All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Pramipexole prolonged release tablets (Mirapexin®)

Boehringer Ingelheim Ltd

Advice No: 0810 – April 2010

Recommendation of AWMSG

Pramipexole prolonged release (Mirapexin prolonged release®) is recommended as an option for use within NHS Wales for the treatment of the signs and symptoms of idiopathic Parkinson's disease, alone or in combination with levodopa.

Pramipexole prolonged release should be initiated by a specialist experienced in the treatment of Parkinson's disease. AWMSG is of the opinion that pramipexole prolonged release may be suitable for shared care in accordance with appropriate local guidance.

In order to limit potential errors, pramipexole prolonged release should be prescribed by brand as Mirapexin prolonged release®.

This report should be cited as:

ABBREVIATIONS

AWMSG	All Wales Medicines Strategy Group
ADL	Activities of Daily Living
BNF	British National Formulary
CGI-I	Clinical Global Impression - Improvement
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COMT	Catechol-O-methyl transferase
EMEA	European Medicines Agency
FAS	Full Analysis Set
IR	Immediate Release
LOCF	Last Observation Carried Forward
MOA-B	Monoamine Oxidase B
MR	Modified Release
NICE	National Institute for Health and Clinical Excellence
PD	Parkinson's Disease
PGI-I	Patient Global Impression - Improvement
RCT	Randomised Controlled Trial
SPC	Summary of Product Characteristics
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 28th April 2010

The recommendation of AWMSG is:

Pramipexole prolonged release (Mirapexin prolonged release®) is recommended as an option for use within NHS Wales for the treatment of the signs and symptoms of idiopathic Parkinson's disease, alone or in combination with levodopa.

Pramipexole prolonged release should be initiated by a specialist experienced in the treatment of Parkinson's disease. AWMSG is of the opinion that pramipexole prolonged release may be suitable for shared care in accordance with appropriate local guidance.

In order to limit potential errors, pramipexole prolonged release should be prescribed by brand as Mirapexin prolonged release®.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Pramipexole prolonged release tablets are indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease (PD), alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations)[1].

2.2 Dosing

Pramipexole prolonged release tablets are to be taken once daily at around the same time each day. The Summary of Product Characteristics (SPC)[1] recommends that patients already taking pramipexole immediate release (IR) tablets may be switched across to pramipexole prolonged release tablets overnight at the same total daily dose. When initiating pramipexole treatment using the prolonged release tablets, doses should be increased gradually from a starting dose of 0.26mg of base (0.375mg of salt) per day and then increased every five to seven days to achieve a maximal therapeutic effect. During maintenance treatment, the individual dose of pramipexole should be in the range of 0.26mg of base (0.375mg of salt) to a maximum of 3.15mg of base (4.5mg of salt) per day. However, it should be noted that the incidence of somnolence is increased at doses higher than 1.05mg of base (1.5mg of salt) per day. It is recommended that the dose of levodopa is reduced during both the dose escalation and the maintenance treatment with pramipexole, depending on reactions in individual patients. Renal impairment may necessitate slower dose titration and adjustment. Treatment discontinuation should be slow, using dose tapering, to reduce the risk of neuroleptic malignant syndrome. See the SPC for full details[1].

2.3 Market authorisation date

8 October 2009[1,2]

2.4 UK Launch date

20 October 2009[3].

3.0 DECISION CONTEXT

3.1 Background

PD is a common, progressive neurodegenerative condition resulting from the death of the dopamine-containing cells of the substantia nigra[4]. It is primarily a movement disorder, which classically presents as bradykinesia, rigidity and rest tremor. Other impairments frequently develop over time, including autonomic disturbances, pain and psychiatric problems such as depression and dementia. The condition progresses to cause significant disability with impaired quality of life for the affected person, families and carers may also be affected indirectly[4]. In 2006, the National Institute for Health and Clinical Excellence (NICE) estimated PD to affect 100 to 180 people per 100,000 of the population, with an annual incidence of 4 to 20 per 100,000. There is a rising prevalence with age and a higher prevalence and incidence of PD in males[4].

