rotigotine 2mg/24 hours, 4mg/24 hours, 6mg/24 hours, 8mg/24 hours transdermal patch (Neupro®) (No: 289/06)

Schwarz Pharma Ltd.

7 July 2006

The Scottish Medicines Consortium has completed its assessment of the above product and advises the 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 not recommended for use within NHS Scotland for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. without levodopa).

Rotigotine was superior to placebo in two randomised controlled trials. However, in one active comparator study non-inferiority to another non-ergolinic dopamine agonist comparator was not shown. The economic case has not been demonstrated.

Overleaf is the detailed advice on this product.

Vice Chairman
Scottish Medicines Consortium

Rotigotine 2mg/24hrs, 4mg/24hrs, 6mg/24hrs, 8mg/24hrs transdermal patch (Neupro®)

Indication

Treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. without levodopa)

Dosing information

Starting dose: 2mg/24 hours.
Increase in weekly increments of 2mg/24 hours to an effective dose up to a maximal dose of 8mg/24 hours. Patches are changed every 24 hours.

UK launch date

5 April 2006

Comparator medications

The National Institute for Health and Clinical Excellence (NICE) (June 2006) *Parkinson's disease (PD); diagnosis and management in primary and secondary care* recommends levodopa, dopamine agonists and monoamine oxidase inhibitors for symptomatic treatment in early PD.

Cost of relevant comparators

Drug class	Drug	Daily dose range* (all oral administration except for rotigotine)	Annual cost **(£)
Dopamine agonists	**Rotigotine**	**2- 8mg daily**	**1007-1861**
	Ropinirole	9-16mg daily	1848-2334
	Pramipexole	1.08-3.18mg daily (dose as base)	1351-3500
	Lisuride	0.2-5mg daily	165-4131
	Bromocriptine	10-40mg daily	254-1015
	Pergolide	2-2.5mg daily	286-399
Levodopa	Co-beneldopa (Madopar®)	400mg to 800mg daily***	126-215
	Co-careldopa (Sinemet®)	300mg to 800mg daily***	123-554
MAO-B inhibitor	Selegiline (Eldepryl®)	10mg daily	90
	Rasagiline	1mg daily	922

* based on usual dose ranges (with maximal dose range for pramipexole and lisuride) in the 51st edition of the British National Formulary.
** costs from eVadis drug dictionary accessed on 02/05/06
*** dose expressed in terms of levodopa.

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

Summary of evidence on comparative efficacy

Rotigotine is a non-ergolinic dopamine agonist, with a structural analogy to dopamine and apomorphine. It has been developed for transdermal administration due to its low oral bioavailability and suitable physico-chemical properties for transdermal administration.

Two multi-centre, randomized, double-blind, placebo-controlled (and ropinirole-controlled in the second study) parallel group studies have been conducted in patients with early stage PD of = 5 years in duration, having a Unified PD Rating Scale (UPDRS) motor score (part III) of = 10 at baseline, a Hoehn & Yahr stage = 3, and at least 2 or more of the following cardinal signs: bradykinesia, resting tremor, rigidity, postural instability; and without any other known or suspected cause of Parkinsonism. The primary efficacy variable was the percentage of patients with a = 20% decrease in parts II (activities of daily living [ADL]) and III (motor score) combined of the UPDRS. The mean change from baseline in the UPDRS (parts II and III combined; range 0 to 108), with higher scores indicating more severe disease) was also analysed.

In the first trial, patients were randomised (2:1) to rotigotine transdermal patch (2-6mg/24hrs) or placebo. Rotigotine treated patients started at a dose of 2mg/24hrs and a three week dose escalation period allowed titration to optimal (defined as the dose that gave maximal reduction in PD symptoms without intolerable side effects) or maximal dose. Placebo treated patients also underwent a titration to maintain blinding. The dose maintenance period lasted 24 weeks. The numbers of patients randomised to rotigotine and placebo were 181 and 96, respectively, and the percentages of 20% responders in the UPDRS (part II and III) were 48% and 19%, respectively. The mean change from baseline in the UPDRS (part II and III) was -3.98 and 1.31 respectively. The difference between the rotigotine and placebo groups was significant; -5.28, 95% confidence interval (CI) -7.60, -2.96, $p<0.0001$.

