HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION
19 December 2012

SIFROL 0.088 mg/0.125 mg, tablets
B/30 (CIP code : 34009 363 467 9-6)
B/100 (CIP code: 34009 363 468 5 -7)
SIFROL 0.18 mg/0.25 mg, tablets
B/30 (CIP code: 34009 363 469 1-8)
B/100 (CIP code: 34009 363 471 6-8)
SIFROL 0.35 mg/0.5 mg, tablets
B/30 (CIP code: 34009 363 472 2-9)
B/100 (CIP code: 34009 363 473 9-7)
SIFROL 0.7 mg/1.0 mg, tablets
B/30 (CIP code: 34009 363474 5-8)
B/100 (CIP code: 34009 363475 1-9)

APPLICANT: BOEHRINGER INGELHEIM FRANCE

INN	pramipexole
ATC code (2012)	N04BC05 (dopaminergic agonist)
Reason for the review	**Re-assessment of the Actual Benefit and Improvement in Actual Benefit for the symptomatic treatment of idiopathic restless legs syndrome (RLS at the request of the Committee (pursuant to article R 163-21 of the French Social Security Code)**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Inclusion for Hospital Use** (French Public Health Code L.5123-2)
Indication concerned	**"In adults: symptomatic treatment of moderate to severe idiopathic restless legs syndrome in doses up to 0.54 mg of base (0.75 mg of salt)"**

Actual Benefit:	Moderate in patients with very severe idiopathic RLS.
Improvement in Actual Benefit:	SIFROL provides a minor improvement in actual benefit (IAB IV) in the management of patients with very severe idiopathic restless legs syndrome.
Therapeutic use	First-line treatment in patients with very severe idiopathic RLS
Recommendations	A post-registration study should be carried out. This study will allow to assess the potential difference between the target population in very severe RLS and the population actually treated. The Committee considers that initial medical prescription should be performed by a neurologist or a specialist practitioner working in a sleep centre.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial (centralised European procedure): 14 October 1997 Extension of indication: 06 April 2006 Ongoing European Risk Management Plan (RMP)[1]
Prescribing and dispensing conditions/special status	List I

ATC Classification	2012	
	N	Central nervous system
	N04	Anti-Parkinsonian medicine
	N04B	Dopaminergics
	N04BC	Dopaminergic agonists
	N04BC05	Pramipexole

02 BACKGROUND

SIFROL (pramipexole), a dopaminergic agonist, is a proprietary medicinal product already registered for the symptomatic treatment of Parkinson's Disease (substantial AB and IAB V compared with bromocriptine, opinion of 2 June 2004). It has been 65% refundable (non-LTC) in this indication since July 2005.

The Committee recommended inclusion on the list for symptomatic treatment of idiopathic restless legs syndrome (IRLS), only in very severe forms (substantial AB and IAB IV in management, opinion of 28 February 2007). This proprietary medicinal product has never been listed in this indication.
This favourable opinion is accompanied by a recommendation that initial prescription is performed by a neurologist or by a specialist doctor practising in a sleep centre and that a study is conducted in order to assess the difference between the target population for reimbursement (very severe patients) and the actual population and to confirm the correct use of the medicine, particularly because of the risk of treatment with it in patients who do not require it.

Very severe patients are defined as those with severe disturbances of sleep and/or significant negative consequences on everyday family, social and/or occupational life and IRLS score of 31 or greater.

Two other dopaminergic agonists are also indicated for the symptomatic treatment of RLS (moderate to severe forms): ADARTREL (ropinirole) and NEUPRO (rotigotine). The first was rescinded in March 2012 and the company which markets the second has never applied for it to be listed; NEUPRO however is listed on the national health insurance and hospital use lists for Parkinson's Disease.

As the availability of therapies, particularly drug therapies, for patients with very severe RLS raises a problem, the Committee has decided to reassess SIFROL (pramipexole) in this indication.

[1] Cf. ANSM Website: http://ansm.sante.fr/Activites/Surveillance-des-medicaments/Medicaments-sous-surveillance-renforcee2/Medicaments-sous-surveillance-renforcee/Agonistes-dopaminergiques-et-Levodopa/(language)/fre-FR.

03 THERAPEUTIC INDICATIONS

"In adults:
- 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[2] up to 0.54 mg of base (0.75 mg of salt): cf. Dosage and method of administration.**" (Indication being re-assessed).

04 DOSAGE

Restless legs syndrome: the recommended starting dose of SIFROL is 0.088 mg of base (0.125 mg of salt) taken once daily 2 to 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)	(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.

