The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**rotigotine (Neupro®)** is accepted for restricted use within NHS Scotland for the treatment of the signs and symptoms of advanced idiopathic Parkinson’s disease 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).

Rotigotine increased the proportion of patients achieving $\geq 30\%$ reduction in “off” time compared with placebo, but appeared to be less effective than another non-ergolinic dopamine agonist. Rotigotine trans-dermal patch offers an alternative non-ergolinic dopamine agonist at a lower cost in a formulation that does not have to be taken by mouth. It is restricted to patients where this route would facilitate treatment.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium
**Indication**
Treatment of the signs and symptoms of advanced idiopathic Parkinson’s disease 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).

**Dosing information**
Transdermal patch applied once daily and left on skin for 24 hours. Initially 4mg/24 hours, increasing in weekly increments of 2mg/24 hours to an effective dose, up to a maximal dose of 16mg/24 hours.

**Product availability date**
1 February 2007

**Summary of evidence on comparative efficacy**
Rotigotine is a non-ergolinic dopamine agonist (DA) that shows a close structural analogy to dopamine and apomorphine. The formulation is a matrix-type transdermal patch designed to release rotigotine continuously.

Two double blind, controlled trials evaluated the efficacy, safety and tolerability of rotigotine adjuvant to levodopa in advanced idiopathic Parkinson’s disease (PD) as compared to placebo and, in one trial, also to pramipexole. Patients were included if they had been diagnosed with idiopathic PD of > 3 years duration, had a Hoehn and Yahr stage II – IV in both the “on” and “off” state, were on a stable dose of levodopa of $\geq 300$mg/day in the active-controlled trial, and $\geq 200$mg/day in the placebo-controlled trial, for at least 28 days and had $\geq 2.5$ hours of daily “off” time. In both trials the primary efficacy outcome was determined by response to therapy. A responder was defined as having achieved $\geq 30\%$ decrease in absolute time spent “off” from baseline to end of double blind maintenance phase. Home diaries were used to record time spent “off”, “on with troublesome dyskinesia”, “on without troublesome dyskinesia”, or asleep.

In the active-controlled trial, after a 4-week screening phase, 506 patients were randomised in a 2:2:1 ratio to titration to an optimal dose of rotigotine (up to 16mg/24 hours) or pramipexole (up to 4.5mg salt daily) or placebo. The titration phase was up to 7 weeks and the maintenance phase was 16 weeks. The proportion of responders in the active treatment groups, rotigotine 60% (120/201) and pramipexole 67% (134/200), were significantly higher than in the placebo group 35% (35/100). The difference between rotigotine and placebo was 24.7% (95% confidence interval [CI]; 13.2, 36.3) and between pramipexole and placebo was 32.0% (95% [CI]; 20.6, 43.4). Non-inferiority was not shown for rotigotine versus pramipexole in the final analysis set (FAS) (difference= -7.3%; 95% CI; -16.7, 2.1).

For the secondary endpoint of mean change from baseline in absolute time “off” at the end of the maintenance period, results were -2.5 hours for rotigotine, -2.8 hours for pramipexole and -0.9 hours for placebo and were significant for rotigotine compared to placebo.
Rotigotine and pramipexole also produced larger decreases in the proportions of patients who woke in the 'off' state (23% and 22%, respectively) compared with placebo (11%). These decreases closely corresponded to the increases in patients who woke in the 'on' state without troublesome dyskinesia (rotigotine, 23%; pramipexole, 22%; placebo 11%).

In the placebo-controlled trial, after a 4 week screening phase, 351 patients were randomised equally to titration to an optimal dose of rotigotine (up to 8mg/24 hours), or rotigotine (up to 12mg/24 hours) or placebo. The titration phase was up to 5 weeks and the maintenance phase was 24 weeks. The proportions of responders were 57% (64/113) and 55% (60/109) for rotigotine 8mg/24 hours and 12mg/24 hours respectively compared with 34% (41/119) for placebo. The difference between rotigotine 8mg/24 hours and placebo was 22.2% (95% CI: 9.7, 34.7) and between rotigotine 12mg/24 hours and placebo was 20.6% (95% CI 7.9, 33.2).