The second trial randomised patients (2:2:1) to rotigotine transdermal patch 2-8mg/24hrs (8mg/24hrs given as two 4mg/24hr patches), ropinirole (dose titrated from 0.75 to 24mg/day) or placebo. The dose escalation period for rotigotine lasted up to 4 weeks and for ropinirole 13 weeks, resulting in the dose maintenance period of at least 33 and 24 weeks for rotigotine and ropinirole respectively. The trial was powered to test for non-inferiority between rotigotine and ropinirole. The numbers of patients randomised to rotigotine, ropinirole and placebo were 215, 228 and 118, respectively, and the percentages of 20% responders in the UPDRS (part II and III) were 52%, 68% and 30% respectively. The mean changes from baseline in the UPDRS (part II and III) were -6.83, -10.78 and -2.33, respectively. The difference between the rotigotine and placebo groups was significant; -4.49 (95% CI -6.64, -2.35, $p<0.0001$). The difference between rotigotine and ropinirole was 3.96 (95% CI 2.18, 5.73). Non-inferiority between rotigotine and ropinirole was not shown, and the European Medicines Agency (EMEA) commented in the European Public Assessment Report (EPAR) that ropinirole was superior to rotigotine.

In both studies the positive treatment effect of rotigotine was predominantly due to improvement in motor function, which was also the case for ropinirole in the second study. The mean change from baseline in UPDRS part III scores for rotigotine in studies one and two were -3.5 and -5.3 points, respectively, and for ropinirole was -8.0. This compares with the mean changes from baseline of UPDRS part II scores (ADL) for rotigotine of -0.3 and -2.0 for the two studies and for ropinirole, -3.0.

Both studies had an open-label extension designed to assess the safety and tolerability of long-term treatment of rotigotine and a pooled analysis of the studies was included in the EPAR for rotigotine. All patients began treatment with rotigotine 2mg/24 hours and were titrated to a maximum dose of 6mg/24 hours, during the first year of open label treatment. The percentage of 20% responders in the UPDRS (part II and III) at six months was 56% and 59% and 49%, for patients previously treated with rotigotine, ropinirole and placebo in the double blind part of the trial. At 12 months the respective values were 49%, 67% and 45%. The responder rate at 18 months was available for previously treated rotigotine patients only, and was 42%.

Summary of evidence on comparative safety

In a pooled analysis of phase II and III subjects with early-stage PD from three clinical trials (including the two trials detailed previously) adverse events were reported in 83% of patients treated with rotigotine and 76% and 74% treated with ropinirole and placebo, respectively. Treatment emergent adverse effects (≥ 5%) occurring in a higher frequency in rotigotine versus placebo treated patients included nausea, application site reactions, somnolence, dizziness, headache, vomiting, insomnia, fatigue, back pain and constipation. The incidences of these side effects were comparable between the rotigotine and ropinirole groups, with only application site reactions (37% vs 8%), headache (14% vs 9%) and insomnia (10% vs 6%) being more common in the rotigotine group and constipation (5% vs 9%) being more common in the ropinirole group.

The percentage of patients in the pooled analysis for whom treatment-emergent adverse affects resulted in the discontinuation of trial medication was the same for rotigotine and ropinirole (13% for both). Adverse effects leading to discontinuation, and which occurred in at least 1% of patients, included application site reactions (5% for rotigotine vs. 0% for ropinirole) nausea (2% for rotigotine vs. 3% for ropinirole) and vomiting (1% for both).

Summary of clinical effectiveness issues

In both studies the majority of patients in the rotigotine group were titrated to the highest dose of rotigotine; in the first trial 92% received rotigotine 6mg/24 hours and in the second trial 93% received 8mg/24 hours. The EMEA commented in the EPAR, that the available data for the lower doses (2mg/24 hours and 4mg/24 hours) suggest that rotigotine 4mg/24 hours may be an effective dose in some patients.

