Scottish Medicines Consortium

pramipexole salt 0.125mg, 0.250mg, 1.0mg tablets (Mirapexin®) No. (247/06)

Boehringer-Ingelheim

New indication: for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome

10 March 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 full submission

Pramipexole (Mirapexin®) is accepted for use within NHS Scotland for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS). It should only be used in patients with a baseline score of 15 points or more on the International Restless Legs Scale (IRLS).

In three double blind placebo-controlled studies pramipexole was associated with a 4 to 9-point improvement on the patient-administered 40-point IRL scale in comparison with placebo based on the core clinical features of the syndrome.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Pramipexole 0.125mg, 0.25mg, 1.0mg salt tablets (Mirapexin®)

Indication

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS)

Dosing information

Initially 0.125mg of pramipexole salt taken once a day 2-3 hours before bedtime. The dose may be increased every 4-7 days to a maximum of 0.75mg per day.

UK launch date

April 2006

Comparator medications

There are no licensed comparators although benzodiazepines, opioids and anticonvulsants are used off licence. Ropinirole is expected to receive a licence for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in February 2006.

Cost of relevant comparators

Drug	Dose	Cost for 28 days treatment	Cost of one year's treatment
Pramipexole salt	**0.25mg – 0.75mg daily**	**£17.28 - £51.80**	**£225 - £675**

Summary of evidence on comparative efficacy

Restless Legs Syndrome (RLS) is a chronic neurological disorder characterized 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). Pramipexole is a non-ergoline dopamine agonist with preferential affinity for the D_3 receptor subtype.

There have been four, double-blind randomised placebo-controlled studies of varying design; three evaluated the short and long term efficacy of pramipexole in moderate to severe idiopathic RLS and one the effect of withdrawal of pramipexole after 6 months of open-label treatment. None of the studies have been published. The inclusion criteria for all studies were similar and included patients who had a score = 15 on the International Restless Legs Syndrome Rating Scale (RLSRS), a patient-administered scale of ten questions that reflect the 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 are graded 0 to 4, where 0 represents no problem and 4 a severe problem; responses are totalled to give an overall score ranging from 0 to 40 points. Two studies used fixed-dose regimens and two a flexible-dose regimen. Trial durations ranged from 3 to 46 weeks for the double-blind phases and up to 6 months for the open-label phases. The pramipexole salt dose studied ranged from 0.125 to 0.75 mg daily, taken 2-3 hours before bedtime. The main primary outcome measure in three of the trials was the change from baseline in the RLSRS severity rating score. In addition, patients were evaluated using the disease-independent

Clinical Global Impression-Global Improvement (CGI-I) Scale. In more than 80% of RLS patients, a condition known as periodic limb movement (PLM) disorder, an involuntary, repetitive leg twitching is also present. PLMs are associated with worsening RLS symptoms and therefore the remaining study used polysomnography to measure the change in PLM during time in bed Index (PLMI) as the primary outcome. This three-week study in 107 patients found a significantly greater reduction in the PLMI for all doses of pramipexole compared with placebo ($p<0.0001$). The two studies of 6 and 12 weeks in 328 and 339 patients, investigating the short term efficacy of pramipexole in RLS, found a significant reduction in the adjusted mean RLSRS severity rating score in the pramipexole group compared with placebo (-12.3 (SE±0.6) vs -5.7 (SE±0.9), $p<0.0001$ and -13.5 (SE±0.6) vs -9.3 (SE±0.1), $p=0.0001$, respectively). In all three studies, the percentage of CGI-I responders was significantly greater in the pramipexole group compared with placebo (76% vs 43%, $p=0.0038$; 63% vs 33%, $p<0.0001$ and 72% vs 51%, $p=0.0005$), as was the percentage of RLSRS responders, defined as ≥50% reduction in RLSRS severity score (71% vs 33%, 52% vs 29%, and 62% vs 42%, all $p<0.002$)

Long-term efficacy of pramipexole was evaluated in the 46 and 26 week open-label extensions of the three and six week double-blind studies and the initial 6 month open-label treatment in the withdrawal study. Outcomes at six months were presented and showed that compared with baseline substantial reductions in RLSRS severity scores had been achieved and maintained over the 6 months with high RLSRS and CGI-I responder rates reported. In the final study, following on the 6 months of open label pramipexole treatment, 150 responders (RLSRS severity score <15) were randomised to double-blind treatment with pramipexole or placebo to evaluate sustained efficacy and to differentiate between placebo effect and pharmacological treatment. The primary endpoint of "time to target event" evaluated sustained efficacy defined as "minimally worse", "much worse", or "very much worse" on the CGI-I, in combination with an increase of the RLSRS total severity score to > 15. Kaplan-Meier survival analysis showed that the "time to target event or worsening of RLS" was significantly shorter with placebo than pramipexole. Within the first 10 days, 71% of placebo and 9% of pramipexole patients had a target event and at the end of 3 months 86% of placebo patients had reached a target event compared to 21% of pramipexole patients ($p<0.0001$).

