Scottish Medicines Consortium

Re-submission

ropinirole tablets (Adartrel^{Ò})

GlaxoSmithKline **No. (165/05)**

New indication: moderate to severe restless legs syndrome

10 February 2006 *(Issued June 2006)*

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 re-submission

ropinirole (Adartrel^{Ò}) is accepted for restricted use within NHS Scotland for the treatment of moderate to severe idiopathic restless legs syndrome (RLS). Its use should be restricted to patients with a baseline score of 24 points or more on the International Restless Legs Scale (IRLS).

Compared with placebo, ropinirole was associated with a 4-point improvement on the 40-point IRLS in a pooled analysis restricted to patients with IRLS score of 24 points.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Ropinirole tablets (Adartrel®)

Indication

Symptomatic treatment of moderate to severe idiopathic restless legs syndrome, typically represented by patients who suffer insomnia or severe discomfort of the limbs.

Dosing information

Treatment initiation (week 1)

The recommended initial dose is 0.25mg once daily for 2 days. If well tolerated the dose should be increased to 0.5mg once daily for the remainder of week 1.

Therapeutic regimen (week 2 onwards)

Following treatment initiation, the daily dose should be increased until optimal therapeutic response is achieved, in increments of 0.5mg each week up to 3mg then, if necessary, by an increment of 1 mg to a maximum daily dose of 4mg. The average dose in clinical trials was 2mg.

UK launch date

May 2006

Comparator medications

There are no licensed comparators for the treatment of restless legs syndrome. Current off-label treatments include other dopaminergic drugs used in parkinsonism and some anticonvulsants, e.g. carbamazepine and gabapentin.

Cost of relevant comparators

There are no licensed comparators. From information supplied by the manufacturer in the submission the cost per patient of 52 weeks' treatment would be £204-£1023 over the dose range 0.5 to 4 mg daily. A 1-week titration pack would cost £3.94.

Summary of evidence on comparative efficacy

Restless legs syndrome (RLS) is characterised by unpleasant sensations in the legs and an uncontrollable urge to move. It is more common at rest and during sleep and is associated with disturbance of sleep and adverse effects on the patient's mood and functioning. Ropinirole is a non-ergoline dopamine agonist.

Three phase III, multi-centre, double-blind, trials of 12 weeks duration randomised 267, 286 and 380 patients between the ages of 18 and 80 years who met criteria for primary RLS established by the International RLS Study Group (IRLSSG), to treatment with ropinirole or

placebo. Patients additionally had an IRLSSG Rating Scale (subsequently referred to as the IRLS scale) total score of ≥15 indicating moderate to severe RLS and had experienced a minimum of 15 nights with symptoms during the previous month. If the patient was receiving treatment for RLS, the investigator could use clinical judgement to assess whether the patient would have suffered a minimum of 15 nights with symptoms in the previous month without treatment. Two of those trials were described in the company submission as pivotal, while the third recruited exclusively in the United States.

A fourth smaller, pivotal study with identical inclusion and exclusion criteria additionally required patients to have a periodic leg movement index (PLMI) of ≥5 with associated clinically significant complaints of sleep disruption or daytime consequences of sleep disturbance. The study randomised 65 patients to treatment with ropinirole or placebo.

In all four studies the dose of ropinirole was flexible, ranging from 0.25mg to 4.0mg daily taken one to three hours before bedtime with all patients initiating therapy at 0.25mg daily of ropinirole or matching placebo. Doses were titrated within a set regimen against individual efficacy and tolerability then maintained at a stable dose for four weeks prior to the week 12 assessment. Patients were required to discontinue any current RLS medications or those affecting sleep before study entry.

In the three larger trials the primary endpoint in the intention-to-treat (ITT) population with last observation carried forward (LOCF) for missing data, was the mean change from baseline in the IRLS scale total score at week 12. The IRLS scale is a physician administered, subjective scale based on the core clinical features of RLS. The scale consists of 10 questions that reflect a subjective assessment of the primary sensorimotor features of the disorder, the associated sleep problems and the impact of symptoms on mood and daily life. Answers to the questions are graded from 0, representing absence of a problem to 4, a very severe problem. The patient responses are combined to give an overall IRLS scale total score ranging from 0-40 points. In the smaller trial the change in IRLS was a secondary endpoint and the main objective was to investigate improvements in the motor symptoms of RLS.

Data on the change in IRLS scores from baseline to 12 weeks were pooled for the four studies described above, and the relationship between baseline IRLS score and IRLS response was investigated in a single covariate analysis. This indicated that there was a linear increase in the magnitude of the IRLS response with increasing baseline severity. As a result the pooled data were re-analysed with stratification for baseline IRLS score of 14-23 and 24-40. The lower limit reflected the entry criteria for the studies making allowance for 4 patients below the threshold for entry but included in the analysis.

The adjusted treatment difference at week 12 compared to placebo of -4.0 ($p<0.0001$) was statistically significant, in favour of ropinirole in the pooled analysis relating to patients with a baseline IRLS score in the range 24-40. The secondary endpoints included change from baseline in the IRLS scale total score at week 1 using observed cases: -4.0 ($p<0.0001$); the percentage of responders, defined as patients 'very much improved' or 'much improved' on the Clinical Global Impression of Improvement (CGI-I) scale at week 12: 60% vs 43%; and CGI-I at week 1: 35% vs 19% (all LOCF). Ropinirole showed numerical advantages over placebo in treating the motor symptoms of RLS and significant advantages for sleep parameters.