There is currently no cure for PD and treatment focuses on regulating dopamine levels and obtaining effective symptomatic control[4]. Options for treatment in early stage PD (people who have developed functional disability and require symptomatic therapy) include levodopa, dopamine agonists and monoamine oxidase B (MAO-B) inhibitors (selegiline, rasagiline). Eventually, most patients will require levodopa therapy, and dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors may be used as adjuvant therapy[4]. The aim of adjuvant drugs is to reduce

the motor fluctuations and dyskinesia that manifest as “on-off” periods with long-term levodopa use[4,5].

Pramipexole is a non-ergot dopamine agonist that alleviates motor deficit in PD by stimulating dopamine receptors in the striatum[1]. The IR tablet formulation has been available for over 10 years[2] and is licensed for PD and restless legs sydrome[6]. Pramipexole prolonged release is a new once daily oral formulation that is licensed for treating PD only[1]. The company submission suggests that pramipexole prolonged release may improve adherence compared with the IR formulation and ensures continuous dopaminergic delivery, which may impact on the development of motor fluctuations[2].

3.2 Comparators

- Pramipexole IR tablets – although other dopamine agonists are available, the company submission focuses on the comparison of pramipexole prolonged release with IR tablets, as requested by WMP[7].

3.3 Guidance and related advice

- NICE issued a clinical guideline on the diagnosis and management of PD in 2006[4]. This concludes that it is not possible to identify a universal first-choice drug therapy for either early or for adjuvant drug therapy for late stage PD (people on levodopa who have developed motor complications), but where a dopamine agonist is appropriate, a non-ergot derived dopamine agonist (i.e. pramipexole, rotigotine, ropinirole) should be the preferred choice of treatment[4].
- Scottish Intercollegiate Guidelines Network. Diagnosis and pharmacological management of Parkinson’s disease. A national clinical guideline (113). January 2010[8].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The company submission includes details of two phase III trials in early and advanced PD. The Committee for Medicinal Products for Human Use (CHMP) concluded that the primary and secondary efficacy analyses from these trials confirmed the non-inferiority of pramipexole prolonged release against pramipexole IR. Mean daily doses at follow up were the same for both the prolonged release and IR formulations. A third clinical study, in patients with early PD who were stabilised on pramipexole IR, demonstrated that the majority of patients could be safely switched overnight to the equivalent daily dose of prolonged release formulation. However, around 15% of patients required subsequent dose adjustment, and 8% of patients experienced clinically relevant worsening of their condition despite dose adjustment. The safety and tolerability profile of pramipexole prolonged release was similar to that of the IR formulation, both when used to treat patients with early PD not on levodopa and when used to treat patients with advanced PD on concomitant levodopa therapy.

4.2 Review of the evidence on cost-effectiveness

Based on the evidence of non-inferiority of the prolonged release formulation to the IR formulation, and price parity per mg, the economic evidence in support of the prolonged release formulation consists of a simple description of the daily doses of the prolonged release and IR formulation in the three clinical studies included in the submission, and a conclusion of cost neutrality for the pramipexole prolonged release and IR formulations. This approach may be reasonable, but is limited as it considers only patients with PD for whom pramipexole IR is an alternative. The analysis does not consider other potential costs when patients who are already stabilised on pramipexole

IR are switched across to the prolonged release formulation. A proportion of patients who were switched overnight to pramipexole prolonged release required dose adjustment, and a proportion of these failed to maintain adequate efficacy. Patients who are to be switched from the IR to the prolonged release formulation may therefore need additional clinic visits for monitoring and dose adjustment, etc. Such additional clinic visits attract additional costs, which should be considered in an analysis of the switch from the IR to the prolonged release formulation.

4.3 Limitations of the evidence

- The pivotal efficacy and safety data are available in only conference abstract and poster presentation form and therefore limits the ability of WMP to fully appraise the data.
- Data on the ability to switch patients from the IR to the prolonged release formulation are limited to patients with early PD. There are no data available from patients with advanced PD, in whom concomitant levodopa use would be more substantial.
- There is no direct evidence of adherence advantages for the pramipexole prolonged release over pramipexole IR
- The simple cost analysis presented as economic evidence fails to consider all relevant costs associated with switching patients from the IR to the prolonged release formulation.

