

DRUG UPDATE

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PRAMIPEXOLE AND ROPINIROLE FOR RESTLESS LEGS SYNDROME

Non-drug treatments and lifestyle changes are the first-line treatments for restless legs syndrome. RLS should only be diagnosed by a suitably experienced clinician. Pramipexole and ropinirole are useful and safe treatments for a proportion of patients; if a dopamine agonist is used, frequent review for signs of worsening symptoms, tolerance and effectiveness are recommended. On current evidence it is not possible to recommend one drug over the other.

What are they?

Pramipexole and ropinirole are centrally acting dopamine agonists.^{1,2} Both drugs have been available in the UK for a number of years for the treatment of Parkinson's disease. In spring 2006 they were granted additional licences for the treatment of moderate to severe idiopathic restless legs syndrome (RLS). Pramipexole doses for this indication range from 88 to 540 micrograms once daily,¹ and doses of ropinirole range from 0.5 to 4 mg once daily.² Recommended doses for the treatment of RLS are substantially lower than those commonly used to treat Parkinson's disease.

What is the rationale for use?

Both drugs have been evaluated for the treatment of RLS in phase III placebo-controlled randomised trials, although there are no direct comparisons between them.

Ropinirole has been evaluated at licensed doses² in three 12 week studies of identical design (n = 932, 464 randomised to treatment with ropinirole and 468 to placebo).³⁻⁵ The primary outcome measure was the change, over 12 weeks, in the International Restless Legs Scale (IRLS) score (range 0 to 40). The results were consistently in favour of ropinirole with mean adjusted changes of -11.0, -11.2, and -13.5. However a substantial placebo effect was also observed with mean adjusted changes of -8.0, -8.7, and -9.8, yielding differences between the mean values of 3.0, 2.5, and 3.7 respectively. No published reports of longer-term treatment of RLS with ropinirole have been identified.

Analysis by GlaxoSmithKline of this data⁶ and including data from another RLS study (n = 65)⁷ suggest that patients with a baseline IRLS score ≥ 24 'can be expected to gain increased clinical benefit from ropinirole compared to placebo'.⁶

Pramipexole has also been studied at licensed doses¹ in three phase III trials currently available as abstracts only.⁸⁻¹⁰ In a 6 week placebo-controlled study (n = 345)⁸ the mean change in the IRLS score was -12.3 with pramipexole compared to -5.7 with placebo, a difference of 6.6. Another study of pramipexole (also n = 345) using the same primary outcome measure was carried out over 12 weeks⁹ to evaluate the

efficacy and safety of three doses of pramipexole. Consequently the change in IRLS score is reported separately for each dose used; 180, 350, and 540 micrograms. The changes observed were -12.8, -13.8, and -14.0 compared to -9.3 with placebo, yielding differences between each mean and placebo of 3.5, 4.5, and 4.7 respectively. Pramipexole has also been studied over the longer term in a 9 month study comprising of a 6 month open label run-in period followed by a 3 month double-blind, placebo-controlled period for treatment responders (n = 147).¹⁰ At the end of the 3 month double-blind treatment period the IRLS score had worsened by 14.9 points for those randomised to placebo and 2.0 points for those maintained on pramipexole, a difference of 12.8.

What is the clinical significance of the results?

IRLS scores of 11-20 are described as moderate, 21-30 as severe and 31-40 as very severe.¹¹ The observed differences in IRLS score from the use of ropinirole and pramipexole with placebo are all statistically significant at the 5% level in each of the above studies (i.e. $p < 0.05$).^{3-5,8-10} However the clinical significance of the observed differences has not been determined.

How safe are they?

Ropinirole and pramipexole have been used for the treatment of Parkinson's disease in the UK for a number of years and a comprehensive adverse effect profile has been established.^{1,2,12} In the three key trials of ropinirole in RLS³⁻⁵ the most important common effects compared to placebo respectively were nausea (40.3%, 7.5%), somnolence (12.6%, 6.9%), dizziness (11.9%, 5.2%), and vomiting (11.0%, 1.7%). In total 6.9% of ropinirole patients withdrew due to an adverse event compared to 5.6% of placebo patients.