Patients who had successfully completed a previous study of ropinirole in RLS were eligible for inclusion in two 52-week open-label continuation studies (n=307, n=80). In an analysis of the ITT population with LOCF for missing data the mean (SD) adjusted change from baseline to week 52 for IRLS scale total score were –10 (SD=10), and –12 (9.3) respectively.

Summary of evidence on comparative safety

In the pooled analysis (unstratified for baseline IRLS score) the proportion of patients who reported at least one adverse event (AE) was 83% for the ropinirole groups (n=496) compared to 71% in the placebo groups (n=500). The most frequently reported AEs in the ropinirole groups were nausea (40% compared with 8.0% for placebo), headache (20% in both groups), vomiting (12% vs 1.6%), somnolence (12% vs 6.2%) and dizziness (11% vs 4.8%). There were three reports of worsening of RLS symptoms during treatment in 496 patients treated with ropinirole in the pooled analysis (0.6%). The incidence of AEs in the two 52-week continuation studies was similar to that seen in the 12-week studies. However, 2.3% and 10% of patients experienced worsening of RLS symptoms.

Summary of clinical effectiveness issues

In the studies for which data were pooled and stratified by baseline IRLS score, the mean IRLS score was adjusted for baseline severity as well as country or study centre, and the significance of this in assessing the stratified analysis is unclear.

In the two pivotal trials which had IRLS score as the primary endpoint, there was a significant treatment difference in favour of ropinirole over placebo of -2.5 and –3 points in the unstratified analysis. A clinical overview provided by the manufacturer states that data from the ropinirole clinical studies have been reviewed by the RLS Advisory Board formed by international clinical experts in the field of RLS, and the company has confirmed that it arranged and funded the board in response to concerns raised by the regulatory authorities. The overview states 'This panel consistently rated the treatment differences seen in ropinirole studies as clinically meaningful' and suggests that a treatment difference of >3 points is clinically meaningful.'

There were three cases of worsening of RLS symptoms (augmentation) with ropinirole in the 12-week pivotal trials. In the two 52-week continuation studies 78%-84% of patients were exposed to ropinirole for approximately 52 weeks and worsening of RLS was reported in 2.3% and 10% of patients. Thus, the incidence of worsening of RLS may increase with prolonged therapy.

In the three pivotal trials 98%-99% of patients were of white origin. Therefore the efficacy and safety of ropinirole in non-white patients is unclear.

Summary of comparative health economic evidence

The manufacturer provided an economic model looking at the cost–effectiveness of ropinirole in patients with moderate to severe RLS (IRLS score = 24). Ropinirole was compared to placebo or 'current practice/ real life' and used patient-level data from two of the trials to populate the model. The current practice scenario modelled treatment in RLS patients likely to be identified in clinical practice using a three-question algorithm and made the assumption that the average basket of current drug treatments (e.g. antidepressants, anticonvulsants, analgesics, quinine) was no more effective than placebo. Cost data were largely taken from the resource use collected in the clinical trial. Utility values were obtained by mapping the domains of the disease-specific IRLS measure into the EQ5D tool. This mapping exercise was carried out by 2 groups; a panel of 4 clinicians and a panel of 9 Scottish GPs. The utility

estimates from the clinicians were used in the baseline analysis as they were more conservative. Baseline mean utility values for patients with RLS were 0.47 and 0.32 from each group respectively. The model looked at the costs and benefits over the 12-week period of the clinical trial and also extrapolated to one year.

The results of the model indicated an incremental cost-effectiveness ratio (ICER) of ropinirole versus placebo of £6500 per QALY at one year and £5500 per QALY compared to current practice. Sensitivity analysis indicated that there was a high likelihood that ropinirole was cost-effective at a willingness to pay of £20000 per QALY. One-way sensitivity analysis indicated that if the utility gain with ropinirole was reduced by 10%, the ICER doubled. If the effectiveness of current practice was increased by 20%, this led to a doubling of the ICER in the real life analysis. Use of the utility values from the GP mapping exercise reduced the ICER by a small amount.

The baseline utility values seem rather low, and the marked sensitivity of the ICER to changes in the utility gain is a potential weakness in the economic model. However, the analysis indicates that ropinirole is likely to be a cost-effective treatment for RLS in patients with a baseline IRLS score = 24.

Patient and public involvement

Patient Interest Group Submission: Ekbom Support Group.

Budget impact

The manufacturer provided budget impact estimates that included both the cost of drugs and also the cost of any additional GP visits required. The figures were net of the cost of current spending on dopaminergic therapy and associated GP visits and assumed a mean daily dose of ropinirole of 2mg. The estimated net budget impact was £86,500 in year 1 for 226 patients treated rising to £1.04 M in year 5 for 835 patients treated.

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 19 May 2006.

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

The undernoted references were supplied with the submission.

Trenkwalder C, Garcia-Borreguero D, Montagna P et al. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. J Neurol Neurosurg Psychiatry. 2004;75:92-97.

Walters AS, Ondo WG, Dreykluft T et al. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: A 12-week, double-blind, randomized, parallel-group, placebo-controlled study. Mov Disord. 2004; 19(12):1414-1423

Allen R, Becker PM, Bogan R et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with Restless Legs Syndrome. Sleep. 2004; 27(5): 907-914.