HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 February 2007

SIFROL 0.088 mg unscored tablets, B/30 - cip 363 467.9
SIFROL 0.18 mg scored tablets, B/30 - cip 363 469.1 and B/100 - cip 363 471.6
SIFROL 0.35 mg scored tablets, B/30 - cip 363 472.2
SIFROL 0.7 mg scored tablets, B/30 - cip 363 474.5 and B/100 - cip 363 475.1

Applicant : BOEHRINGER INGELHEIM

Pramipexole

List I

Marketing authorisation dates (centralised procedure): 14 October 1997, 6 April 2006 (extension of indication), 7 August 2006.

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use in hospital in the indication: symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in doses up to 0.54 mg of base (0.75 mg of salt)

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Pramipexole

1.2. Indications

Treatment of the signs and symptoms of idiopathic Parkinson's disease, 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).

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in doses up to 0.54 mg of base (0.75 mg of salt)

1.3. Dosage

Restless legs syndrome

The tablets should be taken orally, swallowed with water, and can be taken either with or without food.

The recommended starting dose of SIFROL is 0.088 mg of base (0.125 mg of salt) taken once daily 2-3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4-7 days to a maximum of 0.54 mg of base (0.75 mg of salt) per day (as shown in the table below).

Dose Schedule of SIFROL		
Titration Step	Once Daily Evening Dose (mg of base)	Once Daily Evening Dose (mg of salt)
1	0.088	0.125
2*	0.18	0.25
3*	0.35	0.50
4*	0.54	0.75

* if needed

As long-term efficacy of SIFROL in the treatment of Restless Legs Syndrome has not been sufficiently tested, patient's response should be evaluated after 3 months treatment and the need for treatment continuation should be reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

Treatment discontinuation
Since the daily dose for the treatment of Restless Legs Syndrome will not exceed 0.54 mg of base (0.75 mg of salt) SIFROL can be discontinued without tapering off. Rebound (worsening of symptoms after abrupt discontinuation of treatment) can not be excluded.

Dosing in patients with renal impairment
The elimination of pramipexole is dependent on renal function. Patients with a creatinine clearance above 20 ml/min require no reduction in daily dose.
The use of SIFROL has not been studied in haemodialysis patients, or in patients with severe renal impairment.

Dosing in patients with hepatic impairment
Dose adjustment in patients with hepatic failure is not required, as approx. 90% of absorbed active substance is excreted through the kidneys.

Dosing in children and adolescents
The safety and efficacy of SIFROL in children and adolescents below the age of 18 years have not been established.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

N NERVOUS SYSTEM
N04 ANTI-PARKINSON DRUGS
N04B DOPAMINERGIC AGENTS
N04BC Dopamine agonists
N04BC05 Pramipexole

2.2. Medicines with a similar therapeutic aim

Ropinirole - ADARTREL

Treatment of moderate to severe idiopathic restless leg syndrome (RLS) which causes sleep disorders and/or has a negative impact on daily, family, social and/or professional life.

3. ANALYSIS OF THE AVAILABLE DATA

The transparency dossier refers to four comparative studies versus placebo carried out for the extension of indication and submitted to the marketing authorisation authorities (reports of studies 248.515, 248.520, 248.543 and 248.546) and to the results of a meta-analysis comparing pramipexole to ropinirole (analytical report dated 27.09.2006).

3.1. Comparative studies versus placebo

Pramipexole was evaluated in four placebo-controlled clinical trials in more than1,000 patients with moderate to very severe idiopathic Restless Legs Syndrome according to the criteria of the IRLSSG[1] (see chapter 4.3). The comparative studies versus placebo that have been submitted (see table 1) assessed the efficacy of pramipexole at doses ranging from 0.088 mg to 0.54 mg of base (0.125 mg to 0.75 mg of salt) a day in moderate to severe idiopathic restless legs syndrome. The patients included had an initial score on the IRLS scale[2] (which ranges from 0 to 40) greater than 15. They had had symptoms at least two to three days a week during the three months prior to inclusion.

