Scottish Medicines Consortium

rotigotine, 1mg, 2mg and 3mg per 24 hours transdermal patch (Neupro®) No. (548/09)

UCB Pharma Ltd

09 April 2009 *(Issued 10 July 2009)*

The Scottish Medicines Consortium (SMC) 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 use within NHS Scotland for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS) in adults.

It should only be used in patients with a baseline score of 15 points or more on the International Restless Legs Scale (IRLS). Compared with placebo, rotigotine was associated with improvements on a patient-administered scale based on the core clinical features of the syndrome and on the incidence of periodic limb movements during time in bed.

Other dopamine agonists licensed for use in RLS are available at a lower cost.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults.

Dosing information

A single daily dose delivered via a transdermal patch should be initiated at 1mg/24 hours. Depending on the individual patient response, the dose may be increased in weekly increments of 1mg/24hours to a maximal dose of 3mg/24hours.

Product availability date

June 2009

Summary of evidence on comparative efficacy

Restless Legs Syndrome (RLS) is a chronic neurological disorder characterised by unpleasant sensations in the legs accompanied by an irresistible urge to move them. These symptoms characteristically become worse at rest. Moderate to severe RLS can result in sleep impairment and a negative impact on Quality of Life (QoL). Rotigotine is one of three non-ergotamine dopamine agonists licensed for this indication.

Three pivotal phase III randomised, double-blind, parallel group studies have compared the efficacy of rotigotine to placebo following dose titration and a pre-specified maintenance treatment period in patients with moderate to severe idiopathic RLS defined as International Restless Legs Syndrome Rating Scale (IRLSRS) scores ≥15. Patients were aged 18 to 75, had either responded to or not been treated with previous dopaminergic therapy for RLS and had Clinical Global Impression (CGI) Item 1 scores ≥4 indicating that they were at least moderately ill.

The IRLSRS is a patient-administered scale of ten questions that reflect the subjective assessment of sensorimotor features of the condition and the associated sleep problems and impact on mood and daily life. Individual scores range from 0 to 4 with increasing severity, and are totaled to give an overall score ranging from 0 to 40 points. The CGI Item 1 scale is used in a number of therapeutic settings to assess severity of illness with scores ranging from 0=not assessed and 1=normal to 7=among the most extremely ill.

The co-primary end points in two of these studies were change from baseline to the end of the six-month maintenance period in IRLSRS and CGI Item 1 scores, on a modified intention-to-treat principle with last observation carried forward. The first trial assessed active doses of 1mg/24 hours, 2mg/24hours and 3mg/24 hours while the second also assessed the unlicensed dose of 0.5mg/24 hours. The primary analysis was designed to demonstrate superiority of rotigotine over placebo for both end points at a one-sided significance level of 0.025, with sequential testing of each dose level.

The purpose of the third study was to obtain objective sleep data and particularly to assess periodic limb movements (PLM) during time in bed. This is a disorder involving involuntary repetitive leg twitching and the primary end point was the number of PLM per hour in bed. In this trial the dose of rotigotine was optimized for each patient within the range 1mg/24 hours to 3mg/24 hours.

Rotigotine was superior to placebo for the change from baseline in IRLSRS and in CGI Item 1 score at all three doses assessed in the first trial and at doses of 2mg/24 hours and 3mg/24 hours in the second. Baseline IRLSRS scores were 28 in all groups in the first trial and 23 to 24 in the second: the reductions in LSM IRLSRS over placebo are shown in the table below, where placebo was associated with reductions of 8.6 and 9.0 respectively.

Table 1: Least Squares Mean change from baseline in International Restless Legs Syndrome Rating Scale scores: Net effect over placebo (95% CI)

	Rotigotine 1mg/24 hours	Rotigotine 2mg/24 hours	Rotigotine 3mg/24 hours
First study	-5.1 (-7.6 to –2.7)	-7.5 (-10 to –5.1)	-8.2 (-11 to –5.7)
Second study	-2.3 (-4.6 to 0.0)	-4.5 (-6.9 to –2.2)	-5.2 (-7.5 to –2.9)

For CGI Item 1, baseline scores were 5.0 to 5.1 in the first study and 4.6 to 4.7 in the second. The reductions in LSM scores over placebo are shown in the table below where placebo was associated with reductions of 1.3 and 1.4 respectively.