Rotigotine 8 mg/24 hours and 12 mg/24 hours significantly decreased the absolute ‘off’ time from baseline to the end of double-blind maintenance treatment by 2.7 hours and 2.1 hours, respectively, compared with 0.9 hours in placebo-treated patients. The average treatment effect for the reduction of “off” time was 1.8 hours (95% CI: -2.6, -1.0) and 1.2 hours (95% CI: -2.0, -0.4), respectively). Both doses of rotigotine produced larger decreases in the UPDRS Part II and III scores at the end of the maintenance phase compared with placebo. There were no meaningful differences between treatment groups in terms of UPDRS Part IV component scores.

Other data were also assessed but remain commercially confidential.*

<table>
<thead>
<tr>
<th>Summary of evidence on comparative safety</th>
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<tbody>
<tr>
<td>No new safety concerns arose. Aside from the adverse events (AEs) associated with the transdermal patch method of administration, the safety profile of rotigotine in advanced PD is similar to that of other DAs. No dose relationship was observed with respect to AE occurrence.</td>
</tr>
<tr>
<td>In the active-controlled trial treatment-emergent AEs occurred at a similar frequency in patients receiving rotigotine, pramipexole, and placebo. AEs occurring more frequently in rotigotine-treated patients compared with pramipexole or placebo included application site reactions, nausea, and somnolence.</td>
</tr>
<tr>
<td>In pooled data from both trials, AEs led to discontinuation in 13% and 8% of those receiving rotigotine and placebo respectively. AE terms that resulted in discontinuation of &gt;1% of rotigotine-treated subjects included nausea (4%), vomiting (2%), and application and instillation site reactions (2%). Application and instillation site reactions occurred in 31% of rotigotine-treated patients although most were mild or moderate in intensity and had resolved by the end of the maintenance phase.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Summary of clinical effectiveness issues</th>
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<tbody>
<tr>
<td>Apart from the pramipexole trial described above, there are no other controlled trials comparing rotigotine with other medicines licensed for this indication including monoamine oxidase B (MAO-B) inhibitors and catechol-O-methyl transferase (COMT) inhibitors as well as other DAs.</td>
</tr>
</tbody>
</table>
Although there would appear to be a theoretical advantage in the 24 hour duration of the transdermal rotigotine effect, there was no significant difference in the proportion of patients who awoke in the “on state without troublesome dyskinesia”, between patients receiving rotigotine or pramipexole.

Potential advantages of a once daily patch over multiple oral tablets include convenience, improved concordance, and a treatment option for patients with swallowing difficulties. These advantages would have to be balanced against the high incidence of application site reactions.

In an open label uncontrolled trial to assess the tolerability of overnight switching from ropinirole, pramipexole or cabergoline to rotigotine, 77% of patients “agreed” or “strongly agreed” that they preferred using patches compared with oral medication.

*Other data were also assessed but remain commercially confidential.*

### Summary of comparative health economic evidence

The manufacturer presented a simple one year cost utility model based around the responder rates of the clinical trial that compared rotigotine with pramipexole. The additional comparators of ropinirole and cabergoline were also considered. Expert opinion was used in the model to support the assumption that ropinirole would attain a response rate of the midpoint between pramipexole and rotigotine, and cabergoline a response rate equivalent to rotigotine.

Treatment during the titration phase was assumed to result in no patient benefit, which is likely to have been to the detriment of ropinirole with a 16 week titration phase in contrast to the 7 weeks required for the other treatments. The full response rates of 59.7% for rotigotine and 60.0% for pramipexole were only achieved by week 24. The 24 week response rates were assumed to continue to week 52. As it is likely that greater proportions of patients were benefiting from the treatments prior to the 24 week point, these assumptions may have underestimated the relative benefit of pramipexole over rotigotine.

A utility increment of around 0.1 for responders was estimated through the EQ-5D visual analogue scale which had been administered during the trial assessing rotigotine relative to placebo. Adverse events impacted upon costs and quality of life, rates for these being drawn from the trial for rotigotine and pramipexole. Adverse event rates for ropinirole and cabergoline were drawn from their product monographs. Trial drop-outs were not considered. Dosing for rotigotine and pramipexole was drawn from the trial, while for ropinirole and cabergoline it was drawn from expert opinion.