Two randomised, double-blind pivotal studies assessed the efficacy of pramipexole (0.088 mg to 0.54 mg of base a day) versus placebo using the IRLS and CGI-I scales[3] after 6 weeks (study 248 520) and 12 weeks (study 248 543) of treatment. Patients had an average initial IRLS score of 24 at the inclusion.

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1 Allen RP et al. (a). Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology - A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Medicine 2003;4(2):101-119.
2 Subjective score based on 10 questions (frequency and severity of symptoms, impact on everyday activities), response scoring from 0 to 4 (absence to very severe) - total score ranging from 0 to 40.

Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med. 2003; 4:121-32.

3 Clinical Global Impressions-improvement scale. Seven-point scale: 1 (very much better) to 7 (very much worse).

The mean changes from baseline in the Restless Legs Syndrome Rating Scale (IRLS) were greater in patients taking pramipexole than in patients taking the placebo: The adjusted mean differences were -6.6 points [95% CI -8.6;-4.5, p<0.0001] (study 248 520) and -4.3 points [95% CI -6.4;-2.1, p<0.0001] (study 248 543). The respective improvements in patients taking pramipexole were -12.3 points (versus -5.7 among patients taking the placebo) and -13.5 points (versus -9.3 among patients taking the placebo). The placebo effect was significant in both studies.
CGI-I responder rates (improved, very much improved) were observed after six weeks among 63% of patients taking pramipexole versus 32.5% of patients taking the placebo (study 248 520). After 12 weeks, CGI-I responder rates were 51.2% and 72.0% for placebo and pramipexole, respectively (difference 20% CI 95%: 8.1%; 31.8%, p<0.0005). (study 248 543).
An improvement in relative sleep satisfaction measured using a 100-mm visual analogue scale (studies 248 520 and 248 543) and in the global impact on the patient's life measured using a score based on 10 items (1-5, 7-10 et 13) in the RLS-QoL questionnaire[1] (study 248 543) were observed.

Post-hoc analyses of variations in the IRLS scores according to the initial severity of the symptoms were performed:

Study 248 520: IRLS score variations after 6 weeks' treatment compared with the initial values:

Treatment	N	Variation compared with the initial values	Difference *vs* PL[?*] (95% CI)
IRLS (11-20)			
Pramipexole	50	-8.2	-3.9 (-7.4; -0.5)
Placebo	31	-4.3	
IRLS (21-30)			
Pramipexole	146	-12.3	-5.6 (-8.3; -2.8)
Placebo	66	-6.7	
IRLS (31-40)			
Pramipexole	28	-20.6	-17.7 (-25.5; -9.8)
Placebo	17	-3.0	

? Adjusted covariance analysis

Study 248,543: IRLS score variations after 12 weeks' treatment compared with the initial values:

Treatment	N	Variation compared with the initial values	Difference *vs* PL[?*] (95% CI)
IRLS (11-20)			
Pramipexole	84	-9.3	-2.4 (-5.9; 1.1)
Placebo	28	-6.9	
IRLS (21-30)			
Pramipexole	144	-14.8	-5.1 (-8.2; -2.1)
Placebo	51	-9.6	
IRLS (31-40)			
Pramipexole	26	-16.0	4.0 (-15.3; 23.2)
Placebo	6	-19.9	

? Adjusted covariance analysis

Two additional studies were also submitted:

Study 248.515 (n=109) assessing the efficacy of pramipexole (0.088 mg to 0.54 mg of base a day) versus placebo on the variation of the periodic leg movement index (PLMI) while resting in bed after three weeks of treatment showed pramipexole to be superior: -30.9 to -41.1 movements an hour in patients taking pramipexole versus -8.45 movements an hour in patients taking the placebo.

1 Abetz L, Arbuckle R, Allen RP, Mavraki E, Kirsch J. The reliability, validity and responsiveness of the Restless Legs Syndrome quality of Life questionnaire (RLSQoL) in a trial population. Health and Quality of Life Outcomes. 2005;Dec 5;3:79.

