, dry, intact healthy skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. Reapplication to the same site within 14 days should be avoided. Rotigotine patches should not be placed on skin that is red, irritated or damaged.
- Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the protective liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is folded back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch should be pressed down firmly with the palm of the hand for about 20 to 30 seconds, so that it sticks well.
- In the event that a patch should fall off, a new patch should be applied for the remainder of the 24 hour dosing interval.
- The patch should not be cut into pieces.

- **Dose in hepatic and renal impairment**
  Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis. Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Rotigotine has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment. Unexpected accumulation of rotigotine levels may also occur with acute deterioration of renal function.

- **Special Populations**
  Safety and efficacy in children and adolescents has not been established. Therefore use in patients under 18 years of age is not recommended.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Magnetic resonance imaging or cardioversion (The backing layer of Rotigotine patches contains aluminium. To avoid skin burns, the Rotigotine patch should be removed if the patient has to undergo magnetic resonance imaging (MRI) or cardioversion).

Special warnings and precautions for use

- **Orthostatic hypotension**
  Dopamine agonists are known to impair the systemic regulation of blood pressure resulting in postural hypotension. It is recommended to monitor blood pressure, especially at the beginning of treatment, for the development of this complication.

- **Sudden onset of sleep and somnolence**
  Rotigotine has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness of any warning signs, has been reported. Prescribers should continually reassess patients for drowsiness or sleepiness, as patients may not acknowledge these symptoms unless directly questioned. A reduction of dosage or termination of therapy should be carefully considered.

- **Impulse control disorders**
  Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including rotigotine.

- **Neuroleptic malignant syndrome**
  Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore it is recommended to taper treatment.

- **Heat application**
  External heat (excessive sunlight, heating pads and other sources of heat such as sauna, hot bath) should not be applied to the area of the patch.

- **Applications site reactions**
  Application site skin reactions may occur and are usually mild or moderate in intensity. It is recommended that the application site should be rotated on a daily basis (e.g. from the right side to the left side and from the upper body to the lower body). The same site should not be used within 14 days. If application site reactions occur, which last for more than a few days or are persistent, if there is an increase in severity, or if the skin reaction spreads outside the application site, an assessment of the risk/benefit ratio for the individual patient should be made.
  If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin colour.
  If a generalised skin reaction (eg. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Rotigotine is observed, it should be discontinued.

- **Effects on ability to drive and use machines**
  Rotigotine may have major influence on the ability to drive and use machines. Patients being treated with rotigotine and presenting with somnolence, including sudden sleep episodes, must be informed not to drive or engage in activities (e.g. operating machines) where impaired alertness may put them, or others, at risk of serious injury or death, until somnolence has improved to the extent whereby it is no longer judged to impair safety.

- **Pregnancy and Breast Feeding**
  Rotigotine should not be used during pregnancy or breast feeding.

Side Effects

- At the beginning of therapy dopaminergic adverse reactions such as nausea and vomiting may occur. These are usually mild or moderate in intensity and transient even if treatment is continued.
- Adverse drug reactions (ADRs) reported in more than 10% of patients treated with Rotigotine Patches are nausea, application site reactions, asthenic conditions and headache.
- For full details of potential adverse effects refer to the Summary of Product Characteristics for Rotigotine Patches (Neupro®).

Monitoring

- Laboratory tests are not required to monitor patient response to Rotigotine patch administration. However, it is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of orthostatic hypotension associated with dopaminergic therapy.

Drug Interactions

- As rotigotine is a dopamine agonist, it is assumed that dopamine antagonists, such as neuroleptics (eg. phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of Rotigotine, and co-administration should be avoided.
- Due to the possibility of additive effects, caution should be advised when patients are taking sedating medicinal products or other central nervous system (CNS) depressants (eg. benzodiazepines, antipsychotics, antidepressants) or alcohol in combination with rotigotine.
- Rotigotine may potentiate the dopaminergic adverse reactions of L-dopa and may cause and/or exacerbate pre-existing dyskinesia.
- Co-administration of rotigotine (3 mg/24 h) has not been found to affect the pharmacodynamics and pharmacokinetics of oral contraceptives (0.03 mg ethinylestradiol, 0.15 mg levonorgestrel). Interactions with other forms of hormonal contraception have not been investigated.

Cost

- Papworth Hospital will ensure that PCT funding for Rotigotine treatment is in place before initiating patient therapy. Papworth Hospital will prescribe and supply the first six weeks treatment. Patients will be reviewed before the end of this initiation period and if therapy is to continue this will be communicated to the patient and their G.P. Patients will be reviewed in a further 3 months and then routinely every 6 to 12 months to ascertain on-going need for treatment.
- Please refer to the latest edition of the BNF for current price or contact the Pharmacy department at Papworth Hospital for more information.

References

1. www.emc.medicines.org.uk accessed 11/08/2011 SPC last updated 17/06/2011.

2. Scottish Medicines Consortium Assessment No. 548/09; issued 10/07/2009.

Guidelines:
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