5.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

5.1 Clinical evidence

The company submission focuses on three double-blind clinical studies: two phase III randomised controlled trials (RCTs) to evaluate safety and efficacy in early (Study 524)[9,10] and advanced PD (Study 525)[12], and a study to evaluate dose requirements and safety of an overnight switch from the IR to the prolonged release formulation in early PD (Study 636)[13,14]. These are published only as abstracts and conference posters (see Tables 1A to 1C in Appendix 1 for study details).

5.1.1 Early PD (Study 524)

Patients with early PD (n=539) and a need for additional therapy, or introduction of therapy, to manage their symptoms were randomised (2:2:1) to receive pramipexole prolonged release, pramipexole IR or placebo[2,9,10]. Treatment was started at a dose of 0.375mg/day and was titrated to a maximum of 4.5mg/day within the first seven weeks. This was followed by a maintenance phase of up to 26 weeks. The study was powered to test for superiority of pramipexole prolonged release versus placebo at 18 weeks (n=253), and non-inferiority of pramipexole prolonged release versus pramipexole IR at 33 weeks (n=539), based on the change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) parts II + III combined (see Glossary). Secondary endpoints included responder rates for Clinical Global Impression of Improvement (CGI-I) and Patient Global Impression of Improvement (PGI-I) (see glossary). Several other secondary endpoints are also listed in the company submission, including measures of health-related quality of life measures, pain and depression, but data for these are not reported.

Key results are presented in Table 1A, Appendix 1. Both pramipexole prolonged release and IR formulations reduced UPDRS II+III scores significantly compared with placebo at 18 weeks. Levodopa rescue medication was required by three patients randomised to pramipexole prolonged release, two randomised to pramipexole IR and eight randomised to placebo. Excluding these patients, pramipexole prolonged release and IR remained statistically superior to placebo[9]. Secondary endpoint data at 18

weeks and descriptive analyses at 33 weeks confirmed the superiority of the pramipexole formulations over placebo[11]. The CHMP noted that, based on sub-group analyses of 18 week data, the mean change from baseline in UPDRS II+III was only statistically significantly different from placebo in patients receiving pramipexole at a dose greater than 3mg/day[11]. Although the sub-groups providing these data are small, which warrants caution in their interpretation, this issue is not further discussed by the company or CHMP.

Pramipexole prolonged release was demonstrated to be non-inferior to pramipexole IR at 33 weeks, based on the pre-specified criterion of the lower limit of the 95% confidence interval (CI) for the difference from baseline in UPDRS II+III being greater than -3 points[10]. These results were consistent using the full analysis and per protocol data sets. The mean daily dose at 33 weeks was 2.9mg (salt) in both groups[10].

5.1.2 Advanced PD (Study 525)

This study was conducted in 517 patients with advanced stage PD who were stabilised on levodopa treatment (with or without the COMT inhibitor entacapone)[12]. Pramipexole prolonged release and IR was initiated and titrated in the same manner as in Study 254. However, a protocol amendment permitted patients who completed 18 weeks of treatment to enter straight into an open-label extension study, and so 33 week data are based on only a subset (385 patients) of the randomised population[2].

The study was powered to test for superiority of pramipexole prolonged release versus placebo at 18 weeks based on the change from baseline in UPDRS parts II + III combined. Both pramipexole formulations were statistically superior to placebo for this primary endpoint and for secondary endpoints including the change in hours 'Off' time from baseline. Mean daily doses were 2.8mg (salt) in both pramipexole groups[12]. Descriptive analyses at 33 weeks were consistent with the 18-week findings[11]. In contrast to Study 524, this trial was not powered or designed to test the non-inferiority of pramipexole prolonged release versus IR. However, based on numerical comparisons, the CHMP concluded that there were no clinically relevant differences in efficacy observed between the formulations[11].

