



# Rotigotine

(Neupro<sup>®</sup>▼)

For the treatment of Parkinson's Disease

Committee's Verdict: **CATEGORY B (Q3)**

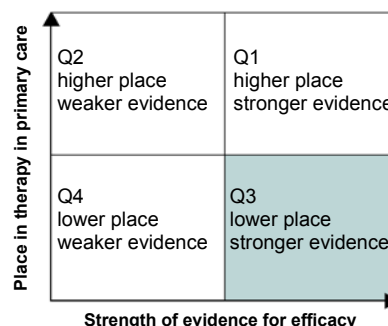
BNF: 4.9.1

**Parkinson's disease should be diagnosed and managed in secondary care. Rotigotine is suitable for prescribing in primary care after specialist initiation and stabilisation of the dose. NICE guidelines recommend regular access to specialist care for clinical monitoring and medication adjustment.**

**Category B:** suitable for restricted prescribing under defined conditions

**Q3 rating:** The evidence for the efficacy of rotigotine in Parkinson's disease is relatively strong. In early Parkinson's disease, rotigotine was more effective than placebo in improving scores on the Unified Parkinson's Disease Rating Scale, but in data submitted for licensing it was shown to be less effective than ropinirole. In advanced disease, rotigotine was more effective than placebo in reducing daily 'off' time. The need for specialist initiation and stabilisation of dose, and the availability of alternative drugs give rotigotine a low place in therapy in primary care.

**The Q rating relates to the drug's position on the effectiveness indicator grid.** The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.



MTRAC reviewed this drug because it is a new product with potential for prescribing in primary care.

### Licensed indication

Treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease (PD) as monotherapy (i.e. without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or 'on-off' fluctuations).<sup>1</sup>

### Background information

Parkinson's disease is a neurological condition associated with resting tremor and progressive motor disability, i.e. rigidity and bradykinesia.<sup>2</sup> Pathological findings from brain sections show that nigral dopamine neurons are greatly diminished in number and Lewy bodies are present in the remaining neurons.<sup>2</sup> Parkinson's disease affects about 120,000 people in the UK (about 200 per 100,000), with symptoms appearing usually in patients aged over 50 years.

The symptoms of Parkinson's disease are not usually treated until they cause significant interruption of daily activities.

**Dopamine agonists** (bromocriptine, cabergoline, lisuride, pergolide, pramipexole, ropinirole and rotigotine) are often used first-line in younger and healthier patients because they rarely cause

dyskinesia (fragmentary or incomplete movements). They are also used as an adjunct to levodopa in more advanced disease. The Committee on Safety of Medicines, however, have warned of adverse reactions with the use of some of these drugs.<sup>3,4</sup>

**Levodopa** (in combination with the dopa-decarboxylase inhibitors benserazide or carbidopa) is the most potent antiparkinsonian drug. It is the mainstay of treatment for the majority of the course of the disease in all patients. One complication of long-term levodopa treatment is motor complications including response fluctuations and dyskinesia.

**Selegiline, entacapone, tolcapone and amantadine** are used as adjuncts to levodopa for the alleviation of end-of-dose fluctuations or dyskinesia in patients with later disease.

Rotigotine was launched in April 2006. It is a new non-ergolinic dopamine agonist for the treatment of Parkinson's disease. It is formulated as a transdermal patch delivering 2, 4, 6 or 8 mg rotigotine over 24 hours.

### Clinical efficacy

Two double-blind RCTs (total n = 519)<sup>5,6</sup> evaluated rotigotine in patients with early Parkinson's disease who had not yet been treated with levodopa. A third RCT evaluated patients with advanced Parkinson's disease whose symptoms were not adequately controlled using levodopa.<sup>8</sup>

## Early Parkinson's disease

The trials in early PD comprised a 14-week dose-ranging study (n = 242)<sup>5</sup> that evaluated patches delivering 2 to 8 mg rotigotine in 24 hours compared with placebo, and a second study (n = 277),<sup>6</sup> in which rotigotine was titrated to an optimum dose over four weeks before a 24-week maintenance phase. The primary outcome in both studies was the mean change in the sum of the Unified Parkinson's Disease Rating Scale (UPDRS) subscores for Activities of Daily Living (ADL) and motor skills, from baseline to the end of treatment. The second study also measured the number of responders, defined as the proportion of patients who showed at least a 20% improvement in UPDRS scores.

