All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Ropinirole prolonged-release (Requip XL®▼) for the treatment of idiopathic Parkinson's disease

GlaxoSmithKline UK

Advice No: 1409 – August 2009

Recommendation of AWMSG

Ropinirole prolonged-release (Requip XL®▼) is recommended for use within NHS Wales for the treatment of idiopathic Parkinson's disease in patients already taking ropinirole immediate-release tablets (Requip®) and in whom adequate symptomatic control has been established.

Substitution of ropinirole prolonged-release tablets for ropinirole immediate-release may be used as:

(i) Monotherapy, alone (without levodopa) in idiopathic Parkinson's disease
(ii) Adjunctive therapy in addition to levodopa to control 'on-off' fluctuations which might permit a reduction in the total daily dose of levodopa.

In order to limit errors, prolonged-release ropinirole should be prescribed by brand as Requip XL®▼.

AWMSG is of the opinion that prolonged-release ropinirole (Requip XL®▼) may be suitable for shared care in accordance with appropriate guidance.

ABBREVIATIONS

ADL	Activity of daily living
AOR	Adjusted odds ratio
AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
CGI-I	Clinical Global Impression - Improvement
CHM	Commissions on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COMT	Catechol-O-methyl transferase
EASE-PD	Efficacy And Safety Evaluation in Parkinson's disease
EPAR	European Public Assessment Report
IR	Immediate release
ITT	Intent-to-treat
LOCF	Last observation carried forward
MAO-B	Monoamine oxidase B
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Clinical Excellence
NMG	New Medicines Group
OD	Odds Ratio
PP	Per protocol
PR	Prolonged release
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SPC	Summary of Product Characteristics
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
WMP	Welsh Medicines Partnership

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.'

Date: Wednesday, 12th August 2009

The recommendation of AWMSG is:

Ropinirole prolonged-release (Requip XL®▼) is recommended for use within NHS Wales for the treatment of idiopathic Parkinson's disease in patients already taking ropinirole immediate-release tablets (Requip®) and in whom adequate symptomatic control has been established.

Substitution of ropinirole prolonged-release tablets for ropinirole immediate-release release may be used as:

(i) Monotherapy, alone (without levodopa) in idiopathic Parkinson's disease
(ii) Adjunctive therapy in addition to levodopa to control "on-off" fluctuations which might permit a reduction in the total daily dose of levodopa.

In order to limit errors, prolonged-release ropinirole should be prescribed by brand as Requip XL®▼.

AWMSG is of the opinion that ropinirole prolonged-release (Requip XL®▼) may be suitable for shared care in accordance with appropriate guidance.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Ropinirole prolonged release (PR) (Requip XL®▼) is indicated for the treatment of idiopathic Parkinson's disease in patients already taking ropinirole immediate release (IR) tablets (Requip®) and in whom adequate symptomatic control has been established[1].

Substitution of ropinirole PR tablets for ropinirole IR release may be used as:

(i) Monotherapy, alone (without levodopa) in idiopathic Parkinson's disease

(ii) Adjunctive therapy in addition to levodopa to control "on-off" fluctuations which might permit a reduction in the total daily dose of levodopa[1].

2.2 Dosing

Ropinirole PR tablets should be taken once daily and at a similar time each day. The tablets must be swallowed whole and not chewed, crushed or divided[1].

Substitution of ropinirole PR for ropinirole IR tablets should be supervised by appropriate specialists in Parkinson's disease.

The dose of ropinirole PR tablets should be based on the total daily dose of ropinirole IR formulation that the patient was receiving. Patients should be maintained on the lowest dose of ropinirole PR that maintains symptomatic control. The maximum daily dose of ropinirole PR is 24mg. For full details of the dosing regimens, see the Summary of Product Characteristics (SPC). Monitoring of the dose after switching is recommended to achieve effective symptomatic control[1].

Ropinirole has not been studied in patients with severe renal or hepatic impairment or in patients under 18 years of age and therefore use in these patients is not recommended[1].

2.3 Market authorisation date

7th May 2008[1].

2.4 UK Launch date

June 2008[2].

3.0 DECISION CONTEXT

Parkinson's disease is a progressive, degenerative and highly debilitating neurological disease characterised by reduced motor function (tremor, rigidity and bradykinesia). Parkinson's disease is predominantly a movement disorder and as the disease progresses patients experience a gradual deterioration in muscle control, movement and balance. Patients may also experience autonomic disturbances and a loss of cognitive function leading to psychiatric problems such as depression and dementia[2, 3]. In the United Kingdom (UK) the age-adjusted prevalence for Parkinson's disease is estimated to be 168 per 100,000[4], which relates to an estimate of 5,055 people with Parkinson's disease in Wales (based on a total population in Wales of 3.009 million)[2]. Analysis of market share data indicates 31% of patients currently treated for Parkinson's disease receive non-ergot derived dopamine agonists. Of these, 4% of patients receive ropinirole PR and this percentage is expected to rise to 10% in 2010 which equates to an estimated 271 patients in 2010, rising to an estimated 1,719

patients in 2014 (assuming an annual 5% increase in uptake) who are likely to be treated with ropinirole PR per year[2].

There is currently no known cure for Parkinson's disease and treatment focuses on regulating dopamine levels and obtaining effective 24-hour symptomatic control. Options for treatment in early stage Parkinson's disease (defined as people who have developed functional disability and require symptomatic therapy) include levodopa, dopamine agonists and monoamine oxidase B (MAO-B) inhibitors (selegiline, rasagiline). Levodopa may be used as a monotherapy or as adjunct therapy with dopamine agonists. In addition, patients with late stage Parkinson's disease (defined as Parkinson's disease in people on levodopa who have developed motor complications) may also be treated with catechol-O-methyl transferase (COMT) inhibitors[2, 3]. The National Institute for Health and Clinical Excellence (NICE) clinical guidelines for Parkinson's disease recommend that non-ergot derived dopamine agonists (i.e. pramipexole, rotigotine, ropinirole) should be the preferred choice of treatment where a dopamine agonist is appropriate[3].

In patients with Parkinson's disease, the cells of the substantia nigra are damaged leading to destruction of neurones which in turn causes a reduction in the production and transportation of dopamine to the striatum. Non-ergot dopamine agonists alleviate dopamine deficiency in the nigral striatal system by stimulating striatal dopamine receptors[1]. Ropinirole is one of three non-ergot derived dopamine agonists currently used for the treatment of Parkinson's disease[3].