Study 248.546 (n=224) versus placebo assessed the worsening of symptoms after withdrawal of treatment with pramipexole in patients who had responded to six months of treatment in an open-label study (n=150). The median time for the onset of worsening on the CGI-I scale ("worse" to "very much worse") associated with an IRLS score of > 15 was seven days in the placebo group and over 84 days in the pramipexole group.

In total 889 patients were given at least one dose of pramipexole (0.088 mg to 0.54 mg of base, equivalent to 0.125 to 0.75 mg of salt a day) during these four studies (295 patients were given the placebo).
575 patients were treated with pramipexole in a double-blind study versus placebo (223 patients). Adverse events leading to premature discontinuation of treatment were more frequent in the pramipexole group (6.8% *vs* 4.9% in the placebo group).
The most frequently reported adverse events were nervous system disorders (30.4% pramipexole, 26% placebo) and gastrointestinal disorders (29.7% pramipexole vs 13.9% placebo). The most frequent adverse events in patients taking pramipexole were nausea (15.7% vs 5.4%), headache (16.2% vs 14.8%), fatigue (8.7% vs 7.2%) and somnolence (6.1% vs 3.1%).

3.2. Meta-analysis of pramipexole versus ropinirole

The aim of this meta-analysis was to compare the efficacy and safety of pramipexole versus ropinirole in the symptomatic treatment of idiopathic restless legs syndrome.
A systematic bibliographic review was carried out on randomised, double-blind, placebo-controlled clinical trials carried out with pramipexole and ropinirole in the treatment of restless legs syndrome. The change in the overall score on the IRLS scale compared to the initial values was the main criteria of assessment in these studies.

Five studies were analysed:

Active treatment	Number of studies	Number of patients (ITT)	
		Active ingredient	Placebo
Pramipexole†	2	478	199
Ropinirole*	3	464	466

* 12-week studies versus placebo at varying doses (0.25 to 4 mg/d)
† Studies vs placebo: 6 weeks at varying doses (0.125 to 0.75 mg/d) and 12 weeks at fixed doses (0.125, 0.25, 0.5 and 0.75 mg/d) - Studies 248.520 and 248.543

Patients had an average initial IRLS score of 24 at inclusion.
The results compared to ropinirole are expressed as the mean difference in variations compared to the initial values for the IRLS scale and as the odds ratio for the CGI-I and the safety results (AEs affecting more than 5% of patients):

Efficacy criterion	Mean/odds ratio	95% CRI**
IRLS	-2.33	-4.23; -0.41
CGI improvement*	1.50	0.97; 2.32

* % of respondents (patients whose condition was "much better" or "very much better")
** Credibility interval
Δ IRLS non-inferiority = 2.5 points
Δ CGI-I non-inferiority = 10%

The premature discontinuation of treatment percentages were 11% (76/684) in the pramipexole group and 18% in the ropinirole group (169/933).

Tolerance criterion	Odds ratio	95% CI
Premature discontinuation	1.27	0.68; 2.47
- adverse events	1.29	0.53; 3.44
- insufficient (or no) efficacy	1.54	0.47; 5.54
Nausea	0.37	0.18; 0.84
Headaches	1.27	0.72; 2.29
Fatigue	0.76	0.30; 2.02
Somnolence	0.89	0.35; 2.48
Vomiting	0.21	0.05; 0.93
Dizziness	0.47	0.20; 1.13
Insomnia	1.26	0.50; 3.39
Nasopharyngitis	0.90	0.36; 2.33

Nausea, vomiting and dizziness were more common in the ropinirole group.

Analysis of the efficacy data produced by the meta-analysis showed that pramipexole was not inferior to ropinirole. Pramipexole was found to be superior in terms of the IRLS score (-2.3 points) and the CGI-I score (OR 1.5), but the clinical relevance of this is uncertain.
Bayesian analysis shows the probability of pramipexole being superior to ropinirole to be 0.99 and of it being clinically superior to ropinirole (difference of > 2.5 points on the IRLS score) to be 0.43.