Table 2: Least Squares Mean change from baseline in Clinical Global Impression Item 1 scores: Net effect over placebo (95% CI)

	Rotigotine 1mg/24 hours	Rotigotine 2mg/24 hours	Rotigotine 3mg/24 hours
First study	-0.76 (-1.1 to –0.38)	-1.1 (-1.4 to –0.69)	-1.2 (-1.6 to –0.83)
Second study	-0.32 (-0.69 to 0.05)	-0.65 (-1.0 to –0.28)	-0.90 (-1.27 to –0.54)

In the third study, the primary end point, rate of PLMI, was reduced from a baseline of 51/hour to 7.7/hour at the end of the four-month maintenance phase with rotigotine which was significantly superior to the change from 37/hour to 33/hour with placebo. The net effects (95% Confidence Intervals [CI]) over placebo for changes in LSM IRLSRS and CGI Item 1 were -6.1 (-11 to –1.5) and -0.89 (-1.6 to –0.17) respectively.

At licensed doses in the three studies, rotigotine also showed significant advantages over placebo for the proportion of patients who were IRLSRS and CGI Item 1 responders (≥50% improvement) and who were remitters (with a IRLSRS score of ≤10 at the end of maintenance phase) or were symptom-free (IRLSRS score=0). There were also advantages for rotigotine over placebo for sleep parameters and quality of life assessments.

An open-label extension to a randomised double blind phase II dose-finding study recruited patients who completed the original trial if they were IRLSRS non-responders at study end or, if they had responded, had worsened within a week of down-tapering of their dose. They were then titrated or re-titrated to an optimal dose of rotigotine within the range 0.5mg/24 hours to 4mg/24 hours (upper and lower doses unlicensed). In an interim analysis at three years IRLS scores decreased by 14.8 points from the open-label baseline of 28 points, and improvements were recorded for other outcome measures including CGI Item 1 scores.

Summary of evidence on comparative safety

The adverse events observed during clinical trials are typical of dopaminergic agents delivered transdermally. The most common adverse events were application site reactions, followed by nausea, headache, fatigue, insomnia, dry mouth and nasopharyngitis. The European Public Assessment Report (EPAR) from the European Medicines Agency indicates that in terms of safety, no new concerns emerged with rotigotine in the RLS population in comparison with the safety profile in the Parkinson's Disease population where the maximum rotigotine dose is much higher (16mg/24 hours).

Summary of clinical effectiveness issues

Patients were required to be responders to previous dopaminergic treatment or to be previously untreated, thus favouring recruitment of a 'responder rich' population. The proportion of dopamine agonist pre-treated patients varied between the two main rotigotine studies which had IRLS as primary endpoint (71% of patients in the first study and 36% in the second). Both clinical study reports state that no clinically important differences between sub-groups were detected (including sub-group by pre-treatment) and that results of the sub-group analyses were consistent with the main IRLS results.

There are no direct comparative data versus any other agents used to treat RLS. An indirect comparison using recognised methodology indicates that rotigotine is associated with a greater improvement in IRLSRS relative to placebo than either ropinirole or pramipexole, though this is subject to limitations inherent in indirect comparisons.

Augmentation is a phenomenon involving worsening of symptoms on treatment including appearance of symptoms earlier in the day. Guidelines from the European Federation of Neurological Societies (EFNS) published in 2006 indicate that augmentation has not been well studied for any of the non-ergot dopaminergic agents. The European Public Assessment Report (EPAR) for rotigotine states that, although an absence of augmentation and rebound following discontinuation was shown with the available short-term data, these effects cannot be ruled out with dopamine agonists.

The health economic model assumes a lower incidence of augmentation with rotigotine than with ropinirole and pramipexole based on indirect comparison, however this comparison has significant flaws including differences in the definitions of augmentation used and in study methodology and duration.

Clinical experts indicated that the availability of a medicine for transdermal administration in this condition may be useful in patients unable to swallow tablets.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis over a 1 year time horizon comparing rotigotine with ropinirole and with pramipexole in patients with moderate to severe RLS. Indirect comparisons were necessary as direct comparative data were not available. Utility values were derived from a mapping exercise where improvements in RLS symptoms based on the IRLSRS scores were mapped to the EQ5D. Resource use was largely based on clinical opinion but only differed slightly between treatments due to adverse event treatment costs, with routine monitoring costs assumed to be the same for all treatments. For the comparison versus ropinirole, the manufacturer estimated an ICER of £5,725 per QALY

based on an increased cost of £506 and a QALY gain of 0.088. For the comparison versus pramipexole, the manufacturer estimated an ICER of £9,729 based on an increased cost of £603 and a QALY gain of 0.062.

An augmentation rate of 1.5% was applied to the rotigotine arm of the model based on a post-hoc analysis of the two pivotal studies, and a weighted average rate of 10.4% was estimated for ropinirole and pramipexole based on data from the literature. The costs of different strategies for managing augmentation were included but the analysis effectively assumed that patients derived no benefit from these strategies as they remained in the augmentation health state with a low utility value of 0.3 for the remaining 6 months of the model.