It is well established that long-term treatment with levodopa is associated with the development of debilitating motor complications which comprise of motor fluctuations and dyskinesia and manifest themselves as the "on-off" phenomena[2]. Adjuvant drugs to take with levodopa have been developed with the aim of reducing these motor complications and improving quality of life. Ropinirole PR is a new once daily oral formulation for treating Parkinson's disease in patients who are stabilised on the three times daily formulation, ropinirole IR[1]. The company submission suggests that ropinirole PR offers patients an easier and more convenient treatment option with a pharmacokinetic profile that ensures a steady delivery of drug leading to constant symptomatic relief throughout the day[2]. The Medicines and Healthcare products Regulatory Agency (MHRA) guidance notes that dopamine agonists are generally administered two or three times per day. They also state that patients with Parkinson's disease are known to underuse or omit medication and a non-ergot dopamine agonist with a simplified titration regimen and a once daily dosage could be of benefit to these patients[5].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The company submission is based on two phase II studies and three phase III studies. The main evidence submitted relating to the use of ropinirole PR within its licensed indication are the EASE-PD monotherapy study and the PREPARED study. The EASE-PD monotherapy study demonstrated that ropinirole PR is effective in alleviating the primary motor symptoms of Parkinson's disease and that equivalent doses of ropinirole IR and ropinirole PR have similar therapeutic effects. Ropinirole PR was proven to be non-inferior to ropinirole IR and overnight switching from ropinirole IR to ropinirole PR, on an approximate milligram to milligram basis, could be performed effectively with a low incidence of adverse events. However, it must be noted that the mean dose of ropinirole PR was 18.0 (±5.73mg/day), compared with 7.0 (±2.12mg/day) for ropinirole IR in the EASE-PD study which may indicate supratherapeutic dosing with

the PR formulation and difficulty in comparing efficacy of both products on a dose for dose basis. The PREPARED study claimed treatment benefits with ropinirole PR when compared to ropinirole IR and the number of reported adverse events was similar in both treatment groups. Overall, ropinirole PR was well tolerated and any adverse events were representative of those associated with non-ergot derived dopamine agonists.

4.2 Review of the evidence on cost-effectiveness

The company submission describes a simplistic cost minimisation analysis which, in effect, compares a strategy of six months of treatment with ropinirole IR tablets followed by 18 months of treatment with ropinirole PR tablets against 24 months of treatment with pramipexole tablets, or 24 months of treatment with rotigotine patches. Ropinirole IR tablets are assumed not to be a comparator for ropinirole PR tablets in the base case analysis. This would appear to be inappropriate given the licensed indication for ropinirole PR tablets.

In the base case and most of the additional analyses that have been provided, the use of ropinirole PR is estimated to result in costs savings compared with pramipexole or rotigotine. However, there is a range of uncertainties in relation to the estimated costs of the dopamine agonists, which warrants caution in the interpretation of the results. The most plausible scenario analysis of two years of treatment with ropinirole IR as the comparator, results in higher drug acquisition costs compared with switching to ropinirole PR after six months (£4,818 compared with £4,686). However, the full costs of ropinirole PR are underestimated for lack of consideration of the costs associated with the additional monitoring and dose adjustment following switching.

The appropriate application of cost minimisation analysis requires that the dopamine agonists are therapeutically equivalent in all dimensions of health outcome (clinical effectiveness, impact on health-related quality of life, adverse event profile etc.). There is no robust evidence of equivalence for the doses of the dopamine agonists that are considered in the company submission. Assumptions of dose equivalence are extrapolated from expert opinion and appear subject to considerable uncertainty. In addition, only drug acquisition costs are considered in the analysis, which fails to account for the additional monitoring and dose adjustment that may be required when switching from the IR to the PR ropinirole formulation. Further, the approach taken to estimating the drug acquisition costs appears to bias the model significantly against rotigotine patches. Although several supplementary analyses are provided to explore a range of assumed doses and costs, these essentially represent hypothetical scenarios and appear to be of limited value.

5.0 LIMITATIONS OF DECISION CONTEXT

- Ropinirole PR is only licensed for patients already taking ropinirole IR tablets and in whom adequate symptomatic control has been established.
- In the EASE-PD monotherapy study all patients had early stage Parkinson's disease whereas in the PREPARED study all patients had advanced Parkinson's disease. This influenced which measurements were used to determine any changes in motor symptoms or therapeutic benefit and makes it difficult to directly compare the two studies.
- The Commission on Human Medicines (CHM) considered the EASE-PD monotherapy study to be inadequate with regard to proving non-inferiority of ropinirole PR compared to ropinirole IR. The MHRA guidance notes that both the medical and statistical assessors agreed that the design of the EASE-PD

monotherapy study was flawed[5]. The CHM state that the assessment of a new formulation was combined with the assessment of a new titration regimen and it used a model with considerably shorter treatment periods than is recommended in the Committee for Medicinal Products for Human Use (CHMP) guidelines[5] Following advice from the CHM, the company provided further clinical data and statistical analysis to the MHRA to support the claim of non-inferiority, although no further detail is available[5].

- There are no studies which consider the long-term efficacy or safety of ropinirole PR.

6.0 CLINICAL EVIDENCE

The company submission provides details on two phase II and three phase III studies which form the ropinirole PR clinical programme[6-9]. The phase II studies were conducted to characterise the steady-state pharmacokinetics of ropinirole PR in patients with early-stage Parkinson's disease and will not be discussed in detail in this report[6] The following two phase III studies provide the main evidence relating to the use of ropinirole PR within its licensed indication. Table 1A in Appendix 1 provides details of these studies, with a summary of the results. The company include reference to a number of other studies; however these do not directly relate to the use of ropinirole PR and therefore will not be discussed in this report[2].

6.1 Clinical efficacy

6.1.1 EASE-PD Monotherapy Study[2, 8]

This was a phase III multicentre, randomised, double-blind, cross-over study that evaluated non-inferiority of ropinirole PR versus ropinirole IR. A total of 161 patients (≥30 years) with a diagnosis of early stage Parkinson's disease (Hoehn and Yahr stages I to III) were randomised to one of four treatment regimens, following a seven day placebo run-in period:

(i) ropinirole IR – ropinirole IR – ropinirole PR
(ii) ropinirole IR – ropinirole PR – ropinirole PR
(iii) ropinirole PR – ropinirole PR – ropinirole IR
(iv) ropinirole PR – ropinirole IR – ropinirole IR.

Patients entered a 12 week dose titration period with the first formulation in the treatment regimen. The titration regimen differed for each formulation; the dosing regimen for ropinirole IR was in accordance with its approved labelling (0.75-24mg/day) and the dosing regimen for ropinirole PR was based on data from phase II clinical trials and covered a similar dose range (2-24mg/day)[8]. Patients who achieved a stable Unified Parkinson's Disease Rating Scale (UPDRS) motor score at the end of the titration period entered the first of three eight week maintenance periods. After each eight week treatment period patients underwent overnight switching to the closest dose of the alternative ropinirole formulation or underwent a dummy overnight switch. This meant that over the course of the three maintenance periods patients received a dosage of ropinirole which stabilised the disease, irrespective of formulation switches.