When estimating the quantitative effect of pramipexole versus placebo, the combined analysis of the two studies 248.520 and 248.543 cannot be considered completely relevant in view of the heterogeneous effects observed in these two trials, even though a random-effects model was used (difference of 2.3 points on the IRLS scale). The likeliest explanation of this heterogeneity is that the monitoring period in study 248.520 was twice as short (six weeks rather than 12 weeks in all the other studies), which means that the effect of pramipexole may have been overestimated.

Furthermore, in terms of the indirect comparison between pramipexole and ropinirole, the sensitivity analysis carried out excluding study 248.520 shows that the results are no longer significant. An approach modelling the therapeutic effect over time would have allowed an additional sensitivity analysis. In any case, the level of evidence of pramipexole's superiority to ropinirole remains weak.

3.3. Safety data

It is estimated that from 1 September 2005 (date on which the product was first sold in France) and 31 March 2006, exposure to pramipexole for Parkinson's disease in France amounted to around 2,900 patient-years (based on a dose of 1.1 mg of base or 1.5 mg of the salt form a day). During this period 19 reports were submitted relating to 24 adverse events, six of which were serious.

The most recent periodic safety update report (18 March 2001 to 17 March 2002) records a world exposure estimated at 186,054 patient-years. 264 cases were reported during this period, equivalent to 14.2 cases for every 10,000 patient-years. Pramipexole had been prescribed for the treatment of restless legs syndrome in 10.6% of cases. The most common adverse events were those associated with dopamine agonists: somnolence (2.2/10,000 patient-years), nausea (1.6/10,000) and hallucinations (1.3/10,000). Twelve cases of sudden-onset sleep (0.6/10,000) were reported; in ten of these cases patients were being treated with doses of more than 0.54 mg of base (0.75 mg of salt) a day.

3.4. Conclusion

The efficacy of pramipexole in the treatment of moderate to severe idiopathic restless legs syndrome has been demonstrated versus placebo in short-term studies (up to 12 weeks). The benefit observed versus placebo was modest, around 4 to 6 points on the IRLS scale (0 to 40).
The percentages of respondents on the CGI-I scale (improved, very much improved) ranged from 60 to 70% in the pramipexole group and from 30 to 50% in the placebo group.

No efficacy data is available for treatments lasting more than 12 weeks. It remains to be seen whether pramipexole is effective in the longer term, and the decision as to whether to continue with treatment should be considered after three months.
The Committee regrets that no direct comparative studies with ropinirole are available.

A meta-analysis of five studies (2 pramipexole studies, n=677, 3 ropinirole studies, n=930) assessing the efficacy of treatments over periods up to 12 weeks showed that pramipexole is not inferior to ropinirole (difference of 2.3 points on the IRLS scale). The efficacy results showing the superiority of pramipexole are insubstantial.

Analysis of adverse events occurring in patients being treated with pramipexole for RLS showed adverse events typical of dopamine agonists. The events most often observed with pramipexole in the course of the development phase of the product were nausea, headache, asthenia and somnolence. Pramipexole must be introduced gradually.

The CHMP has asked for a six-month controlled study versus placebo to be conducted in order to assess the phenomena of symptoms worsening under treatment and of rebound on termination.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual Benefit

Restless leg syndrome is a condition classified as one of the causes of organic chronic insomnia. It is not life-threatening and does not cause severe complications. It is typically characterised by paraesthesia and dysaesthesia in the legs associated with motor agitation. These symptoms are worst when the patient is at rest, in the evening on retiring, or at night, and are relieved by activity. Almost 80% of patients experience periodic leg movements while asleep. Sleep disorders can sometimes have a severe impact on quality of life.

Pramipexole treats the symptoms. The short-term (12 weeks) efficacy/adverse reactions ratio is modest. The efficacy/adverse effects ratio in the longer term remains to be determined.