5.1.3 Overnight switching from IR to prolonged release formulation in early PD (Study 636)

Patients with early PD who had been stabilised on pramipexole IR (n=156) were randomised to continue with their current dose of pramipexole IR or to switch overnight to pramipexole prolonged release at the same total daily dose. The dose could be adjusted only at week 4 and at week 5 visits, after which the dose was maintained up to week 9. The primary endpoint was the proportion of patients who had switched successfully, defined as experiencing less than a 15% worsening of baseline UPDRS II+III scores, irrespective of whether dose adjustment was required, at week 9[11]. Non-inferiority of pramipexole prolonged release versus IR was defined as the lower 95% CI for the difference in rates of successful switches not exceeding 15%[13]. Secondary endpoints included the proportion successfully switched without dose adjustment at week 4, CGI-I and PGI-I responder rates and mean change from baseline in UPDRS II+III[11].

Non-inferiority based on the primary endpoint was not formally demonstrated for pramipexole prolonged release; the lower limit of the 95% CI exceeded the 15% difference in the proportion of patients successfully switched[13] (see Table 1C, Appendix 1). However, the CHMP accepted the company's explanation that the use of a relative change from baseline of 15% to define successful switching was the reason for pramipexole prolonged release not meeting the non-inferiority criterion. The trial demonstrated that there were no statistically significant differences in the proportion of

successful switches (i.e. maintenance of efficacy) between the two formulations, or in any of the secondary endpoints. In addition, *post hoc* analyses demonstrated the absolute mean change from baseline in UPDRS II+III scores was numerically greater with the prolonged release formulation than the IR formulation, and that the lower limit of 95% CI for the difference in the mean change from baseline was greater than -3, which was the threshold for demonstration of non-inferiority in study 524[11].

5.2 Safety

CHMP[11] considered the safety and tolerability profile of pramipexole prolonged release was similar to that of the IR formulation, both when used to treat patients with early PD not on levodopa and when used to treat patients with advanced PD on concomitant levodopa therapy. The frequency of overall adverse events, serious adverse events, or adverse events leading to drug discontinuation does not appear to differ significantly from that with the IR formulation, and no new or unexpected safety or tolerability issue emerged during the clinical development program of the prolonged release formulation[11].

The most common adverse events with pramipexole compared to placebo were nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucination, headache and fatigue. The incidence of somnolence is increased at doses higher than 1.5mg pramipexole salt per day. Dyskinesia occurs more frequently when pramipexole is used in combination with levodopa. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast[1]. Sudden onset of sleep, impulse control disorders and compulsive behaviours have been reported with dopamine agonists including pramipexole[1]. The SPC should be consulted for full details of warnings and precautions for use[1].

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The CHMP concluded that the primary and secondary efficacy analyses from the phase III trials in early and advanced PD confirm the non-inferiority of pramipexole prolonged release against pramipexole IR[11]. Mean daily doses at 33 weeks in the trial in early PD[10], and at 18 weeks in the trial in advanced PD[12], were the same for both the prolonged release and IR formulations. These trials involved the initiation of pramipexole treatment, rather than a switch from the IR to the prolonged release formulation.
- In a separate trial to assess the safety and dose requirements of switching from the IR to the prolonged release formulation, the majority of patients (around 70%) who were stabilised on pramipexole IR met the criteria for successful switching overnight to the prolonged release formulation without dose adjustment. However, around 15% of patients who met the criteria for successful switching required dose adjustment, and around 8% of patients were unable to maintain their pre-switch efficacy with dose adjustment. The percentage of patients successfully switched (irrespective of dose adjustment) to pramipexole prolonged release was numerically lower in patients receiving a concomitant levodopa treatment (81.8%) compared to patients not treated with levodopa (87.5%). This finding is based on sub-group analyses involving small patient numbers and the clinical significance of this is uncertain. The CHMP concluded that switching from the IR to the prolonged release formulation is possible, independent of concomitant levodopa treatment[11]. However, it should be noted that the overnight switch trial was conducted in patients with early PD, rather than in advanced PD where levodopa use is more substantial.
- The safety and tolerability profile of pramipexole prolonged release appears to be similar to that of the IR formulation, both when used to treat patients with

early PD not on levodopa and when used to treat patients with advanced PD on concomitant levodopa therapy[11].