The primary efficacy population was the per protocol (PP) population (n=114), which excluded patients with major protocol violations. The primary efficacy endpoint was the mean change in UPDRS total motor score between the period baseline (visit at which the patient entered each flexible maintenance period) and endpoint, as assessed at the end of each maintenance period (last observation carried forward [LOCF]). Following the initial dose titration, treatment with ropinirole PR or ropinirole IR demonstrated little change in UPDRS total motor score within and between each maintenance period despite switches in tablet formulation. Over the three maintenance periods the overall

mean change from period baseline (adjusted for period carryover effect and period baseline score) for ropinirole PR was -0.1 (±0.28) compared with 0.6 (±0.3) for ropinirole IR (95% confidence interval [CI]: -1.51, 0.10; p=0.0842) which falls within the predefined margin for non-inferiority)

Before entering the first flexible-dose maintenance period, patients in both groups showed a clinically relevant reduction in mean change in the UPDRS motor score between study baseline and the end of dose titration [ropinirole PR: -10.4 (±6.04); ropinirole IR -8.9 (±5.9)]. At the baseline of the first maintenance period, the mean UPDRS total motor score was 2.5 units lower with ropinirole PR compared to ropinirole IR; however there was little change in mean score in either treatment group at the end of this maintenance period. When patients switched formulation of ropinirole, their mean UPDRS motor score was maintained, indicating that similar doses of each formulation had similar efficacy.

One of the secondary efficacy endpoints was the proportion of patients with a score of one or two on the Clinical Global Impression-Global Improvement (CGI-I) scale. Overall, the proportion of responders was 63% for ropinirole PR and 60% for ropinirole IR[8].

Points to note:

- All patients in this study were defined as having early Parkinson's disease; the median duration from onset was 2.7 years.
- At the end of the titration phase, although patients had reached a similar mean dosage level for each formulation due to the different titration regimens this equated to significantly different mean daily doses; that for ropinirole PR was 18.0 (±5.73mg/day), compared with 7.0 (±2.12mg/day) for ropinirole IR.
- The higher mean doses received by patients who were initially given ropinirole PR during the titration phase did not provide additional clinical benefit when compared with the lower doses received by those who were given ropinirole IR. It is likely that those patients who started treatment with ropinirole PR reached a clinical ceiling effect; and were therefore given supratherapeutic doses.
- During the initial titration phase and the first maintenance period (prior to the first treatment switch), there were numerical differences in favour of ropinirole PR on the UPDRS motor score and CGI-I scale; however these did not reach statistical significance.
- The PP population was comprised of only 71% of the intention to treat (ITT) population.
- The ceiling effect of ropinirole PR demonstrated in this study suggests that a direct comparison in a more advanced Parkinson's disease patient population may be beneficial.

6.1.2 PREPARED Study[2, 9]

This was a phase III multicentre, randomised, double-blind, parallel group study comparing the efficacy of 24 weeks of treatment with ropinirole PR and ropinirole IR in patients with advanced Parkinson's disease (Hoehn and Yahr stages II-IV) and whom were not adequately controlled by levodopa. A total of 350 patients (≥30 years) were randomised to 2mg/day ropinirole PR (n=177) or 0.75mg/day ropinirole IR (n=173). The primary efficacy population was the ITT population (n=343), which comprised of patients who had received at least one dose of randomised study medication and for whom at least one post-baseline efficacy assessment was available. Patients underwent a four-week fixed-dose titration period through the first four out of 13 dose levels to a minimum dose of 8mg/day ropinirole PR or 3mg/day ropinirole IR. Dosing

was subsequently adjusted until the optimal therapeutic dose was achieved; up to a maximum of 24mg/day of either formulation.

The primary efficacy endpoint was the proportion of patients who maintained ≥20% reduction from baseline in daily awake time spent "off" at week 24 (LOCF and at the time point immediately preceding this endpoint). There was a significant benefit for ropinirole PR over ropinirole IR (adjusted probability of response for patients achieving a ≥20% maintained reduction from baseline in daily awake time spent "off": ropinirole PR: 66%; ropinirole IR 51%). The odds of a patient having a ≥20% maintained reduction from baseline were nearly twice as high in patients receiving ropinirole PR (adjusted odds ratio [AOR]: 1.82; 95% CI: 1.16, 2.86; p=0.009)[9].

Points to note:

- This study has not been published; it was presented as an abstract at the 12th International Congress of Parkinson's Disease and Movement Disorders in June 2008[9].
- This study was conducted in patients with advanced Parkinson's disease.
- Treatment with ropinirole PR significantly increased the proportion of responders on the CGI-I scale compared to ropinirole IR. However, patients treated with ropinirole PR attained higher daily doses (18.6 ±6.5mg/day) compared with patients treated with ropinirole IR (10.4 ±6.4mg/day); therefore the difference in efficacy may be attributed to the mean dosage difference.

6.2 Safety

In addition to the EASE-PD monotherapy[8] and the PREPARED study[9], safety data for ropinirole PR is included from two phase II studies (study 164 and study 165)[6] and a phase III study[7]. In studies 164 and 165, treatment emergent adverse events were reported in 65% and 75% of patients, respectively. In study 164; 98% of the reported adverse events were reported to be mild or moderate and only 19% and 35% of the adverse events were reported to be related to ropinirole PR, from study 164 and 165, respectively[6]. In the phase III study most of the adverse events were reported to be mild or moderate in nature with the most frequently occurring being dyskinesia and nausea. The proportion of patients who withdrew as a result of adverse events or serious adverse events was no greater in the ropinirole PR group compared with the placebo group[7].

In the EASE-PD monotherapy study the incidence of adverse events with ropinirole PR was similar to those reported with ropinirole IR (54% and 56%, respectively). The most common overall adverse events were of similar prevalence for both preparations; nausea (20%) and somnolence (13%); these occurred most frequently in the titration period with very few additional incidences occurring during the final maintenance period. The majority of the reported adverse events were mild or moderate in intensity; those considered to be severe in intensity were reported by eight patients (6%) who received ropinirole PR and in twelve patients (8%) who received ropinirole IR. Serious adverse events were reported for six patients: three while receiving ropinirole PR and three while receiving ropinirole IR. Adverse events led to patient discontinuation in 8.7% of the ITT population and the only adverse events leading to withdrawal of more than one patient per treatment group were hallucinations (three patients receiving ropinirole PR and one patient receiving ropinirole IR) and hypoaesthesia (two patients; both receiving ropinirole IR). No patients required a reduction in dosage after overnight approximate milligram to milligram switching and there was no indication of an increase in the incidence of adverse events immediately following this[8].

In the PREPARED study, adverse events were reported by 128/177 patients (72%) in the ropinirole PR group and 105/173 patients (61%) in the ropinirole IR group. The most common reported adverse events were nausea (17%), dyskinesia (9%), dizziness (8%) and somnolence (7%). In the ropinirole PR group 22/177 patients (12%) withdrew from the study due to an adverse event compared to 15/173 patients (9%) in the ropinirole IR group. Six percent of patients in the ropinirole PR group reported serious adverse events compared to five % in the ropinirole IR group[9].