Ropinirole is also indicated for this condition. Non-drug alternatives (advice on ways of improving sleep in particular) are appropriate for all forms of the condition and are generally adequate to deal with the milder forms.

Public health benefit :

As the nosology of restless legs syndrome (RLS) is unclear and in view of the lack of data on the epidemiology and severity of forms described as idiopathic, and on the natural course of RLS, it is impossible to assess the burden of the disease in terms of public health. The fact that in the vast majority of cases the condition is benign and even in the severest form has only a moderate impact on quality of life suggests that the burden of the disease is minor.

The fact that some severe forms might have an impact on quality of life, and the lack of a codified therapy for RLS, indicates that there is an unmet therapeutic need, but that therapy need not necessarily involve drugs. Taking the aforementioned arguments into account, and given the lack of data on the clinical management of RLS in practice, it is impossible to quantify this need in public health terms.

Given the results of clinical trials SIFROL is likely to have a small impact on morbidity and quality of life.

The subjective and polysemic nature of the syndrome and the difficulty in identifying patients likely to benefit from drug treatment in non-specialist clinics (severe idiopathic forms) mean that transposability of the results to real life is difficult. In particular, the symptoms of RLS may be the expression of other diseases, particularly psychiatric disorders that require a specific treatment.

The argument that this drug could avoid the use of drugs that would not be beneficial, especially psychotropic substances is not well founded.

Therefore, SIFROL is not expected to have any public health impact on RLS.

The Committee opinion is that the actual benefit of SIFROL will be substantial in very severe forms of idiopathic RLS. It considers that the actual benefit of SIFROL is insufficient for all other forms.

4.2. Improvement in actual benefit

SIFROL share the same the level of ASMR IV with ADARTREL (ropinirole) in the management of patients with very severe idiopathic restless legs syndrome.

4.3. Therapeutic use

Restless legs syndrome is a condition that is diagnosed clinically. Four subjective diagnostic criteria were established by the IRLSSG in 1995 and revised in 2003[1] :

- an overwhelming need to move the limbs, often associated with uncomfortable and unpleasant sensations. The upper limbs and other body parts are sometimes concerned;
- the overwhelming need or the unpleasant sensations appear or worsen during periods of rest or inactivity, such as when the patient is lying or sitting;
- the overwhelming need or unpleasant sensations are partially or entirely relieved by movement, such as walking or stretching, at least while this activity is maintained;
- the overwhelming need or unpleasant sensations appear or worsen in the evening or at night.

Validated diagnostic criteria are recent and still not fully understood. The symptoms experienced are not specific and a differential diagnosis is necessary.
Pramipexole is reserved for the treatment of idiopathic forms. Physicians should look for a secondary disease associated with RLS (in particular, iron deficiency, chronic renal impairment, peripheral neuropathy, endocrine disorder), or another cause (iatrogenic drug-related disorder, pregnancy).

Interviews with patients are an important part of assessing the severity of the condition, its impact and how it is progressing.
The most common forms of restless legs syndrome are benign and a non-pharmacological approach may be beneficial and sufficient (advice on diet and lifestyle, taking more exercise).

The Committee believes that patients with very severe forms of restless legs syndrome would gain most from treatment with SIFROL.
Symptoms can be regarded as very severe if:

- they cause significant sleep disorders and/or have a notable negative effect on the patient's daily, family, social and/or professional life.
- the severity score on the IRLS scale is 31 or more.

The initial diagnosis of the syndrome, evaluation of its severity and elimination of differential diagnoses require particular clinical experience and must be performed in the context of consultation with a specialist (neurologist or doctor working in a sleep centre).

The severity of symptoms can vary over time, and little long-term data is available on the use of pramipexole in this pathology. Patients must be monitored in order to assess their response to treatment: the syndrome can paradoxically worsen during treatment, the effect may wear off, the patient may suffer adverse events.

SIFROL must be introduced gradually in line with the dose levels defined in the marketing authorisation in order to limit the development of adverse events associated with pramipexole.