- The company suggests that the once daily formulation may offer benefits to patients in terms of improving adherence when compared with multiple daily dosing regimens[2]. In addition, the SPC states the once daily administration of the prolonged release tablets causes less frequent fluctuations in the pramipexole plasma concentration over 24 hours compared to the three times daily administration of IR tablets[1], which the company implies may result in fewer 'Off' periods.
- No health-related quality of life or patient preference data have been provided.

7.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

7.1 Context

The company anticipates that pramipexole prolonged release would be used primarily in patients in whom pramipexole IR would be appropriate[2]. Based on the evidence of non-inferiority of the prolonged release formulation to the IR formulation, and price parity per mg, the economic evidence in support of the prolonged release formulation consists of a simple description of the daily doses of the prolonged release and IR formulation in the three clinical studies discussed in section 5, and associated costs.

7.2 Methods

The company considers the available clinical evidence, discussed in section 5, to demonstrate comparable efficacy between the prolonged release and IR formulation. It further implies that clinical effectiveness in practice may be better for the prolonged release formulation due to potential improvements in adherence and fewer fluctuations in pramipexole plasma concentrations compared with the three times daily administration of the IR formulation[2]. In support of this, the company refers to a study of adherence conducted using electronic drug monitoring bottles over a period of four weeks in patients receiving levodopa[15]. This study concluded that adherence to once daily treatment was significantly greater than with treatment administered several times per day, and that sub-optimal adherence to medication (defined as less than 80% prescribed medication being taken) was associated with a significantly higher motor scores on UPDRS III (i.e. worse motor function) compared with satisfactory adherence[15].

The company provides a breakdown of the number of patients using each of the available daily drug doses used in each of the three clinical trials. Price parity currently exists between the prolonged release and the IR formulation (£2.547 per mg salt). Only marginal differences existed in the daily dose requirements in each of the trials, due to chance. Drug acquisition costs are therefore considered to be exactly the same for the prolonged release and the IR formulations.

7.3 WMP critique of the company's economic evidence

Strengths of the economic evidence provided in the company submission include:

- On the assumption of equivalent effectiveness, safety and tolerability, the approach to costing and the conclusion of cost neutrality in patients who are initiating pramipexole treatment appear reasonable.

Limitations of the economic evidence provided in the company submission include:

- The analysis does not consider that there are potentially other costs involved beyond drug acquisition costs when patients who are already stabilised on pramipexole IR are switched across to the prolonged release formulation. Based on study 636[13], around 15% of patients who were switched overnight to

pramipexole prolonged release required dose adjustment, and around 8% failed to maintain adequate efficacy[11]. Patients who are to be switched from the IR to the prolonged release formulation may therefore need an initial clinic visit at the time of switch, plus additional clinic visits for monitoring and dose adjustment, etc. Such additional clinic visits attract additional costs, which should be considered in an analysis of the switch from the IR to the prolonged release formulation.

- The company suggests that the use of the prolonged release rather than the IR formulation may lead to improvements in adherence and benefits related to motor control. However, no direct evidence related to the pramipexole prolonged release formulation is provided. Although health-related quality of life was listed by the company as a secondary endpoint in the phase III trials, no data are provided.
- There are no scenario analyses presented by the company to indicate whether or not pramipexole prolonged release is cost-effective when compared with alternative non-ergot derived dopamine receptor agonists, such as rotigotine and ropinirole.

7.4 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published evidence on the cost effectiveness of pramipexole prolonged release.

8.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

8.1 Methods and Results

Based on commercial market research data, the company estimates that there are 5,400 PD patients in Wales, of which 4,300 are currently treated with medicines[2]. It appears from the company submission that around 500 patients are currently treated with pramipexole IR. It is simply assumed that a substantial proportion of these patients are expected to be treated with pramipexole prolonged release in the future.