The SPC states that due to the pharmacological action of ropinirole, patients with severe cardiovascular disease should be treated with caution[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

Ropinirole PR is a non-ergot derived dopamine agonist licensed in patients already taking ropinirole IR tablets and in whom adequate control has been established. Ropinirole IR (with or without levodopa) is therefore considered to be the most suitable comparator for ropinirole PR. Two other non-ergot derived dopamine agonists licensed for the treatment of idiopathic Parkinson's disease are pramipexole and rotigotine. However, the company submission is for patients already stabilised on the IR formulation in accordance with the licensed indication. Ergot-based dopamine agonists are not considered as appropriate comparators as, in line with current guidelines, they are likely to be prescribed only in special circumstances.

7.2 Comparative effectiveness

- The company submission proposes that ropinirole PR is at least as effective as ropinirole IR in the treatment of both early and late stage Parkinson's disease[2, 7,8,9].
- The company also proposes that the option of once daily administration of ropinirole PR rather than a three times daily dosage, as with ropinirole IR and pramipexole, has advantages for patients with Parkinson's disease.
- Non-ergot derived dopamine agonists which can be used as monotherapy or as an adjunct to levodopa are recommended over ergot-derived dopamine agonists because of the additional monitoring required with ergot-derived dopamine agonists due to adverse events[3].
- Ropinirole has not been associated with side effects associated with ergot-based dopamine agonists e.g. skin inflammation, digital vasospasm, paraesthesias, pleural effusion, pulmonary infiltrates or erthromelagia[2].
- There are no head to head trials comparing the clinical effectiveness of ropinirole PR with either pramipexole or rotigotine. Analysis of the effectiveness of ropinirole PR versus these therapies is limited to indirect comparisons based on data from placebo controlled trials.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether the additional benefits offered by ropinrole over the relevant comparator(s) justify the additional costs and if so, whether the total budgetary impact of supporting the use of ropinirole is acceptable (see section 9.0).

8.2. Description and critique of the company's submission

The company submission[2] describes a simplistic cost minimisation analysis which, in effect, compares a strategy of six months of treatment with ropinirole IR tablets followed by 18 months of treatment with ropinirole PR tablets against 24 months of treatment with pramipexole tablets, or 24 months of treatment with rotigotine patches. Ropinirole IR tablets are assumed not to be a comparator for ropinirole PR tablets. This assumption would appear inappropriate given the licensed indication of ropinirole PR tablets, and a scenario analysis does provide information on this comparison.

The appropriate application of cost minimisation analysis requires that the dopamine agonists are therapeutically equivalent in all dimensions of health outcome (clinical effectiveness, impact on health-related quality of life, adverse event profile etc.). There is no robust evidence of equivalence for the doses of the dopamine agonists that are considered in the company submission. The implicit assumption of equivalence is made on the basis that the current NICE clinical guideline on Parkinson's disease does not recommend any one non-ergot derived dopamine agonist in preference to another, and the company considers that the heterogeneous nature of the clinical trials of these agents presents methodological difficulties in making robust comparisons. In the analysis, there is no consideration given to the differences in formulations between the dopamine agonists (e.g. once daily oral administration for the ropinirole PR tablets compared with thrice daily oral administration for pramipexole tablets compared with rotigotine patches applied once daily) that may potentially lead to differences in patient preference and convenience, treatment adherence or quality of life.

Assumptions of dose equivalence are extrapolated from expert opinion and appear subject to considerable uncertainty. In addition, only drug acquisition costs are considered in the analysis, which fails to account for the additional monitoring, supervision and dose adjustment that may be required when switching from the IR to the PR ropinirole formulation. Further, the approach taken to estimating the drug acquisition costs appears to bias the model significantly against rotigotine patches. The range of uncertainties in relation to the estimated costs of the dopamine agonists warrants caution in the interpretation of the results. Although several supplementary analyses are provided to explore a range of assumed doses and costs, these essentially represent hypothetical scenarios and appear to be of limited value.

8.3 Population

The company submission states that the analysis considers patients who meet the licensed indication for ropinirole PR, i.e. patients with idiopathic Parkinson's disease for whom non-ergot derived dopamine agonists are a treatment option either as monotherapy or as adjunct to levodopa[2]. The licensed indication for ropinirole PR tablets stipulates its use in patients already taking ropinirole IR tablets in whom adequate symptomatic control has been established[1].

8.4 Perspective and time horizon

The analysis is conducted from the perspective of NHS Wales, and considers only drug acquisition costs[2]. Treatment of Parkinson's disease is lifelong. It is assumed that, once effective treatment control has been achieved; the overall costs of therapy are unlikely to vary from one year to the next. However, patients who are treated with ropinirole will initially receive the IR formulation until symptomatic control has been achieved. It is assumed in the model that treatment with the IR ropinirole formulation will be for six months, before switching to ropinirole PR occurs. As the acquisition costs of the ropinirole PR and ropinirole IR formulations differ, costs in the first year of treatment would be different to subsequent years. Therefore, a two-year time horizon has been assumed[2].

8.5 Comparator

In effect, the model compares a strategy of six months of treatment with ropinirole IR tablets followed by 18 months of treatment with ropinirole PR tablets against 24 months of treatment with pramipexole, or 24 months of treatment with rotigotine.

It is considered in the company submission that the use of ropinirole PR represents a sequential step in the use of ropinirole treatment and therefore ropinirole IR tablets would not be considered as a comparator[2]. The company submission states that the comparators of interest are those considered most likely to displace ropinirole PR tablets as a treatment for Parkinson's disease, which are considered to be the non-ergot derived dopamine agonists pramipexole and rotigotine[2]. Ergot-derived dopamine agonists are not considered to be comparators in the analysis as the NICE Parkinson's disease clinical guideline indicates that non-ergot derived dopamine agonists should generally be preferred[3], and company market research data reportedly indicate that ergot-derived dopamine agonists make up a small and decreasing share of the market[2].

However, the appropriate comparator would be the treatment that would be displaced by ropinirole PR tablets (i.e. the treatment that patients would be most likely to receive if ropinirole PR tablets were not available). The licensed indication for ropinirole PR tablets states it is for use in patients who are already taking ropinirole IR tablets and in whom adequate symptomatic control has been established[1]. In patients who are stabilised and adequately controlled on ropinirole IR tablets, there would be no reason to switch to pramipexole or rotigotine unless there were adverse effect, tolerability or treatment adherence issues. The economic evidence submitted by the company does not consider adverse effects, tolerability or adherence issues, as it is implicitly assumed within the cost minimisation framework that there are no such differences between the treatments. As patients could continue to receive IR ropinirole tablets, the IR ropinirole formulation is the treatment that would be displaced by ropinirole PR tablets and would be a relevant comparator. Scenario analysis has been conducted in which ropinirole treatment is considered to consist of only the IR ropinirole formulation (see section 8.9.2).