4.4. Target population

The prevalence of restless legs syndrome (RLS) reported in recent international epidemiological studies ranges from 2.5% to 15%[2].
The INSTANT epidemiological study[3] carried out in France on a sample of over 10,000 people aged 18 or over produced an estimate of annual prevalence of RLS of 8.5%[4] (95% CI 8.0;9.0): 56% of patients have moderate to very severe RLS (IRLS score of 11 to 40): 35% have moderate RLS (11 to 20), 17% have severe RLS (21 to 30) and 4.4% have very severe RLS (31 to 40).

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1 Allen RP et al. (a). Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology - A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health
Sleep Medicine 2003;4(2):101-119.

2 Zucconi M, Ferini-Strambi L. Epidemiology and clinical findings of restless legs syndrome. Sleep Med. 2004;5,293-9.

3 Tison F, Crochard A, Leger D, Bouee S, Lainey E, El Hasnaoui A. Epidemiology of restless legs syndrome in French adults: a nationwide survey: the INSTANT Study. Neurology 2005;65:239-246.

4 This prevalence figure includes patients visiting a doctor at least once a year with RLS symptoms.

The moderate and severe forms of the syndrome affect 4.4% and 0.4% of the general adult population respectively. Extrapolating this data to the French population aged over 18 (about 49 million people) gives an estimate of the number of patients with very severe RLS at around 183,000; 75% of these patients, or around 130,000 patients, probably have idiopathic RLS.

4.5. Recommendations

As patients with very severe forms of restless legs syndrome would gain most from treatment with SIFROL,

As the initial diagnosis of these forms, evaluation of their severity and elimination of differential diagnoses require particular clinical experience and must be performed in the context of consultation with a specialist (neurologist or doctor working in a sleep centre),

The Transparency Committee recommends the inclusion of the medicinal products in the list of medicinal products reimbursed by National Insurance and of the medicinal products in the list of medicinal products approved for use by hospitals and various public services,

- in very severe forms of restless legs syndrome: patients suffering from significant sleep disorders and/or for whom the condition causes a notable negative effect on their daily, family, social and/or professional life, and an IRLS score of 31 or more.
- provided that the initial prescription is issued by a neurologist or a specialist doctor working in a sleep centre.

The Transparency Committee doesn't recommend the inclusion of the medicinal products in the list of medicinal products reimbursed by National Insurance and of the medicinal products in the list of medicinal products approved for use by hospitals and various public services in the moderate or severe forms of the condition.

The Transparency Committee requests the pharmaceutical company to conduct a study to assess the gap between the target population for RLS and the population accessed, particularly in view of the possibility of:
- medicalisation of patients in whom the severity of the condition has not been thoroughly assessed,
- inappropriate medical treatment of patients for whom this condition is a somatic expression of a psychiatric disorder requiring specific treatment.

This data-collection exercise should be conducted more than once in order to ascertain how practices are evolving.

The committee wishes to re-examine these product in the light of the results obtained at the end of the first year of this study.

If scheduled or ongoing studies, in particular within the scope of the European Risk Management plan, do not answer all the questions raised by the Transparency Committee, a specific study must be conducted.

4.5.1 Packaging

The packaging is adapted to prescription requirements in the indication.

4.5.2 Reimbursement rate: 65%

Table 1: summary of clinical studies assessing the efficacy of pramipexole versus placebo

