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REGIONAL DRUG AND THERAPEUTICS CENTRE

NEW DRUG EVALUATION

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ROTIGOTINE

Rotigotine (Neupro®) is a dopamine-receptor agonist delivered through a silicone-based transdermal patch that is changed daily as treatment for the signs and symptoms of early-stage idiopathic Parkinson's disease (IPD). Two unpublished studies show that rotigotine is more effective than placebo in reducing symptoms of early-stage PD; however, it is less effective than oral ropinirole. It has a similar side-effect profile to other oral dopamine agonists and application site reactions are common. The longer-term efficacy and safety of rotigotine has not been established. Rotigotine should therefore not be routinely used in preference to the more established dopamine agonists.

What is it?

Rotigotine (Neupro®, Schwarz Pharma) is a novel $D_3/D_2/D_1$ dopamine-receptor agonist delivered through a silicone-based transdermal patch, which is changed daily, as monotherapy for the signs and symptoms of early-stage IPD.[1] It is available as a range of patches designed to release 2 mg, 4 mg, 6 mg, or 8 mg rotigotine over 24 hours. The recommended starting dose is 2 mg / 24h, increased by 2 mg / 24h each week to a maximum of 8 mg / 24h. The patch should be applied at approximately the same time every day. The patch remains on the skin for 24 hours and is then replaced with a new patch at a different site. The same site must not be used again within two weeks.[1] The manufacturer claims that transdermal delivery over 24 hrs ensures stable plasma drug levels, hence avoiding the peaks and troughs which can lead to fluctuations in symptom control. Rotigotine in combination with levodopa has recently received a positive opinion for the treatment of advanced IPD.[2]

How effective is it?

The efficacy of rotigotine in the treatment of early-stage IPD has been assessed in two, as yet unpublished, randomised, double-blind placebo controlled trials.[3-5] Both studies measured scores before and after treatment using the Unified PD Rating Scale (UPDRS) parts II and III, which assess a patient's ability to perform everyday activities and evaluate motor systems of PD. Responder rates were used as the primary outcome variable in EU centres and mean change from baseline in UPDRS was used in US centres. A 'responder' was defined as a subject with a 20% or greater decrease in the sum of scores from UPDRS parts I and III. Participants were eligible if they had been diagnosed with IPD of $\leq$ 5 years duration with a UPDRS part III score of $\geq$ 10 at baseline.

In the first study, 277 patients with early-stage IPD were randomised (2 : 1) to rotigotine transdermal patch (2-6 mg / 24h) or placebo.[3,5] After a run-in period of about 28 days patients entered a three-week dose escalation phase in which they were titrated to the optimal or maximum dose (6 mg / 24h), defined as that which gave the maximal reduction in PD symptoms without intolerable adverse effects. In the treatment group 91% of patients received the maximum dose of rotigotine. Patients were maintained at their optimal dose for 6 months. Rotigotine resulted in a higher proportion of 20% responders at the end of treatment compared to placebo (48% vs. 19%, difference 28.8% [95% CI 18.0% to 39.4%], $p < 0.0001$). The mean improvement in UPDRS score (part II & III) was -3.98 points for rotigotine whereas in the placebo group a worsening of +1.31 points was seen (difference -5.28 [95% CI -7.6 to -3.0)], $p < 0.0001$).

In the second study, 561 patients with early-stage IPD were randomised (2 : 2 : 1) to rotigotine transdermal patch (2-8 mg daily), ropinirole (titrated from 0.75 to 24 mg daily) or placebo.[4,5] The usual clinical dose range for ropinirole in PD is 9-16 mg daily.[6] The dose escalation period for rotigotine lasted four weeks (maximal dose 8 mg / 24h), and 13 weeks for ropinirole (maximal dose 24 mg / day). In the rotigotine group 92% of patients received the maximum dose. The percentage of 20% responders was 52% for rotigotine, 68% for ropinirole and 30% for placebo (difference rotigotine vs. placebo 21.7% [95% CI 11.1% to 32.4%], ropinirole vs. placebo 38.4% [95% CI 28.1% to 48.6%], and rotigotine vs. ropinirole -16.6% [95% CI 25.7% to 7.6%]). The mean improvement in UPDRS score (part II & III) was -6.83 points for rotigotine vs. 10.78 for ropinirole and 2.33 for placebo.