8.6 Clinical inputs

8.6.1 Efficacy data

The implicit assumption in this analysis is that there are no differences in efficacy between ropinirole and the comparators. No specific evidence in support of this assumption is presented in the submission. The company submission states that there are a number of methodological difficulties in conducting comparisons between the dopamine agonists considered in this analysis; there are no direct, head-to-head comparative trials, and the available placebo-controlled trials of the individual agents potentially differ in terms of baseline risks of patients, the dose ranges explored, and the duration of titration and maintenance periods[2]. The company submission also points to the current Parkinson's disease guideline issued by NICE in 2006, which does not recommend any one non-ergot derived dopamine therapy in preference to another[3].

The company submission states that no studies have been conducted to establish dose equivalence between the dopamine agonists[2]. For the base case analysis, the equivalent doses of ropinirole and the comparators are derived from estimates based largely on (published) expert opinion[10]. The daily dose of ropinirole PR is assumed to be the same as the total daily dose of ropinirole IR tablets[2].

There is no consideration given to dose adjustment that may potentially be necessary as a result of switching from ropinirole IR tablets to ropinirole PR tablets. The SPC for ropinirole PR tablets notes that, after switching, patients will initially require more frequent and careful monitoring in order to adjust the dose if necessary[1]. The licensed indication is for use as monotherapy or adjuvant therapy in addition to levodopa to control "on-off" fluctuations which might permit a reduction in the total daily dose of levodopa[1]. The use of dopamine agonists as adjuvants to levodopa therapy (such as in advanced phases of the disease) is not considered separately, which would implicitly assume that each agent has the potential to reduce levodopa doses equally and with equal efficacy.

8.6.2 Adverse events

Adverse events are not considered in the analysis; the implicit assumption is that there are no differences in adverse events between ropinirole PR tablets and the comparators.

8.6.3 Utility weights

Utility weights are not employed in the analysis; the implicit assumption is that there are no differences in relation to health-related quality of life between ropinirole PR tablets and the comparators.

8.7 Healthcare resource utilisation and cost

8.7.1 Drug costs

In the base case analysis, the daily dose of ropinirole is assumed to be 12mg, and the daily dose of pramipexole and rotigotine are assumed to be 2.1mg (base) and 8mg, respectively. These daily doses of the comparators are considered in the company submission to be equivalent to ropinirole 12mg. The basis of this assumption is a publication that describes the opinion of German physicians who attended an expert meeting[10]. It appears from this publication that physicians provided their estimates of the doses of different dopamine agonists that were equivalent to levodopa 300mg. The actual dose range considered by these physicians appears to have been 8-12mg for ropinirole, 1.4-2.1mg (base) for pramipexole and 6-8mg rotigotine[10]. Therefore, the use of the upper limit of these dose ranges for the three dopamine agonists to represent equivalent doses might be a source of bias.

For reference, the SPC for ropinirole IR tablets indicates that a therapeutic response may be seen between 3 and 9mg/day, although adjunct therapy patients may require higher doses[12]. The British National Formulary (BNF) suggests that the usual dose range for ropinirole is 9-16mg/day (but notes that higher doses may be required if used with levodopa)[13]. For pramipexole, the SPC states that a maximum dose of 3.3mg/day (base) may be used but notes that at doses above 1.1mg/day (base) the incidence of somnolence is increased[14]. For rotigotine, the SPC notes that in early Parkinson's disease the maximum dose is 8mg/day, some patients achieve an effective dose at 4mg/day, and that most patients achieve an effective dose of 6-8mg/day. In advanced stage disease the maximum dose is 16mg/day, some patients achieve an effective dose at 4-6mg/day, and that most patients achieve an effective dose of 8-16mg/day[15].

The drug acquisition costs are estimated on the basis of the average costs per mg of the above three dopamine agonists. List prices are used to calculate the average cost per mg, although the actual product lines upon which the average cost per mg are based is unclear from the submission. The use of the average costs per mg leads to marginal differences between the costs assumed for ropinirole and pramipexole in the base case analysis, and the costs that would be calculated based simply on the list prices of the products that would provide the assumed doses. However, the use of the average cost per mg when estimating the daily cost of rotigotine leads to an over

estimation of the cost of rotigotine of around 47% in the base case analysis (based on the list price of the 8mg patches the daily cost would be £5.10[13], but when based on the average cost per mg the daily cost in the base case analysis would be £7.52). This is due to the pricing structure of rotigotine patches, which are more expensive on a per mg basis at the lower dose end of the product range[13] (i.e. those doses that would be involved in the early dose titration phase). The impact of the dose ranges and costs are explored in sensitivity analyses (see section 8.9.2).

8.7.2 Treatment of adverse effects

Adverse events are not considered in the analysis[2].

8.7.3 Other health-related resource use and costs

No other health-related resource use and costs are considered in the analysis[2]. It should be noted that the SPC for ropinirole PR tablets states that, after switching from ropinirole IR tablets, patients will initially require more frequent and careful monitoring in order to adjust the dose if necessary[1]. Switching to ropinirole PR tablets would, therefore, be associated with potential additional costs that are not considered in the analysis.

8.8 Discounting

Discounting is not employed in the analysis, despite the time horizon of analysis exceeding one year.

8.9 Results

8.9.1 Base case analysis

The two-year drug acquisition cost for the ropinirole treatment strategy (six months of ropinirole IR tablets followed by 18 months of ropinirole PR tablets at a daily dose of 12mg) is estimated to be £4,679. This is reported to be around £845 less expensive than treatment with pramipexole (£5,524 based on daily dose 2.1mg) and £782 less expensive than treatment with rotigotine (£5,460 based on daily dose of 8mg).

8.9.2 Scenario analyses

A range of analyses have been conducted to explore different assumptions around equivalent doses of the dopamine agonist using the time horizon of two years of treatment, the assumption that ropinirole would be provided as six months of ropinirole IR tablets followed by 18 months of ropinirole PR tablets, and the average cost per mg approach to costing[2]. As there is no robust evidence of equivalence for the doses that are explored, these analyses essentially represent hypothetical scenarios. As in the base case analysis, no consideration is given to the potential need for, and associated costs of, close monitoring and dose adjustment in patients who are switched from ropinirole IR tablets to ropinirole PR tablets.