On the basis of assumed equivalence (see section 7.3 and section 6) and price parity between the pramipexole prolonged release and IR formulations, the company considers that the use of the prolonged release formulation would be cost neutral. However, this approach does not consider that there are potentially other costs involved beyond drug acquisition costs, such as additional clinic visits for monitoring and dose adjustment, when patients who are already stabilised on pramipexole IR are switched across to the prolonged release formulation, as discussed in section 7.3.

8.4 Comparative unit costs

Pramipexole prolonged release and pramipexole IR (Mirapexin®) currently have the same cost per mg (salt), and hence the same acquisition costs (see Table 1). By making the comparison of pramipexole prolonged release with pramipexole IR, it is implied that other dopamine agonists are not appropriate comparators. However, as the NICE clinical guideline found no evidence to distinguish between the different medicine options (except to say that where a dopamine agonist is appropriate a non-ergot derived dopamine agonist is preferred to an ergot-derived dopamine agonist)[4], Table 1 includes example 28-day costs of other non-ergot derived dopamine agonists.

Table 1. Example comparator costs

Regimen	Example doses *	Approximate 28-day cost*[5]
Pramipexole prolonged release tablets (Mirapexin®)	2.625mg (salt) once daily†	£187.18.
Pramipexole IR tablets (Mirapexin®)	0.875mg (salt) three times per day†	£187.18
Ropinirole MR tablets (Requip XL®)	6mg once daily	£94.08
Ropinirole IR tablets (Requip®)	2mg three times per day	£94.53
Rotigotine patches (Neupro®)	6mg patch applied once daily	£142.79
This table does not imply therapeutic equivalence of the regimens and doses *Based on World Health Organisation Defined Daily Doses (DDD) for long term treatment of Parkinson's disease[16], †Based on nearest dose to DDD for pramipexole hydrochloride (2.5mg) using on whole tablets.		

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

- Pramipexole prolonged release should be initiated by a specialist experienced in the treatment of PD. Pramipexole prolonged release may be suitable for shared care in accordance with appropriate guidance.

9.2 Previous AWMSG and NICE advice

- The All Wales Medicines Strategy Group (AWMSG) issued guidance on the use of ropinirole prolonged-release (Requip XL®▼) in August 2009. The guidance stated that ropinirole prolonged-release is recommended for use within NHS Wales for the treatment of idiopathic PD in patients already taking ropinirole IR tablets (Requip®) and in whom adequate symptomatic control has been established[17].
- 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 PD. The clinical and cost effectiveness data presented was not sufficient for AWMSG to recommend its use[18].
- The National Institute for Health and Clinical Excellence (NICE) Clinical Guideline on the diagnosis and management of PD in primary and secondary care; June 2006[4]. See section 3.3.

9.3 Ongoing studies

- A further 12 week double-blind RCT in Japanese patients, and two long term, open-label extension studies in patients who completed studies 524, 525 and 636 are reported to be ongoing, but few further details are provided[2].

9.4 Other

In order to limit errors, pramipexole prolonged release should be prescribed by brand as Mirapexin prolonged release®.

9.5 Patient organisation information

A patient organisation submission by the European Parkinson's Disease Association (EPDA) was provided to members.

9.6 Medical expert summary

Medical expert opinions were provided to members.

GLOSSARY

Clinical Global Impression of Improvement (CGI-I)[4,17]:

The CGI-I scale is used by clinicians to assess improvements or worsening in the patients illness relative to baseline state. Scored on 7-point scale from 1 (very much improved) to 7 (very much worse). There are no universally accepted scoring guidelines; scoring is based on clinical judgement.

Hoehn and Yahr stage scale[4,17]:

The simplest and most commonly used scale to establish the severity of Parkinson's disease. The scale divides Parkinson's disease into the following stages:

Stage	Description
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[19].

'On' or 'Off' states[17]:

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.

Patient Global Impression of Improvement (PGI-I)[4]:

The PGI-I scale is used by patients to assesses their own improvements or worsening in the illness relative to baseline state. Scored on 7-point scale from 1 (very much improved) to 7 (very much worse).

Prevalence:

The proportion of a population that are cases at a point in time[19].

Unified Parkinson's Disease Rating Scale (UPDRS)[4,17]:

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.	