Safety data for pramipexole are not so easily extracted because data are currently available in abstract form only. However the most important adverse events, stated as a range, compared to placebo respectively were nausea (8.9% to 19.0% vs. 4.7% to 6.1%) and insomnia (10.5%, 9.3%).⁸⁻¹⁰

A recognised potentially serious adverse effect of therapy with dopamine agonists is the sudden onset of sleep without warning.^{1,2,12} Few of the studies make any reference to this; Bogan et al⁵ reported no occurrences with ropinirole, and Trenkwalder et al¹⁰ reported no occurrences with pramipexole during their 6 month run in phase. However Winkelman et al⁹ (n = 345) reported two occurrences with pramipexole and one with placebo during their 12-week study.

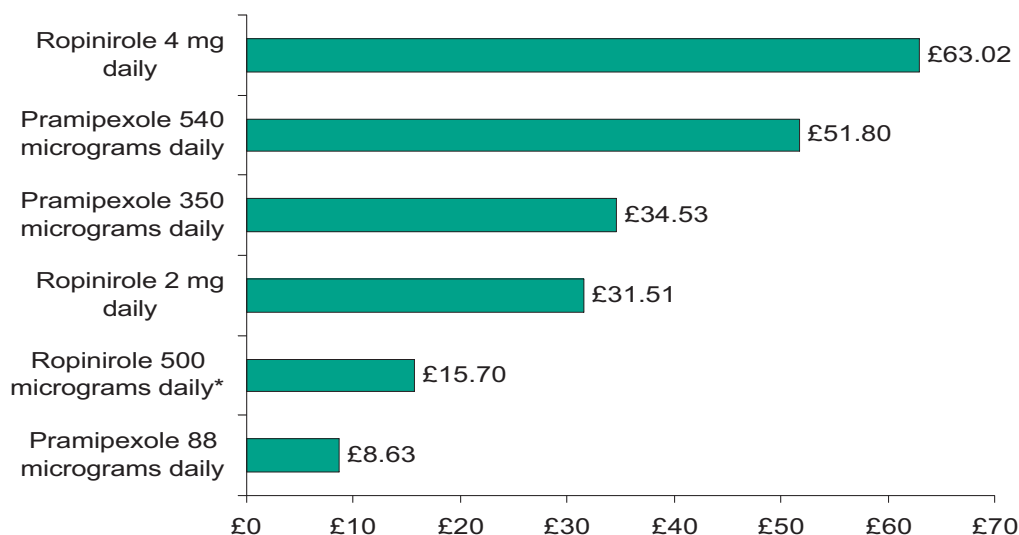
When should they be used?

The diagnosis of RLS relies on some non-specific subjective criteria¹¹ and as such it is advised that diagnosis is made by a clinician with the relevant experience. After consideration of iron-deficiency anaemia first-line treatment should involve measures aimed at improving sleep quality (e.g. avoiding caffeine, keeping cool) and practising techniques such as stretching, exercise, bathing, and massage.¹³ For patients with RLS currently adequately controlled on a drug therapy it

is preferable to maintain those patients on that therapy even if it is not licensed for the treatment of RLS. Newly diagnosed patients requiring drug treatment should be commenced on either pramipexole or ropinirole using the dose initiation schedule specified in the appropriate summary of product characteristics.^{1,2} Both drugs are statistically significantly more effective than placebo for the treatment of RLS in the short term (i.e. ≤ 12 weeks). There is some positive longer-term data in abstract form only.^{6,10,14} Augmentation of symptoms and tolerance may occur with either drug, therefore frequent (e.g. 12 week) reviews of effectiveness with demonstrable clinical benefit are recommended before continuation of therapy.^{1,2} Pramipexole and ropinirole are expensive and adverse effects common. They should be restricted to patients with RLS who have severe symptoms which are unresponsive to practical and non-drug treatment measures.

How much does it cost?

Cost for 28 days treatment
(source: Drug Tariff or *eMIMS, July 2006)



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KEY: Abs - abstract, RCT - randomised controlled trial, R - review

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