The base case analysis used the upper end of the range of equivalent doses considered by the German physicians who attended an expert meeting[10]. Using the lower end of the dose range suggested by these physicians, ropinirole was still estimated to be the least expensive treatment option based on drug acquisition costs (£3,119 for ropinirole 8mg/day, £3,683 for pramipexole 1.4mg/day, and £4,095 for rotigotine 6mg per day)[2]. However, it should be noted that the approach of using the average cost per mg of drug still overestimates the cost of rotigotine at 6mg/day by about 11% compared with the list price for 6mg patches (£5.64/day compared with £5.10/day).

Different daily doses and assumed dose equivalents for ropinirole and pramipexole have been explored, based on earlier dose equivalents suggested by a different group of health care professionals[16] (reference not verified as not provided). Assuming that a

ropinirole dose of 9mg/day is equivalent to a pramipexole dose of 1.62mg/day (base), ropinirole is estimated to be less expensive over the two-year treatment period by around £750 (£3,509 compared with £4,261 for pramipexole). Assuming that a ropinirole dose of 18mg/day is equivalent to a pramipexole dose of 2.64mg/day (base), ropinirole is estimated to be more expensive over the two-year treatment period by around £74 (£7,018 compared with £6,944 for pramipexole)[2].

An analysis is provided to determine the doses of pramipexole and rotigotine that would be required for their costs to approach that of 12mg/day of ropinirole (the dose assumed in the base case analysis). This suggests that a pramipexole dose of 1.8mg/day (base) and a rotigotine dose of 7mg/day would be required, but given the issues with the use of the average cost per mg approach to costing and the fact that there is no evidence to suggest that these doses would be equivalent, this analysis would appear to be of very limited value.

The most plausible scenario of two years of treatment with ropinirole IR tablets as the comparator, results in higher drug acquisition costs compared with switching to ropinirole PR tablets after six months (£4,818 compared with £4,686 in the base case analysis for a dose of 12mg/day). However, the full costs of ropinirole PR may be underestimated for lack of consideration of the costs associated with additional monitoring and dose adjustment following switching. Reducing the cost of ropinirole IR tablets by 10% or 25% predictably results in the overall costs of the ropinirole treatment strategy being lower than in the base case analysis. A 10% reduction in the acquisition cost of the ropinirole IR tablets results in the use of ropinirole PR tablets being more expensive than treatment with only the IR tablets.

8.10 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost-effectiveness of ropinirole PR tablets.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

Two scenarios of ropinirole PR tablet uptake are considered against pramipexole and rotigotine. Assumed doses and dose equivalence, and the approach to estimating drug acquisition costs are as in the cost minimisation analysis, which appear subject to considerable uncertainty. The number of patients expected to receive treatment with these dopamine agonists are estimated based on sources used in the NICE clinical guideline on Parkinson's disease.

In this budget impact analysis, the scenarios that are considered result in costs savings with the use of ropinirole PR tablets. However, the estimates of cost savings are, in effect, hypothetical scenarios, and the extent to which these cost savings would be realised in practice is subject to considerable uncertainty.

9.2 Perspective and time horizon

The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years[2].

9.3 Data sources

9.3.1 Incident and prevalent cases

The prevalence of idiopathic Parkinson's disease has been derived from a community-based cross sectional study conducted in London, which reported an age-adjusted prevalence of 168/100,000 population[4]. The incidence of Parkinson's disease is

estimated to be 12/100,000 population, based on the average across the range of incidence rates reported in the NICE clinical guideline (between 4 and 20/100,000)[3]. The number of new patients with Parkinson's disease is estimated to be 363 in 2010, rising to 370 in 2014.

A range of relative mortality rates for patients with Parkinson's disease has been quoted in the company submission, but a value of 3.2 has been assumed in the analysis, the reason for which is unclear. This has been applied to the mortality rate for England and Wales (9.6/100,000), giving a mortality rate for Parkinson's disease of 30.7/100,000. Combined with the prevalence and incidence estimates above, the net number of patients with Parkinson's disease in Wales is estimated to be 5,417 in 2010, rising to 6,878 in 2014[2]. It is assumed that all patients with diagnosed Parkinson's disease receive treatment.

9.3.2 Projected rate of adoption and market share

Market research data reportedly indicate that 31% of patients with Parkinson's disease receive non-ergot derived dopamine agonists. 52% of these are estimated to receive ropinirole IR tablets and 4% of these are estimated to receive ropinirole PR tablets[2].

The company estimates that the proportion of patients likely to be treated with ropinirole PR tablets in 2010 is 5%, rising by 5% each year to 25% in 2014. The company, therefore, estimates that 271 patients will be treated with ropinirole PR in 2010, rising to 1,719 in 2014[2]. An additional scenario of 60% uptake of ropinirole PR is considered in these patients (with the remainder of patients split 30% and 10% between pramipexole and rotigotine) (see section 9.5).

9.3.3 Costs and resource use

As in the cost minimisation analysis, the budget impact analysis considers the daily dose of ropinirole to 12mg, pramipexole 2.1mg and rotigotine 8mg. However, in contrast to the cost minimisation analysis, there is no consideration of the initial use of ropinirole IR tablets in patients who are estimated to take ropinirole PR tablets. Therefore, these estimates implicitly assume that all patients are already stabilised on ropinirole PR tablets. The approach to estimating drug acquisition costs is based on the average cost per mg across all product lines for each drug. As in the cost minimisation analysis, this has the effect of significantly overestimating the costs of rotigotine patches (see section 8.7.1), which would overestimate the cost savings with the use of ropinirole PR tablets instead.

9.4 Results

Two scenarios have been considered to estimate direct savings with the use of ropinirole PR tablets: (i) all patients who the company estimate are likely to be treated with ropinirole PR tablets receive ropinirole PR tablets instead of all receiving pramipexole, or instead of all receiving rotigotine, and (ii) 60% of these patients receive ropinirole PR tablets, with the remainder split 30% and 10% between pramipexole and rotigotine.

Table 1. Company estimates of direct savings with the use of Ropinirole PR tablets

	2010	2011	2012	2013	2014
Number of patients	271	578	922	1302	1719
Additional cost if all treated with pramipexole (£)	119,317	254,618	406,012	573,613	757,530
Additional cost of all treated with rotigotine (£)	110,716	236,262	376,743	532,261	702,920
Additional cost if 60% treated with ropinirole PR tablets, 30% pramipexole, 10% rotigotine (£)	46,867	100,011	159,478	225,310	297,551

These estimates of cost savings are, in effect, based on hypothetical scenarios, and the extent to which these cost savings would be realised in practice is subject to considerable uncertainty.

9.5 Sensitivity analysis

No further sensitivity analyses have been conducted for the budget impact analysis.

9.6 Relevant comparator costs

Treatment for Parkinson's disease must be individually tailored to the patient. The current NICE clinical guideline on Parkinson's disease indicates that, in early symptomatic phase of disease, levodopa, dopamine agonists and MAO-B inhibitors may be used. In later disease, dopamine agonists, MAO-B inhibitors and COMT inhibitors may be used as adjuncts to levodopa[3]. Full details of the NICE recommendations should be consulted, but in general, non-ergot derived dopamine agonists are preferred to ergot-derived dopamine agonists[3]. Table 2 lists example costs of selected agents used in the treatment of Parkinson's disease.