Study	Patients	Methodology/treatments	Endpoints	Efficacy results (ITT)	Safety results
248.520 Europe	Idiopathic RLS*, IRLS>15, symptoms present at least 2 or 3 days a week in the three months prior to inclusion. n=345 patients included n=338 patients analysed (PPX 224, PL 114) Average age: 55.5 Average IRLS: 24.9 (moderate to severe)	Phase 1: 6 weeks: R, DB, PG Phase 2: 46 weeks: DB (respondents), open-label (non-respondents) - <u>PPX at variable doses</u>: 0.125 to 0.75 mg - Placebo	IRLS CGI-I - respondents (much better, very much better)	Δ IRLS at 6 weeks: PPX: -12.3 PL: -5.7 Average adjusted difference: -6/6 (95% CI -8.6;-4.5) CGI-I respondents: PPX: 62.9% PL: 32.5%	Phase 1 Most frequent AEs (%): nausea (12.2 vs 6.1 under PL), headache (13 vs 9.6), fatigue (9.1 vs 6.1). Phase 2 (respondents at 6 weeks) Most frequent AEs (%): nausea (10.6 vs 2.9), headache (8.5 vs 2.9)
248.543 United States	Idiopathic RLS*, IRLS>15, symptoms present at least 2 or 3 days a week in the three months prior to inclusion. n=344 patients included n=339 patients analysed (PPX 254, PL 85) Average age: 51 Average IRLS: 23.5	R, DB, PG, 12 weeks - <u>PPX at fixed doses</u>: 0.25 mg, 0.50 mg or 0.75 mg - Placebo	IRLS CGI-I - respondents (much better, very much better)	Δ IRLS at 12 weeks PPX: -13.5 PL: -9.3 Average adjusted difference: -4.3 (95% CI - 6.4;-2.1) CGI-I respondents PPX: 72.0 % PL: 51.2 %	Most frequent AEs (%): dizziness (9.7 vs 7.0), somnolence (10.1 vs 4.7), nausea (19 vs 4.7) Termination of treatment: 20.2% under PPX, 12.8% under PL (for AE: 11.6 vs 5.8)
248.546 Germany	Idiopathic RLS*, IRLS>15, symptoms present at least 2 or 3 days a week in the three months prior to inclusion. n=150 responsive patients n=147 patients (PPX 78, PL 69) Average age: 58 Average IRLS: 28.5	Phase 1: open-label 6 months n=222 Phase 2: R, DB, PG, 12 weeks among responsive patients (n=150) - PPX at fixed doses: 0.125 to 0.75 mg - Placebo	Median time to onset of aggravation of CGI-I (worse to very much worse) associated with an IRLS score of > 15 on termination of 6 months of treatment with pramipexole (Kaplan-Meier)	Median time to onset of the event: 7 days under PL and > 84 days under PPX	Phase 2 Terminations of treatment: - PPX 7 patients - PL 47 patients

Study	Patients	Methodology/treatments	Endpoints	Efficacy results (ITT)	Safety results
248.515[1] Finland	Idiopathic RLS*, IRLS>15, symptoms present at least 2 or 3 days a week in the three months prior to inclusion. PLMI-index ≥ 5/h n=109 patients n=107 analysed (PPX 86, PL 21) Average age: 56.2 Average IRLS: 23	Phase 1: R, DB, PG, 3 weeks Phase 2: 26 weeks open-label - PPX at fixed doses: 0.125 mg, 0.25 mg, 0.50 mg or 0.75 mg - Placebo	PLMI at 3 weeks	Reduction in PLMI** (mvmnts/h) PL : -8.45 PPX 0.125 mg : -41.1 PPX 0.25 mg : -34.8 PPX 0.50 mg : -33.6 PPX 0.75 mg : -30.9 Respondents' CGI : 42.9% vs 75.6%	Phase 1 Most frequent AEs (%): headache (19.5 vs 31.8), fatigue (18.4 vs 22.7), nausea (14.9 vs 4.5) Worsening of RLS: PPX 4 patients (vs 0 under PL)

R: randomised, DB: double-blind, CO: cross-over, PG: parallel-group, PL: placebo, PPX: pramipexole

* : Idiopathic RLS according to the IRLSSG criteria

** : Periodic Limb Movement Index (PLMI) : number of PLM in bed per hour

1 Partinen M et al. Efficacy and safety of pramipexole in idiopathic restless legs syndrome: A polysomnographic dose-finding study - The PRELUDE study. Sleep Medicine 2006; 1-11 (online)