The EMEA also noted that although some benefits of transdermal drug administration were acknowledged including once daily doses and circumvention of oral administration with no relevant drug or food interactions, the benefit of continuous drug delivery resulting in more constant levels of dopamine agonist (and reducing the risk of early-morning motor impairment, occurrence of dyskinesias, somnolence or hallucinations) has so far not been confirmed.

Non-inferiority between rotigotine and ropinirole was not shown in the second trial. The British National Formulary (51st edition) notes that the usual dose range for ropinirole is 9-16mg/day where as the summary of product characteristics for ropinirole (Requip®) states that a therapeutic response may be seen between 3-9 mg/day, although adjunct therapy patients may require higher doses. The maximum dose of ropinirole is 24mg/day.

Summary of comparative health economic evidence

The manufacturer submitted a cost utility analysis based on a Markov state transition model, with a 3-month cycle length. The model compared rotigotine to 1) ropinirole and 2) "dopamine agonist (DA) practice comparator", consisting of a market-share-weighted mix of ropinirole (55%), cabergoline (22%) and pramipexole (24%).

The model considered a lifetime horizon, estimated to be approximately 20-years of follow-up, as well as a 5-year and 10-year horizon. Six health states were used in the model to represent progression of Parkinson's disease. These corresponded to the 5 Hoehn and Yahr (HY) stages 1-5 and a death state. A base case scenario considered initiation of PD monotherapy treatment with 6mg rotigotine/day in HY stage 2 and full compliance. Alternative scenarios considered initiation of PD treatment in HY stage 1 or 50% stage 1 and 50% stage 2, 8mg rotigotine monotherapy and differential compliance (60% oral DAs and 80% rotigotine). The patients evaluated in the base case scenario were in HY stage 2.

For the base case and a lifetime horizon there was an incremental cost saving of £7,246 and incremental QALYs of 0.07 when rotigotine was compared to ropinirole.

For the base case and a lifetime horizon there was an incremental cost saving of £2,823 and incremental QALYs of 0.07 when rotigotine was compared to DA practice comparator.

Univariate and multivariate sensitivity analyses were performed on efficacy, safety and nursing home costs. A probabilistic sensitivity analysis was performed assessing the joint uncertainty distributions of incremental costs and QALYs gained.

The link between the: clinical effectiveness of the adjunct therapy model, the clinical effectiveness of the monotherapy model and the drug acquisition costs used is uncertain and therefore the economic case has not been demonstrated.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer presented a budget impact estimate which assumed that the replacement of ropinirole with rotigotine would result in cost savings over the first 5-years of up to £1.8m when the 1684 current and incident patients are treated with rotigotine. About £1.5m in savings can be expected when only incident patients are treated with rotigotine instead of ropinirole.

Guidelines and protocols

NICE clinical guideline (June 2006) *Parkinson's disease; diagnosis and management in primary and secondary care*.

The guideline development programme for the Scottish Intercollegiate Guidelines Network includes a guideline on Parkinson's disease, with publication due in 2008.

Additional information

In February 2006, after review of a full submission the Scottish Medicines Consortium issued the following advice;

Rasagiline is not recommended for use within NHS Scotland for the treatment of idiopathic Parkinson's disease as monotherapy (without levodopa). Rasagiline provides symptomatic improvement for patients with early PD. However, there are no comparative data with the other monoamine-oxidase-B inhibitor, which is less expensive. The economic case has not been demonstrated.

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 16 June 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted reference was supplied with the submission. The reference shaded grey is additional to that supplied with the submission.

European Medicines Agency. European Public Assessment Report; EMEA/H/C/826

Watts RL, Wendt J, Nausieda PA. Efficacy, safety, and tolerability of the rotigotine transdermal patch in patients with early-stage, idiopathic Parkinson's disease: a multicenter, multinational, randomized, double-blind, placebo-controlled trial. Mov Disord 2004;19:S258