Table 2. Example costs of selected agents that may be used in the treatment of Parkinson's disease

Drug	Example daily dose	28-day cost[13]
Levodopa		
Co-beneldopa (Madopar®)	600mg (expressed as levodopa) in daily divided doses	£12.37
Co-careldopa (Sinemet®)	750mg (expressed as levodopa) in daily divided doses	£13.33
Dopamine agonists (non-ergot derived)		
Ropinirole (Requip®)	4mg three times a day	£189.06
Ropinirole PR (Requip XL®)	***12mg once daily***	***£168.03***
Pramipexole (Mirapexin®)	0.7mg (base) three times daily	£213.94
Rotigotine (Neupro®)	8mg patch applied once daily	£142.79
MAO-B inhibitors		
Rasagiline (Azilect®)	1mg daily	£70.72
Selegiline (non-proprietary)	10mg once daily	£4.99
COMT inhibitors		
Entacapone (Comtess®)	200mg three times a day	£50.40
Tolcapone (Tasmar®)	100mg three times daily	£79.97

This table does not imply therapeutic equivalence of the drugs or doses. Drugs may be used as monotherapy or as part of combination therapy. See the individual Summaries of Product Characteristics and the NICE Clinical Guideline No. 35[3] for recommendations. All costs calculated from BNF list prices[13]

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- Substitution of ropinirole PR for ropinirole IR tablets should be supervised by appropriate specialists in Parkinson's disease; ropinirole PR if accepted for use, may be suitable for shared care in accordance with appropriate guidance.

10.2 Related advice

- NICE and the National Collaborating Centre for Chronic Conditions published a clinical guideline on the diagnosis and management of Parkinson's disease in primary and secondary care, June 2006[3]. This does not contain recommendations on the use of ropinirole PR, as it was published prior to its launch.
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and pharmacological management of Parkinson's disease (Peer review draft), April 2009[17].

10.3 Previous AWMSG advice

- The All Wales Medicines Strategy Group (AWMSG) issued guidance on the use of co-careldopa intestinal gel (Duodopa®) in August 2007. The guidance stated that co-careldopa intestinal gel should not be recommended for use within NHS Wales for the treatment of advanced levodopa-responsive Parkinson's disease. The clinical and cost effectiveness data presented was not sufficient for AWMSG to recommend its use[19].

10.4 Ongoing studies

The company submission states that no new data for ropinirole PR for the treatment of Parkinson's disease is likely to become available within the next 6-12 months[2].

10.5 Patient organisation information

Patient organisation submissions by The Parkinson's Disease Society and the European Parkinson's Disease Association were provided to AWMSG members.

10.6 Medical expert / Clinical expert summary

A summary of medical / clinical expert views was provided to AWMSG members.

GLOSSARY

Clinical Global Impression – Improvement (CGI-I) Scale and Clinical Global Impression – Severity (CGI-S)[2]:
The CGI-I scale assesses improvements or worsening in the patients illness relative to baseline state.
The CGI-S scale is used to assess the severity of the patient's illness at one particular point in time.

CGI scale	
Description	Two single item scales to assess disease severity or improvement with treatment rated by the clinician
Scale range	CGI-S: 7-point scale from 1 (normal) to 7 (extremely ill) CGI-I: 7-point scale from 1 (very much improved) to 7 (very much worse)
Threshold for clinically significant change	Results in clinical trials often report 'responders' and scored with a 2 or 1. There are no universally accepted scoring guidelines; scoring is based on clinical judgement.

Hoehn and Yahr stage scale[2]:
The simplest and most commonly used scale to establish the severity of Parkinson's disease. The scale divides Parkinson's disease into four stages:

Stage	Description
0	No signs of disease.
I	Symptoms are very mild and appear only on one side of the body.
I.5	Symptoms appear only on one side of the body but with axial involvement.
II	Symptoms appear on both sides without impairment of balance.
II.5	Symptoms appear on both sides are still mild, with recovery on pull test.
III	Symptoms are mild to moderate, some postural instability occurs, but patients are physically independent.
IV	Symptoms are severe; the patient is severely debilitated and needs some assistance, but can still walk or stand unassisted.
V	Symptoms are very severe, the patient is typically wheelchair-bound or confined to a bed, unless aided.

Incidence:
The rate at which new cases occur in a population during a specified period[18].

"On-off" fluctuations:
An "on" period begins after a levodopa dosing and is a period in which disease symptoms are reduced and patients become more active.
An "off" period occurs between two scheduled doses of levodopa and is one during which patients experience symptoms with higher intensity[2].

Prevalence:
The proportion of a population that are cases at a point in time[18].

Unified Parkinson's Disease Rating Scale (UPDRS)[2]:
A six part questionnaire whereby data is collected by interview and examination to assess the signs and symptoms of Parkinson's disease:

Part	Description	Scale Range
I	Mentation, behaviour and mood (Items 1-4)	0-16 points
II	Activities of daily living (Items 5-17)	0-52 points
III	Motor examination (Items 18 – 31)	0-108 points
IV	Complications of therapy	0-23 points
V	Modified Hoehn and Yahr stage (see below)	Stages 1-V
Vi	Modified Schwab and England Activities of daily living	Score - 0% (no independence to 100% (total independence)

Threshold for clinically significant change	Score
UPDRS Total Score (Sum of Parts I,II and III)	+ or – 8 points
Motor score (Part III)	+ or – 5 points
Activities of daily living (Part II)	As below (section 2)
Hoehn and Yahr	Stages I – III
An increase in the unified Parkinson's disease rating scale over time indicates a worsening of symptoms and a decrease indicates and improvement.	

Unified Parkinson's Disease Rating Scale – Activities of Daily Living (UPDRS-ADL)[2]:
This scale is part II of the UPDRS scale and is used to evaluate the impact of Parkinson's disease on activities of daily living which include swallowing, speaking, dressing and hygiene.

It comprises a 13-item questionnaire whereby scores are obtained by an interviewer questioning the patient.

Unified Parkinson's disease rating scale – Activities of daily living	
Description	Speech; dressing; turning in bed; salivation; hygiene; sensory complaint; swallowing; tremor; freezing when walking; handwriting; falling; cutting food; walking.
Scale range	Each item (question) is scored from 0 (unaffected) to 4 (severely affected). Total score of the Unified Parkinson's Disease Rating Scale – Activities of Daily Living ranges from 0 - 52
Threshold for clinically significant change	Hoehn and Yahr Stage I – II: + or – 2 points
	Hoehn and Yahr Stage II.5 – III: + or – 3 points
	An increase in the Unified Parkinson's Disease Rating Scale – Activities of Daily Living score of over time indicates a worsening of symptoms and a decrease indicates an improvement.

