Licensed Indication:
Ropinirole is licensed for ‘the treatment of idiopathic Parkinson’s disease:’
- Ropinirole may be used alone (without levodopa) in the treatment of idiopathic Parkinson’s disease.
- Addition of ropinirole to levodopa may be used to control ‘on-off’ fluctuations and permit a reduction in the total daily dose of levodopa.’

Background information
Parkinson’s disease (PD) is a chronic, progressive, neurological disorder which affects 1.8/1000 people in the UK. Levodopa (in combination with a peripheral dopa-decarboxylase inhibitor [DDI]) is the cornerstone of symptomatic therapy. Unfortunately, within 3-5 years of initiating treatment at least 50% of patients develop fluctuations with dyskinesia and end-of-dose akinesia or ‘wearing-off.’ Current management strategies for fluctuating patients involve the use of controlled release formulations, and adjunct therapies such as dopamine agonists and selegiline, to provide additional symptom control. In very difficult cases subcutaneous administration of apomorphine may be required.

The dopamine agonists currently available are mainly ergot derivatives (bromocriptine, lysuride, cabergoline and pergolide). Bromocriptine and lysuride can also be used first line, however they have no proven, only theoretical, advantages over levodopa and their use is often limited by their side effects. Ropinirole is a new selective, non-ergoline dopamine D2 receptor agonist.

Dosage and Administration
Initiation of ropinirole requires dose titration from 0.25mg tds up to 1mg tds with meals. A therapeutic response can be expected at doses between 3-9mg/day, although patients on adjunct therapy may require higher doses. The maximum recommended dose is 24mg/day. Concomitant administration of ropinirole with levodopa may allow a gradual reduction of levodopa dose of around 20%.

Clinical Efficacy
Ropinirole Monotherapy
Ropinirole monotherapy has been compared with placebo, bromocriptine and levodopa in 4 phase II/III double-blind, randomised, controlled trials in patients with early stage (Hoehn & Yahr stage I-III) PD.

In two placebo-controlled trials (n=63,241), ropinirole treatment for 3-6 months significantly improved parkinsonian symptoms, assessed by Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore (p<0.01).1,2 147 patients from the larger study entered a 6 month extension phase. During the 12 month study, 44% of ropinirole treated patients compared to 22% of placebo treated patients (p<0.001) did not require additional symptomatic levodopa/carbidopa therapy to control their symptoms.3

Ropinirole was compared to bromocriptine in a 3 year, multicentre trial involving 335 PD patients. Patients were stratified according to concomitant selegiline use at baseline. Symptomatic levodopa/DDI therapy was permitted during the study if needed. In both treatment groups, the greatest improvement in UPDRS motor and Activities of Daily Living (ADL) scores occurred during the first 6 months and was then maintained at a generally constant level thereafter. At the 3 year endpoint, no significant differences were noted between the two groups for improvement in motor score, however the mean ADL score was significantly better in the ropinirole group compared with the bromocriptine group (p = 0.009). Over the study period, symptomatic therapy with levodopa was required by 34% of patients in the ropinirole group compared with 42% of the bromocriptine group (p = NS).4

Ropinirole was compared to levodopa in a 5 year, multicentre study. Currently the results of the 6 month interim report are fully published5 and the data for the 5 year report are available from a poster presentation6. At the 6 month endpoint, a significantly greater improvement was demonstrated with levodopa/benserazide (n=89) than ropinirole (n=179) assessed by UPDRS motor score, 44% vs 32%. 58% of levodopa treated patients and 48% of ropinirole treated patients were classified as ‘responders’ (>30% improvement in UPDRS motor score) (p = NS), this was lower than anticipated especially for levodopa treated patients and was suspected to be due to sub-optimal dosing.6 At the 5 year endpoint, ropinirole remained significantly less effective than levodopa, assessed by change from baseline in UPDRS motor score (p = 0.008). Conversely, no significant differences were noted for change in UPDRS ADL score, between baseline and completion for either treatment group.
A significantly lower incidence of dyskinesia was reported in ropinirole treated patients, 20% vs 46% (p < 0.0001). Over the study period, symptomatic therapy with additional levodopa was required by 51% of ropinirole treated patients compared to 35% of levodopa treated patients.5

Ropinirole as an adjunct to levodopa
Ropinirole therapy as an adjunct to levodopa has been compared with placebo (2 fully published, 1 abstract) and bromocriptine (1 abstract) in PD patients with motor fluctuations (either end-of-dose akinesia or ‘on-off’ phenomena) not optimally controlled by levodopa.

In the three placebo controlled trials (n=68,46,149), adjuvant therapy with ropinirole for 12 weeks to 6 months significantly reduced levodopa dose and waking time spent in 'off' phase compared to placebo.7,8,9

Ropinirole adjunct therapy has been compared with bromocriptine adjunct therapy in 555 PD patients. The preliminary results of this study are available in abstract form and data on file. The intention to treat population consisted of 219 ropinirole and 126 bromocriptine patients. A poor response was observed in both treatment groups. The primary efficacy parameter of a 20% reduction in levodopa dose was not achieved; the mean percent change in levodopa dosage was less than 11% in each treatment group.10

Adverse Effects
1364 patients have received ropinirole in therapeutic trials: 515 in early therapy and 849 in adjunct therapy studies. In the early therapy studies, nausea, dizziness and somnolence were the most frequently reported adverse events. In adjunct therapy trials, dyskinesias were the most frequently reported side effect with both ropinirole and bromocriptine; 26%, 21%. Dyskinesias usually occurred when the study drugs were being titrated with the levodopa dose held constant. Other common adverse events during adjunct therapy included nausea, hallucinations and dizziness. Hallucinations occurred much more frequently with adjunct therapy than in early therapy and caused the highest number of withdrawals.1,2,4,7,9

Sudden onset of sleep during daily activities has been reported in rare cases. The Summary of Product Characteristics recommends that patients being treated with ropinirole must be informed not to drive and to avoid other potentially dangerous activities.

Costs
At current prices, one year’s treatment with ropinirole 3-15mg daily costs between £602-2409, compared to £928 with bromocriptine 40mg daily and £2405 with pergolide 3mg/day. There are no data comparing the cost-effectiveness of dopamine agonist treatment in Parkinson's disease patients as monotherapy or adjunct therapy.

Summary
In patients with early disease, ropinirole demonstrated improved efficacy compared to placebo and comparable efficacy to bromocriptine in terms of UPDRS motor score. However, ropinirole was less effective than levodopa alone. In late-stage disease, as an adjunct to levodopa treatment, compared to placebo, ropinirole may allow a greater reduction in levodopa dosage and time spent in 'off' phase. However, a preliminary trial comparing ropinirole and bromocriptine as adjuvant therapies revealed a poor, though similar, response to both drugs.

Ropinirole therefore offers an alternative treatment option to bromocriptine and other dopamine agonists in patients with early Parkinson’s disease. More comparative data are required to assess the drug’s value as an adjunct in more advanced cases, and its long term safety.

References
6. Rascol O, Brooks DJ, Korczyn AD, Deyn PP, Clarke CE et al. Ropinirole reduces risk of dyskinesia compared to L-dopa when used in early PD. Poster presented at the XIII International Congress on Parkinson’s Disease, 1999; Vancouver, Canada.