

NEW PRODUCT EVALUATION

ROPINIROLE and PRAMIPEXOLE for restless legs syndrome

Summary

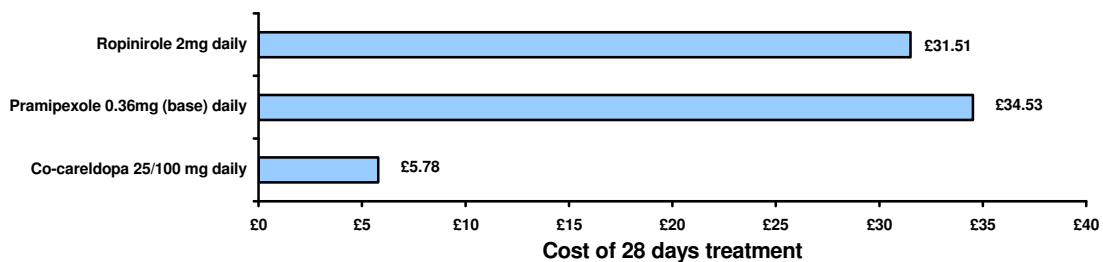
- Ropinirole and pramipexole, both centrally acting dopamine agonists, have recently had their licences extended to include the “symptomatic treatment of moderate to severe idiopathic restless legs syndrome”. Restless legs syndrome (RLS) prevalence in the UK is estimated to be between 3-15%. The RLS:UK suggest that the diagnosis of RLS can be made if the patient fulfils all of the following criteria -urge to move legs, which may be associated with abnormal sensations; symptoms occur at rest or during periods of inactivity and are partially or completely relieved by moving the limb; nocturnal worsening or occurrence of symptoms at night. Secondary causes of RLS, for example anaemia, should be investigated.
- Both drugs have demonstrated statistically significant greater efficacy above placebo in the treatment of restless legs syndrome, although a substantial placebo response was observed. Doses used are lower than those used in the treatment of Parkinson’s disease with a mean daily dose in trials of approximately 2mg for ropinirole. For pramipexole, doses in the range 0.36-0.54mg (of the base) appear to give maximal results, although not all trials are fully published and abstract data are limited.
- From preliminary, unpublished sub-group analysis for ropinirole, patients with more severe symptoms- typically including insomnia or severe discomfort in the limbs-gained the most benefit
- The most common adverse effects with both drugs were nausea, headache, dizziness, and somnolence. Nausea appears to be less common with pramipexole. Patients must be advised to exercise caution while driving or operating machines. For pramipexole, ophthalmologic monitoring is recommended.
- To date there are no trials comparing different dopamine agonists for RLS. The majority of trials have only been short-term (mostly up to 12 weeks). Other studies with these and other dopamine agonists, particularly levodopa have reported augmentation (worsening symptoms, spreading to arms) or rebound effect (recurrence of RLS in the morning) with prolonged use. Patients should therefore be reviewed regularly for continued efficacy or signs of augmentation or tolerance.
- Several unlicensed RLS treatment options do exist, for example gabapentin, benzodiazepines, and other dopamine agonists including pergolide and levodopa and dopadecarboxylase inhibitors, and where efficacious it may be preferable to maintain patients on these therapies.
- The availability of licensed treatments for RLS may be expected to increase patient consultation for the condition but their use may be restricted. Check local recommendations on prescribing.

Product Ropinirole tablets 0.25mg, 0.5mg and 2mg (Adartrel- Glaxo SmithKline),
Pramipexole tablets 0.088mg base (0.125mg salt), 0.18mg base (0.25mg salt) (Mirapexin- Boehringer Ingelheim)

Indication Symptomatic treatment of moderate to severe idiopathic restless legs syndrome

Dosage **Ropinirole-** Initiate at 0.25mg once daily for two days, increasing to 0.5mg once daily for five days, further increases of 0.5mg per week depending upon patient response. Mean daily dose in clinical trials was 2mg; maximum recommended daily dose is 4mg.
Pramipexole- The recommended starting dose is 0.088mg of base (0.125mg of salt) once daily 2-3 hours before bedtime. The dose may be increased every 4-7 days to a maximum of 0.54mg of base (0.75mg of salt) per day. The patient’s response should be evaluated after 3 months treatment and the need for treatment continuation should be reconsidered at this time and on an ongoing basis.

Costs of 28 days treatment (prices from MIMS/ Drug Tariff Jun 2006)



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Produced to provide prescribers with evaluated information soon after the launch of a new product. This review is primarily intended for use within a year of publication. New information may become available and a further literature search may be appropriate.

Introduction

Ropinirole and pramipexole are dopamine receptor agonists licensed for the treatment of Parkinson's disease and, recently, for moderate to severe idiopathic restless legs syndrome. There is no common definition of RLS¹. The RLS:UK suggest that the diagnosis of RLS can be made if the patient fulfils each of the following criteria²:

-urge to move legs, which may be associated with abnormal sensations.

-symptoms occur at rest or during periods of inactivity and are partially or completely relieved by moving the limb.

-nocturnal worsening or occurrence of symptoms at night.

The International RLS Study Group have developed the international restless legs scale, IRLS- a subjective, ten-question questionnaire with total scores up to 40. Symptoms are scored as: mild (1-10 points); moderate (11-20); severe (21-30); very severe (31-40)¹.