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Appendix 1. Additional Clinical Information

Table 1A. Ropinirole Prolonged Release- Summary of Phase III Studies

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Ropinirole Prolonged Release versus Ropinirole Immediate Release						
EASE-PD Monotherapy Study[2, 8] *This is the only study that relates to the use of ropinirole within its licensed indication*.	Phase III, multicentre, randomised, double-blind, non-inferiority, crossover study. 36 weeks 30 centres worldwide including Europe, UK and USA.	161 randomised ITT: 161 (included all patients who received at least one dose of ropinirole and for whom at least one post-baseline efficacy assessment was available) PP: 114 (included all patients in the ITT population who had no major protocol violations and who had missed no more than 3 consecutive days of treatment in 36 weeks study).	Aged ≥ 30 years with a diagnosis of idiopathic PD (Hoehn and Yahr stages I-III) Previous treatment with levodopa (up to 3 months) or with a dopamine agonist (up to 6 months) should have been discontinued at least 2 weeks prior to enrolment. At the end of the titration period, patients who had achieved a stable UPDR score* entered the first 8-week maintenance period.	Mean age: 60 years 54% male Mean age of onset: 58 years Mean disease duration: 2.7 years Hoehn & Yahr Stage: I 20% I.5 25% II 40% II.5 9% III 5% IV 0% V 0%	Patients were randomly assigned on a 1:1:1:1 basis to one of four formulation sequences: 1. Rp IR: Rp IR: Rp PR 2. Rp IR: Rp PR: Rp PR 3. Rp PR: Rp PR: Rp IR 4. Rp PR: Rp IR: Rp IR Patients received a 7 day placebo run-in period followed by a 12 week dose titration period and then 3 consecutive, flexible-dose 8 week maintenance periods. During the 12 week dose-titration period Rp IR was titrated according to the approved labelling (0.75-24mg/day [0.25-8.0mg administered 3 times daily]); titration or Rp PR covered a similar dose range but started at a higher dose and was more rapid (2-24mg/day). At the end of the 1st maintenance period, half of the patients on each formulation group switched to the same or closest dose of the alternative formulation; remaining patients switched at the end of the 2nd maintenance period.	**Primary endpoint: Mean change in UPDRS total motor score† (PP):** Overall mean change for Rp PR: -0.1±0.28 Overall mean change for Rp IR: 0.6±0.30 Adjusted mean treatment difference: -0.7; (95% CI: -1.51, 0.10, falls within the predefined threshold for non-inferiority; p=0.0842 **Secondary endpoints:** **Patients with a score of 1 or 2 on the CGI-I scale:** Titration phase: Rp PR: 70% Rp IR 44% (ns; p=0.0761) Maintenance period 1: Rp PR: 70% Rp IR 57% Maintenance period 2: Rp PR: 61% Rp IR 66% Maintenance period 3: Rp PR: 57% Rp IR 60% Overall Responders: Rp PR: 63%; Rp IR 60% (95% CI: -8.2, 13.9, lower limit exceeds non-inferiority margin of 7.5%) **Patients ≥30% reduction in the UPDRS motor score:** There were no statistically significant differences between Rp PR and RP IR. **Mean change in the UPDRS ADL total motor score; BDI total score; ESS total score; PDSS total Score:** **Time during the first 20 weeks to reach a score of 1 or 2 on the CGI-I scale maintained for the remainder of the 20 week period:** Median Response: Rp PR: 84 days; Rp IR: 140 days (adjusted hazard ratio was 1.18 [95% CI: 0.77, 1.80; p = 0.4459]).

Table 1A. Continued

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Ropinirole Prolonged Release versus Ropinirole Immediate Release						
The PREPARED Study[2, 9]	Phase III, multicentre, randomised, double-blind, parallel-group study. 24 weeks	350 randomised to once daily Rp PR (n=177) or 3 times daily Rp IR (n=173). ITT: 343 (patients who received at least one dose of randomised study medication and for whom at least one post-baseline efficacy assessment was available). Rp PR; n = 174 Rp IR; n= 169	Aged ≥ 30 years with a diagnosis of idiopathic PD (Hoehn and Yahr stages II-IV) Stable levodopa dose for ≥4 weeks before baseline. Suboptimal control with levodopa therapy alone (e.g. end-of-dose wearing off). 3-12 hours awake time spent "off" per day (as measured by patient diaries) during baseline period.	Mean age: 65 years 57% male Mean age of onset: 58 years Mean disease duration: 7.7 years Hoehn & Yahr Stage: I 0% I.5 1% II 34% II.5 23% III 35% IV 7% V 0%	Patients were randomised 1:1 to 2mg/day Rp PR or 0.75mg/day Rp IR. All patients underwent a 4 week fixed-dose titration period through the first 4 out of 13 dose levels to a minimum dose of 8mg/day Rp PR or 3mg/day Rp IR. Dosing was subsequently adjusted until an optimal therapeutic dose was achieved, up to a maximum of 24mg/day. A stable levodopa dose was maintained during the first 4 weeks, and until awake time spent "off" had been reduced from baseline by ≥1.5 hours following which the dose was reduced and complemented by an increase in study medication. Adjustments in levodopa dose and corresponding study medication could be continued until week 20.	**Primary endpoint (ITT):** **Proportion of patients who maintained ≥20% reduction from baseline in daily awake time spent "off" at week 24:** Rp PR: 66% Rp IR: 51% (adjusted odds ratio: 1.82; 95% CI: 1.16, 2.86; p=0.009) **Secondary endpoints (ITT):** **Proportion of responders on the CGI-I scale at week 24 LOCF:** Rp PR: 54% Rp IR: 42% (adjusted odds ratio: 1.67; 95% CI: 1.06, 2.63; p=0.027) **Mean reduction from baseline at week 24 LOCF in levodopa dose:** Rp PR: -162±226mg Rp IR: -113±138mg

ADL: activity of daily living; BDI: Beck Depression Inventory; CGI-I scale: Clinical Global Impression-Global Improvement scale; CI: confidence interval; EASE-PD: The Efficacy And Safety Evaluation in Parkinson's Disease; ESS: Epworth Sleeping Scale; ITT: intention-to-treat population; ns: not significant; LOCF: last observation carried forward; od: once daily; PD: Parkinson's disease; PDSS: Parkinson's disease Sleeping Scale; PP: per protocol population; Rp IR: ropinirole immediate release; Rp PR: ropinirole prolonged releases; UK: United Kingdom; UPDRS: Unified Parkinson's Disease Rating Scale; USA: United States of America;
*Stable UPDRS = no more than a 2-point change between weeks 10 and 12)
† Mean change in UPDRS total score = change between period baseline (visit at which the patient entered each flexible maintenance period) and endpoint (assessed at the end of each maintenance period)