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Appendix 1. Additional Clinical Information

Table 1A. Main clinical studies supporting the use of pramipexole prolonged release (Mirapexin prolonged release®)

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Study 524[2,9-11]	Multi-national, double-blind, placebo-controlled, phase III RCT	539 Early PD patients	**Inclusion criteria:** H-Y stage 1-3 PD diagnosed within last 5 years, no previous levodopa exposure totalling >3 month, no levodopa within prior 8 weeks, no dopamine agonists within prior 4 weeks	**33-week Analysis:** Mean age: approx 62yrs Males: approx 54% (49.5% placebo group; 56.9% pramipexole groups) White: 63.5% Asian: 36.5% Mean PD duration: 1.0yr H-Y stage 1-1.5: 30.8% H-Y stage 2-3: 69.2% Mean UPDRS II+III scores: 29.2	Patients randomised 2:2:1 to Pramipexole prolonged release Pramipexole IR Placebo All started at 0.375mg/day and titrated over 7 weeks to maximum of 4.5mg/day, followed by maintenance phase of up to a further 26 weeks.	**Primary end point (18 weeks) (n=253*):** Superiority of Pramipexole prolonged release vs. placebo by change in UPDRS II+III from baseline: Placebo: -5.1 Pramipexole prolonged release: -8.1 (p=0.0282 vs. placebo) Pramipexole IR: -8.4 (p=0.0153 vs. placebo) **Descriptive analysis at 33 weeks (n=523*):** Superiority of Pramipexole prolonged release vs. placebo by change in UPDRS II+III from baseline: Placebo: -3.8 Pramipexole prolonged release: -8.6 (p=0.0001 vs. placebo) Pramipexole IR: -8.8 (p<0.0001 vs. placebo) Non-inferiority of Pramipexole prolonged release vs IR by change in UPDRS II+III from baseline: Difference: -0.2 (95% CI for difference -2.2 to +1.7) Pre-specified non-inferiority criterion met (lower 95% CI for difference greater than -3) **Secondary endpoints (33 weeks) (n=518):** CGI-I responders: Placebo: 29.4% Pramipexole prolonged release: 43.3% (95% CI 36.5 to 50.3) Pramipexole IR: 46.1% (95% CI 39.2 to 53.2) PGI-I responders: Placebo: 21.4% Pramipexole prolonged release: 34.4% (95% CI 28.1 to 41.2) Pramipexole IR: 33.3% (95% CI 27.0 to 40.2) The company submission reports that QoL, Pain and depression were also measured as secondary endpoints but no data are reported for these outcomes

Table 1B. Main clinical studies supporting the use of pramipexole prolonged release (Mirapexin prolonged release®)

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Study 525[2,11,12]	Multi-national, double-blind, placebo-controlled, phase III RCT	517 Advanced PD patients randomised	**Inclusion criteria:** H-Y stage 2-4 PD during 'on' time, at least 2 cumulative hours of 'off' time during waking hours, diagnosed with PD at least 2 years prior, taking optimised and stable levodopa dose (+/- entacapone)	Mean age: approx 62yrs Males: approx 55% White: 50.3% Asian: 50% Mean PD duration: 6.2yrs 'On' phase H-Y stage 2-3: approx 97% 'Off' phase H-Y stage 2-3: approx 85% Mean UPDRS II+III scores: approx 41 Mean daily 'off' time: 5.9hrs	Patients randomised 1:1:1 to Pramipexole prolonged release Pramipexole IR Placebo All started at 0.375mg/day and titrated over 7 weeks to maximum of 4.5mg/day, followed by maintenance phase of up to a further 26 weeks. A protocol amendment permitted patients who completed 18 weeks of treatment to enter straight into an open-label extension study, and so 33 week data are based on only a subset of the randomised population.	**Primary end point (18 weeks) (n=507*):** Superiority of Pramipexole prolonged release vs. placebo by change in UPDRS II+III from baseline: Placebo: -6.1 Pramipexole prolonged release: -11.0 (p=0.0001 vs. placebo) Pramipexole IR: -12.8 (p<0.0001 vs. placebo) **Descriptive analysis at 33 weeks) (n=385*):** Superiority of Pramipexole prolonged release vs. placebo by change in UPDRS II+III from baseline: Placebo: -6.8 Pramipexole prolonged release: -11.1 (p=0.0135 vs. placebo) Pramipexole IR: -11.5 (p=0.0051 vs. placebo) Trial not powered for test of non-inferiority of Pramipexole prolonged release vs. IR by change in UPDRS II+III from baseline. Numerically similar and 95% CIs overlap for change from baseline **Secondary endpoints (18 weeks) (n=505*):** % change in 'Off' time from baseline: Placebo: -8.8% Pramipexole prolonged release: -13.3% (p=0.0122 vs. placebo) Pramipexole IR: -15.9% (p<0.0001 vs. placebo) Mean change in hours 'Off' time: Placebo: -1.4hrs Pramipexole prolonged release: -2.1hrs (p=0.0199 vs. placebo) Pramipexole IR: -2.5hrs (p<0.0001 vs. placebo) The company submission reports that QoL, pain and depression were also measured as secondary endpoints but no data are reported for these outcomes. Additional information provided as commercial in confidence