Disruption of sleep and reduced QoL are the primary reasons why patients with RLS seek treatment. The effect of pramipexole treatment on sleep and QoL were secondary outcomes in these studies. QoL was assessed using two scales: the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and the Johns Hopkins RLS Quality of Life Questionnaire (RLS-QoL). Pramipexole treatment provided a significant improvement in QoL (RLS-QoL scale) after 12 weeks of treatment (adjusted mean change +20 vs 13.5; ($p<0.0001$) and median change -10 vs 0) with the improvement at 6 months sustained to 9 months in pramipexole responders ($p<0.0001$) Pramipexole improved QoL (measured by the SF-36) for all aspects of physical functioning. However only reduction in bodily pain was significant ($p<0.05$). Overall mental health did not improve significantly but several individual aspects improved significantly, in particular social functioning.

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

Pramipexole has been licensed for the treatment of Parkinson's disease since 1997. No new safety concerns were raised during the clinical trial programme for RLS. Worsening of RLS symptoms was the most common adverse event of severe intensity in both pramipexole (2.3%) and placebo (1.8%) groups with the majority of cases resulting in early withdrawal.

Other data were also assessed but remain commercially confidential.*

Summary of clinical effectiveness issues

The symptoms of RLS vary in severity and duration from person to person. Mild RLS occurs episodically causing little distress, moderately severe symptoms occur once or twice weekly causing significant disruption and severe symptoms occur more than twice a week and result in significant disruption to sleep and impairment of daily living. The mean RLSRS score in the four trials ranged from 23 – 29. In the three double blind trials the RLSRS severity score was significantly reduced by -9, -7 and -4 points on the 40 point scale in comparison to placebo, all greater than a difference of =3 points which it has been suggested is a clinically meaningful difference by a panel of international RLS experts.

Other data were also assessed but remain commercially confidential.*

Summary of comparative health economic evidence

The manufacturer provided a cost-utility analysis comparing pramipexole to no drug treatment or a range of active comparators (ropinirole, cabergoline, pergolide and levodopa) for patients with an RLSRS score of >15. A Markov model was used with transition probabilities derived from the key pramipexole trials and a literature review relating to the comparator medications. The model looked at the cost-effectiveness of treatment over a one, three and five year time horizon. Utility values were derived by mapping RLS scores into the EQ5D instrument. This resulted, for example, in a health state valuation of 0.904 for mild RLS or 0.699 for severe RLS. Resource use was estimated using trial data for drug dosing and by clinical consensus assumptions for non-drug items such as GP visits or neurology outpatient attendances.

The results of the model indicated a cost per quality adjusted life year (QALY) of £7800 at one year or £6100 at five years versus no treatment (a QALY gain of 0.037 at one year). Limited data were available to assess the transition probabilities of patients after the first cycle of the model and therefore these figures assumed that no treatment patients had worse transition probabilities than pramipexole patients. If the transition probabilities were assumed to be the same as for pramipexole patients, the corresponding ratios were £17100 and £24000. Compared to ropinirole, pramipexole was the dominant treatment at one year (cheaper, more effective) or had an incremental cost effectiveness ratio (ICER) of £3600 at five years. Pramipexole was a cost-minimizing alternative to cabergoline or pergolide over all time periods, assuming that all treatments were equally effective. If levodopa were assumed to be 50% as effective as pramipexole then the ICER at one year was £5400 or £12100 at five years. If levodopa were assumed to be as effective as pramipexole the ICERs were £21800 and £49600 at years one and five respectively.

The ICERs for pramipexole compared to the range of treatments that are currently used for RLS appeared broadly acceptable. The model's use of relatively conservative utility estimates was helpful. The model did, however, show sensitivity to assumptions regarding the outcome for 'no treatment' patients and the assumed comparative efficacy of comparator drugs (especially levodopa). The model also assumed that benefits at 12 months were sustained over the longer term, which has not yet been demonstrated.

Patient and public involvement

Patient Interest Group Submission: Ekbom Support Group (ESG)

Budget impact

The manufacturer estimated a gross drug budget impact in years one to five of £294000, £632000, £1020600, £1468000 and £1982000 respectively. These figures assume cumulative patient numbers of 975, 2096, 3386, 4869 and 6574 in years one to five respectively receiving pramipexole, a dose of 0.5mg per day and a compliance rate of 66%. Cost offsets from treatment substitution are likely to be small due to low-cost generic drugs being used as current treatments.

Guidelines and protocols

Included on the RLS: UK website is an algorithm for the treatment of RLS.

Additional information

Ropinirole for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome, typically represented by patients who suffer insomnia or severe discomfort of the limbs was considered at the January meeting of the SMC. Confirmation of the licence date is awaited.

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 7 April, 2006.

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

** 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/