Both studies found that patients treated with rotigotine at doses of 6 mg/24 hours or more showed significantly greater improvement in UPDRS scores compared with placebo (p < 0.001). The second study also showed that a greater proportion of rotigotine-treated patients responded to treatment compared with placebo-treated patients (48% vs. 19%, p < 0.0001).

Additional data submitted for licensing to the European Agency for the Evaluation of Medicinal Products,<sup>7</sup> showed similar results for rotigotine compared with placebo. In a comparison with ropinirole, however, it found that ropinirole was more effective than rotigotine for both improvement in UPDRS scores and the percentage of patients that responded to treatment.

## Advanced Parkinson's disease

In patients with advanced disease, the PREFER study (n = 351) evaluated rotigotine at doses up to either 8 or 12 mg/24 hours compared with placebo in patients receiving concomitant levodopa therapy ( $\geq$  200 mg daily).<sup>8</sup> All patients had at least 2.5 hours daily "off" time according to 24-hour self-report diaries. Rotigotine was titrated to an optimum dose over five weeks before a 24-week maintenance phase. The primary outcomes were the change in number of daily hours in the "off" state and the proportion of patients achieving  $\geq$  30% reduction (responders) in absolute time spent "off", from baseline to the end of the study.

Compared with placebo, daily "off" time decreased by 1.8 hours in the rotigotine 8mg/24 hour group and 1.2 hours in the rotigotine 12 mg/24 hour group (p < 0.005). A higher proportion of patients "responded" to treatment in the rotigotine groups compared with the placebo group (55% to 57% vs. 35%, p  $\leq$  0.001).

## Adverse effects

The most common treatment-emergent adverse events in the trials were nausea, vomiting, somnolence, headache, dizziness, dyskinesia, insomnia, peripheral oedema or application-site reactions (contact dermatitis, itching).

For additional information on adverse events, refer to the Summary of Product Characteristics (SPC).<sup>1</sup>

## Additional information

- The initial dose of rotigotine is 2 mg/24 hours, increased in weekly increments of 2 mg/24 hours. The maximum recommended dose is 8 mg/24 hours in early-stage disease and 16 mg/24 hours in advanced stage disease.<sup>1</sup>
- At current prices, a year's treatment with rotigotine 6 mg/24 hour patch costs £1,438.
- The National Institute for Clinical Excellence (NICE) recently published a Clinical Guideline for the diagnosis and management of Parkinson's disease in collaboration with the National Collaborating Centre for Chronic Conditions.<sup>9</sup> Rotigotine was not included in the report. The authors of the guideline found that it was not possible to identify a universal first-choice drug therapy for the treatment of early or advanced disease.

## References

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3. Committee on safety of medicines. Fibrotic reactions with pergolide and other ergot-derived dopamine receptor agonists. *Current Problems* 2002;**28**:3.
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5. The Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol* 2003;**60**:1721-1728.
6. Watts RL, Jankovic J, Waters C *et al*. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. *Neurology* 2007;**68**:272-276.
7. Neupro. EMEA-H-626-N-02 EMEA. 2006. <http://www.emea.europa.eu/humandocs/Humans/EPAR/neupro/neupro.htm>
8. LeWitt PA, Lyons KE, Pahwa R. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. *Neurology* 2007;**68**:1262-1267.
9. National Collaborating Centre for Chronic Conditions. Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. National Collaborating Centre for Chronic Conditions. 2006. <http://www.nice.org.uk/guidance/CG35>

Launch date: April 2006

Manufacturer: Schwartz Pharma

EU/1/05/331/013

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics  
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

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