The modelling found that pramipexole was more cost effective than rotigotine. The indirect comparison with cabergoline suggested that while rotigotine was more expensive, the lower rates of adverse events associated with rotigotine could enable it to be cost effective relative to cabergoline. The indirect comparison with ropinirole suggested that while rotigotine would be more expensive, it would be cost effective. This last estimate may have been sensitive to the assumptions around titration phases and maintenance phases as outlined above. The differences in the annual costs of treatments ranged between £400 and £800, while the differences in accrued QALYs were small.
Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In 2006, before rotigotine was licensed for the indication under review by SMC, the National Institute for Health and Clinical Excellence (NICE) issued a clinical guideline, CG35 entitled “Parkinson’s Disease: National clinical guideline for diagnosis and management in primary and secondary care”. It cites dopamine agonists, COMT inhibitors and MAO-B inhibitors as first choice options for adjuvant pharmacotherapy in later PD. It also states that it is not possible to identify a universal first choice adjuvant drug therapy for people with later PD. The choice of adjuvant drug first prescribed should take into account clinical and lifestyle characteristics and patient preference, after the patient has been informed of the short- and long-term benefits and drawbacks of the drug classes.

Additional information: previous SMC advice

In September 2006, following a full submission the SMC advised that co-careldopa intestinal gel (Duodopa) is not recommended for use within NHS Scotland for the treatment of advanced levodopa-responsive Parkinson’s disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results. In the pivotal study an increase in “on” time was achieved compared with individually optimised conventional combinations of Parkinson’s disease medication. However, the economic case has not been demonstrated.

In February 2006, following a full submission, the SMC advised that rasagiline (Azilect) is not recommended for use within NHS Scotland for the treatment of idiopathic Parkinson’s disease as adjunct therapy (with levodopa) in patients with end of dose fluctuations. Rasagiline reduces “off” time in patients with Parkinson’s disease and end of dose fluctuations on levodopa, similar to reductions shown with the less effective of two currently marketed catechol-O-methyl transferase inhibitors. However, there are no comparative data with the other monoamine oxidase-B inhibitor, which is less expensive. The economic case has not been demonstrated.

In January 2004, following an abbreviated submission, the SMC advised that the levodopa, carbidopa and entacapone combination preparation (Stalevo®) was accepted for use in NHS Scotland for the treatment of patients with Parkinson’s disease and end of dose motor fluctuations not stabilised on levodopa/dopa decarboxylase inhibitor treatment. This combination preparation allows administration of a single tablet incorporating ingredients that are routinely combined for the indication described above. This may improve convenience to the patient. Depending on the doses and formulations being replaced, conversion to the combination may result in a modest increase in cost or (less commonly) a cost saving.

Additional information: comparators

The non-ergolinic DAs, ropinirole and pramipexole, the MAO-B inhibitors, selegiline and rasagiline and the COMT inhibitor entacapone are all licensed, and recommended by NICE, for adjuvant use with levodopa in advanced PD.
### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Usual dose range</th>
<th>Annual cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine agonists</td>
<td>rotigotine</td>
<td>4-16mg daily</td>
<td>1148-3713</td>
</tr>
<tr>
<td></td>
<td>pramipexole</td>
<td>1.05 - 3.15mg daily (dose as base)</td>
<td>1390-4171</td>
</tr>
<tr>
<td></td>
<td>ropinirole</td>
<td>9 -24mg daily</td>
<td>1843-3966</td>
</tr>
<tr>
<td>MAO-B inhibitors</td>
<td>rasagiline</td>
<td>1mg daily</td>
<td>919</td>
</tr>
<tr>
<td></td>
<td>selegiline oral lyophilisate</td>
<td>1.25mg daily</td>
<td>727</td>
</tr>
<tr>
<td></td>
<td>selegiline tablets</td>
<td>10mg daily</td>
<td>125</td>
</tr>
<tr>
<td>COMT inhibitor</td>
<td>entacapone#</td>
<td>600 – 2000mg daily</td>
<td>655 - 2184</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence.

Costs accessed from eVadis on 1.5.07

# A triple combination product (containing entacapone, levodopa and carbidopa) is available and is recommended by NICE in people with later PD who are taking entacapone.

### Additional information: budget impact

The manufacturer estimated a gross drug cost of £396k was for year 1 rising to £1.4mn to £1.5mn by year 5. This was based upon a current prevalence of 1,400 patients, coupled with an annual incidence of 250 patients and a market share of around 20% to yield around 134 patients receiving rotigotine in year 1 rising to 556 by year 5.

The net drug cost was estimated as being £123k in year 1, rising to £447k by year 5.
**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 15 June 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/

The references below, shaded grey, are additional to information supplied with the submission.