Data from open-label long-term extensions of the above two studies suggests that efficacy of rotigotine may be maintained for up to 12-18 months.[5]

How safe is it?

Rotigotine was generally well tolerated. Most adverse events were typical of a dopamine-receptor agonist, or with use of a transdermal delivery system.[1,3-5] The most common adverse events occurring in a higher frequency in rotigotine treated patients compared to placebo were application site reactions (ASRs), nausea, somnolence, dizziness, headache, and vomiting.[3] With the exception of ASRs, the incidences of these adverse events occurred in a similar proportion of subjects treated with rotigotine and ropinirole.[4] Overall adverse events were more common during the initial titration phase.

What other options are there?

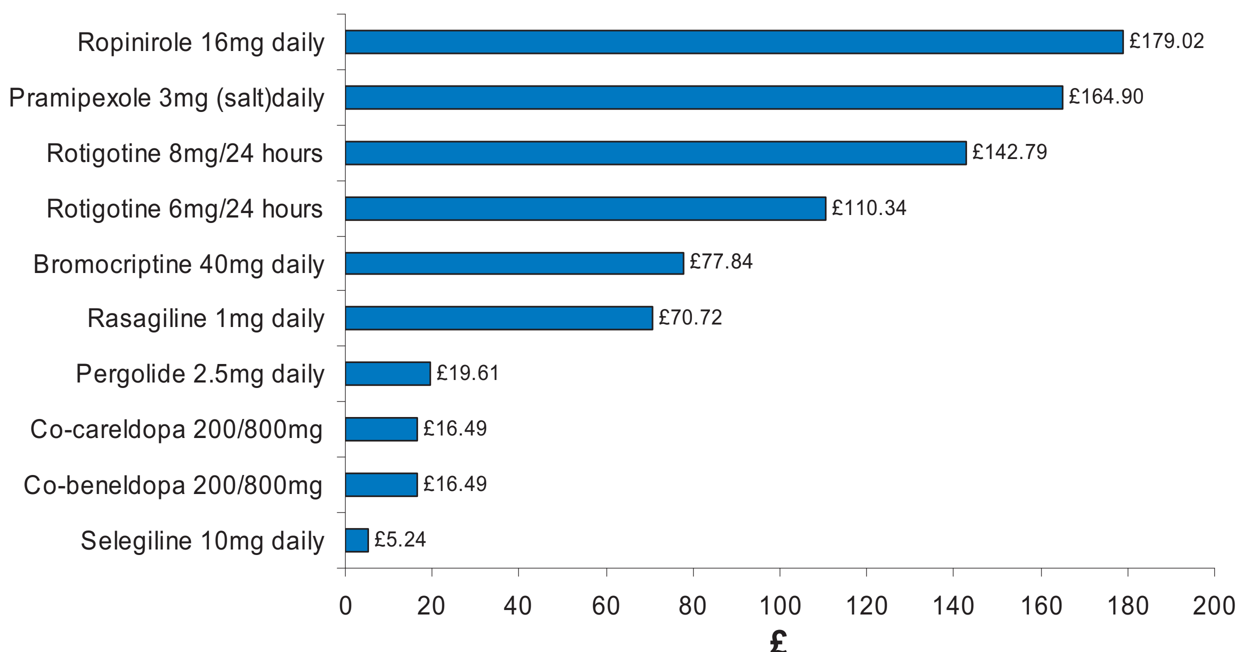
Levodopa, dopamine-receptor antagonists and monoamine oxidase B inhibitors are used for the symptomatic treatment of early PD.[7] Choice should take into account clinical and lifestyle characteristics and patient preference. Dopamine-receptor agonists are considered appropriate initial treatments for early PD, as when used alone these agents are associated with fewer motor complications in long-term treatment than levodopa.[6]

When should it be used?

Rotigotine is more effective than placebo in reducing symptoms of early-stage PD; however, it is less effective than high-dose ropinirole. It has a similar side-effect profile to other oral dopamine agonists, and application site reactions are common. However, the longer-term efficacy and safety of rotigotine has not been established. Rotigotine should therefore not be routinely used in preference to the more established dopamine agonists, unless such agents are ineffective or there are swallowing problems.

How much does it cost?

Cost for 28 days treatment (prices from MIMS/Drug Tariff December 2006)



N.B. Doses shown for general comparison only and do not imply therapeutic equivalence

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KEY RCT - randomised controlled trial, G - guideline, R - review, U - unpublished

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