There were some weaknesses with the analysis:

- The main sources of uncertainty were the augmentation rates used in the base case analysis. Given the low utility value attached to this health state and the higher rate of augmentation associated with ropinirole and pramipexole, this could bias the analysis in favour of rotigotine. However, additional sensitivity analysis was provided by the manufacturer which increased the augmentation utility value to 0.35 and decreased the rate of augmentation for ropinirole and pramipexole to 2%. This increased the ICERs to £8k and £15k per QALY for the comparisons with ropinirole and pramipexole respectively.
- The effectiveness estimates obtained from the indirect comparisons showed that rotigotine was associated with a greater improvement in IRLSRS scores than either ropinirole or pramipexole. The manufacturer provided additional sensitivity analysis to test the effectiveness estimates and this showed that when the estimated difference between treatments was removed the ICERs increased to £20k and £24k per QALY versus ropinirole and pramipexole respectively.
- In order to combine the two aspects of uncertainty the manufacturer was asked to provide a scenario analysis where the estimated difference in effectiveness between the treatments was reduced by 50% and the augmentation rates were equalised. This increased the ICERs to £15k and £30k per QALY for the comparisons with ropinirole and pramipexole respectively.

The baseline utility value used in the economic analysis was 0.42, based on the average of a number of published RLS utility values. This seems particularly low for this condition and it was unclear why the manufacturer did not use the EQ5D data from the mapping exercise to estimate a baseline utility value. The gains from treatments based on the mapping exercise were also quite large with treatments estimated to result in utility gains of between 0.37 and 0.44. However, these absolute values were similar to those seen in previous submissions to SMC for products indicated in RLS and the utility gains of rotigotine over pramipexole and ropinirole were 0.04 and 0.07 respectively, which are relatively small.

Overall, while there were concerns with the effectiveness estimates based on the indirect comparison and the augmentation rates used in the base case analysis, sensitivity analysis provided reassurance that rotigotine remained cost-effective when more conservative assumptions were used. As such, the economic case was considered adequately demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: RLS-UK/Ekbom Syndrome Association.

Additional information: guidelines and protocols

European Federation of Neurological Societies (EFNS) care guideline on management of restless legs syndrome and periodic limb movement disorder in sleep, published 20 September 2006.

Additional information: comparators

Pramipexole and ropinirole are both licensed for RLS.

There are no other licensed comparators although other dopaminergic drugs, benzodiazepines, opioids and antiepileptics are used off-licence.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
rotigotine	**1mg/24 hours to 3mg/24 hours transdermal patch applied daily**	**1,004 to 1,267**
ropinirole ^	0.25mg to 4mg once daily orally	120 to 819
pramipexole	0.088mg to 0.54mg of base once daily orally	116 to 695

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 2 February 2009. Rotigotine 1mg/24 hours and 3mg/24 hours patches are not currently available; anticipated list prices from UCB Pharma Ltd. ^Costs for Adartrel® calculated as the only ropinirole product licensed for RLS.

Additional information: budget impact

The manufacturer estimated a net medicines budget impact of £416k in year 1 rising to £3.1m in year 5 based on estimated patient numbers of 765 and 5,715 respectively. These figures were based on an assumption that approximately 20% of all RLS patients require treatment and, of these, 50% are currently receiving treatment with ropinirole or pramipexole. Market share was estimated to be 7% in year 1 rising to 37% in year 5. These figures are expected to significantly overestimate the actual budget impact of rotigotine as prescribing for RLS is generally conservative and patients with mild symptoms often do not present for treatment.

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 18 February 2009.

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.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Trenkwalder C, Benes H, Poewe W et al. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2008 Jul;7(7):595-604.

Stiasny-Kolster K, Kohnen R, Schollmayer E et al. Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome: a double-blind, placebo-controlled pilot study. Mov Disord. 2004 Dec;19(12):1432-8.

Oertel WH, Benes H, Geisler P et al. Rotigotine patch safety and efficacy in the treatment of moderate to severe idopathic restless legs syndrome results from a multinational placebo-controlled multicentre dose-finding study. Sleep Medicine. 2005;S62(S1\S215).

Garcia-Borreguero D, Poewe W, Hoegl B et al. SP710; Long-term safety and efficacy of rotigotine in idiopathic RLS: 3-year results from a multinational open-label trial. 12th International Congress of Parkinson's Disease and Movement Disorders, The Movement Disorder Society, Chicago, USA, June 22 - 26. 2008.

The European Medicines Agency (EMEA) European Public Assessment Report. rotigotine (Neupro®). 29/08/2008, EMEA H-C-626/II/0019. www.emea.europa.eu.