Table 1C. Main clinical studies supporting the use of pramipexole prolonged release (Mirapexin prolonged release®)

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
Study 636[2,11, 13,14]	Multi-national, double-blind, placebo-controlled, overnight switch study	156 patients	**Inclusion criteria:** H-Y stage 1-3 PD diagnosed within previous 5 years, taking pramipexole IR for ≥3 months and on stable dose ≥1.5mg/day for ≥ previous 4 weeks. Concomitant levodopa or other PD treatments permitted if stable dose for previous 4 weeks and no motor complications.	Mean age: approx 63.5yrs Males: approx 56% Mean PD duration: 3.3yrs Mean UPDRS II+III scores: approx 22 H-Y stage 1-1.5: 41.1% H-Y stage 2-3: 58.9% Pramipexole IR treatment duration: 1.5yrs Mean Pramipexole IR dose: 2.7mg/day Concomitant levodopa: 55%	Following 2-4 week open-label run-in, patients randomised 2:1 to switch to unchanged total daily dose of Pramipexole prolonged release or Pramipexole IR Same daily dose maintained until week 4. Dose adjustment permitted at two consecutive visits at week 4 and week 5, after which dose maintained up to week 9	**Primary end point (9 weeks) (n=156*):** % patients successfully switched between formulations, with or without dose adjustment and no worsening from baseline UPDRS II+III of >15%: Pramipexole IR to prolonged release: 87/103 (84.5%) Pramipexole IR to IR: 49/52 (94.2%) Difference: -9.8% (95% CI -18.8 to 1.7) Non-inferiority **not** formally met **Secondary endpoints:** % patients successfully switched without dose adjustment at week 9: Pramipexole IR to prolonged release: 72/87 (82.8%) Pramipexole IR to IR: 42/49 (85.7%) CGI-I responder rates: Pramipexole prolonged release: 87.4% Pramipexole IR: 78.8% (p=0.1623) PGI-I responder rates: Pramipexole prolonged release: 81.6% Pramipexole IR: 71.2% (p=0.1299) Adjusted mean improvement from baseline in UPDRS II+III score: Pramipexole prolonged release: -1.6 points Pramipexole IR: -0.5 points (p=0.2061) **Post hoc analysis:** Difference from baseline in UPDRS II+III between prolonged release and IR formulations: -1.1 (95% CI -2.8 to 0.6) Lower bound is >-3, which was threshold for demonstrating non-inferiority in Study 524 Additional information provided as commercial in confidence

CGI-I = Clinical Global Impression of Improvement; H-Y stage = Hoehn-Yahr stage; IR = immediate release; PGI-I = Patient Global Impression of Improvement; QoL = health-related quality of life; UPDRS II+III scores = Unified PD Rating Scale part II (Activities of Daily living) + III (Motor examination) combined scores (range 0-160); *=full analysis set using last observation carried forward

Additional data was provided to members as commercial in confidence.