Clinical Efficacy

Ropinirole has been investigated in three large, randomised, double-blind, placebo-controlled trials^{1,3}. The trials were very similar in their design; they included patients with an IRLS score of at least 15, were of 12 weeks duration and had a primary outcome measure of mean change from baseline to week 12 in IRLS score. Doses of ropinirole used in the trials ranged from 0.25 to 4mg daily, with mean daily doses, where stated, ranging from 1.9 to 2.1mg.

The TREAT RLS 1 trial involved 286 patients. The adjusted mean change in IRLS score at week 12 was -11.04 in the treatment group and -8.03 with placebo; a difference between the two groups of -3.01 (95% confidence interval (CI) -5.03 to -0.99, P=0.0036)¹.

TREAT RLS 2 was a parallel study to TREAT RLS 1, with identical design which enrolled 267 patients. The adjusted mean change in IRLS score after 12 weeks was -11.2 with ropinirole and -8.7 with placebo, a difference of -2.5 (CI -4.6 to -0.4, P=0.0197)¹.

The most recently published study also has the largest single trial population with 187 patients randomised to ropinirole and 194 to placebo³. Mean baseline IRLS score was approximately 22. The adjusted mean change in IRLS score after 12 weeks was -13.5 in the ropinirole group and -9.8 with placebo, a difference of -3.7 (CI -5.4 to -2.0, P<0.001).

Although the differences between the two groups were statistically significant, the clinical significance of a 2.5 to 3.7 point difference in the IRLS score, with range 0 to 40, is not stated either in the accompanying commentary to the published trials or in the original publication of the IRLS¹.

The trials were consistent in their results, demonstrating a benefit of ropinirole above that observed with placebo. Of note is the considerable placebo effect observed in the trials. Additionally ropinirole demonstrated statistically significant benefits in most of the secondary outcomes which largely consisted of measures and sub-measures of various quality of life assessments, for example the Clinical Global Impression scale and the Medical Outcomes Study Sleep Scale^{1,3,4}.

Unpublished data from a sub-group analysis of all the pivotal trials found that patients with more severe symptoms (IRLS>24) had a greater response⁵. This is reflected in the licence recommendation of patients who suffer insomnia or severe discomfort in the limbs⁶.

The majority of pivotal trial data for pramipexole are only available from abstracts. Data from abstracts are limited and have not been subject to any peer-review process. NB the following doses are quoted as pramipexole base although original articles use the salt doses.

A 6 week double-blind study randomised 345 patients to pramipexole (titrating from 88micrograms to maximum of 0.54mg daily) or placebo⁷. The final mean dosage is not given. The primary endpoint was mean change in IRLS from baseline to endpoint- this was -12.3 (SE 0.6) with pramipexole and -5.7 (SE 0.9) with placebo (P<0.0001). In addition, 62.9% of patients given pramipexole were rated as responders ("much

improved" or "very much improved" on the CGI-I scale) compared with 32.5% taking placebo.

A 12 week, double-blind, fixed dose study randomised 345 patients to pramipexole (0.18mg, 0.36mg or 0.54mg) titrated over the first 4 weeks or placebo⁸. The primary endpoint was mean change in IRLS from baseline. At week 12 the adjusted mean changes from baseline were: placebo -9.3, pramipexole 0.18mg -12.8, 0.36mg -13.8 and 0.54mg -14 (p<0.01 for all treatment group against placebo). Again responder rates on the CGI-I scale were 51.2% for placebo, 74.7% pramipexole 0.18mg, 67.9% 0.36mg and 72.9% 0.54mg.

A small 3 week, dose-finding study found the greatest reduction in IRLS score occurred with the 0.5mg salt dose (approximately equivalent to 0.36mg base)⁹.

A further study enrolled 224 patients to 6 months of open-label pramipexole (dose range 88micrograms-0.54mg)¹⁰. After 6 months, 65% of patients were classified as responders and were randomised (double blind) to continued pramipexole or to placebo. The primary endpoint for this period was time to worsening as defined by an IRLS of >15 and a CGI-I rating of at least "minimally worse". Time to worsening was 5 days with pramipexole and 42 days with placebo to a Kaplan-Meier survival estimate of 0.85. The proportions of patients who worsened were 20.5% in the pramipexole group compared with 85.5% with placebo (P<0.0001).

Adverse Effects/ Contraindications

The most common adverse effects in trials with both drugs were nausea, headache, dizziness, and somnolence. Incidences of nausea were pramipexole 17.2%, ropinirole 30%. Vomiting is also reported with ropinirole. There was a sex difference in incidence of nausea with pramipexole (females 20.8%, males 6.7%). Other adverse effects included fatigue and insomnia^{6,11}. In their use in Parkinson's disease the dopamine agonists have been associated with sudden sleep attacks, hallucinations, dyskinesias, pathological gambling and other compulsive behaviours^{6,11,12}. To date these have not been reported in the RLS population and may be dose-related, but patients must be advised to exercise caution while driving or operating machines. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. For pramipexole, ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur¹¹.

In severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy.

Reports in the literature indicate that treatment of RLS with dopaminergic medications can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities.

Dopamine agonists should be avoided in pregnancy and can inhibit lactation.

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