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 reinitiated 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.
In a 26 week placebo-controlled trial, rebound of RLS symptoms (worsening of symptom severity as compared with baseline) was observed in 10% of patients (14 out of 135) after abrupt discontinuation of treatment. This effect was found to be similar across all doses.

[2] The doses of pramipexole are always expressed in the literature as salt equivalent. The doses expressed in this text are both for the base form and for the salt form (between parentheses).

Dosage 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.

Dosage in patients with hepatic impairment:

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

05 THERAPEUTIC NEED

Restless legs syndrome (RLS) is a sporadic or inherited neurological disorder involving sensory motor symptoms due to unpleasant sensations mainly affecting the lower limbs and accompanied by an irrepressible need to move. Symptoms are often more severe at the end of the day. They are worsened by prolonged immobility and partially or temporarily relieved by the movement.

Primary or idiopathic forms of RLS can be distinguished from secondary forms (end stage chronic renal failure, pregnancy, peripheral neuropathies and iron deficiency, knowing that iron deficiency worsens idiopathic forms of RLS).[3]
The International Restless Legs Syndrome Study Group validated a scale used mostly in clinical trials to assess the severity of symptoms and their development in 2003.[4] This scale contains 10 items scored from 1 to 4 depending on symptom severity (0 = no symptoms; 4 = very severe symptoms); the maximum score is 40. This scale is also useful for epidemiological studies and used to classify patients into:

- moderate form: IRLS score < 24
- severe form: IRLS score > 24 and < 30
- very severe form: IRLS score > 30.

In equivocal cases (difficulty in expression, dementia patients, children, interference from other pain or co-morbidities), video-polysomnography can establish the diagnosis by showing the patient's behaviour overnight when wakening (continued agitation of many voluntary movements in 100% of cases, more occasionally periodic involuntary movements) and during sleep (periodic involuntary movements in 60% of cases).

The patients complain of sensory problems (electrical discharges, stinging sensation, tension, burning) and affective disorders (tiring, troublesome, intolerable, irritant and depressing). Pain is common (60% of patients in hospital series; Allen, Arch Intern Med 2005; Karroum, Sleep Med 2011). Sleep disturbance may also occur. These are characterised by insomnia with painful, unpleasant, excessive awakeness with periods of sleep lasting less than 4 hours. Daytime drowsiness is reported in a third of patients.

Treatment of idiopathic forms of the condition is with lifestyle and pharmacological therapies. According to the SFRMS, patients are recommended to avoid coffee, tea and white wine and to go to bed at a fixed time, although these recommendations are not based on scientific efficacy evidence. Stopping medicines which worsen the RLS (particularly neuroleptics and antidepressants) when this is medically possible may occasionally be sufficient to relieve the sensations as can correction of hypoferritinaemia.

Several medicines can be prescribed although the assessment of their efficacy is based on clinical data with various levels of evidence. These include levodopa and the dopaminergic agonists, benzodiazepines, opioids and anticonvulsants. Only three medicines, non ergot anti-Parkinsonian

[3] Ekbom K, Ulfberg J. Restless legs syndrome. Ann Intern Med 2009; 266 (5): 419-31.
[4] 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 (2): 121-32.

dopaminergic agonists, have obtained Marketing Authorisation to date in France: ropinirole (ADARTREL) and pramipexole (SIFROL) which are administered orally and (NEUPRO), which is administered percutaneously. According to their Marketing Authorisation wording these have a restricted indication for moderate to severe forms of idiopathic RLS.
Sedatives such as the benzodiazepines (particularly clonazepam), are also prescribed to combat the insomnia and relieve symptoms during the night. If symptoms are intolerable and accompanied by pain, pain relief medicines can be offered (codeine, oxycodone). If involuntary leg movements disturb sleep, anticonvulsant therapy such as gabapentin can be considered.

In particular, the therapeutic need is particularly poorly covered in severe and very severe forms of RLS as these three medicines offer limited efficacy (mild to modest effect which appears to reduce over time), it has not been clearly demonstrated (small numbers, short follow-up periods up to 7 months) and may cause paradoxical worsening of the RLS or serious adverse effects (impulse control difficulties, psychotic problems) or reduced quality of life (psychotic or gastrointestinal problems, sudden episodes of falling asleep).

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicines

Two other dopaminergic agonists have Marketing Authorisation in France for the treatment of idiopathic restless legs syndrome: ropinirole and rotigotine.

NAME (INN) *Company*	Identical pharmaco-therapeutic class? yes/no	Indication	Date of opinion	AB	IAB	Reimburse-ment
ADARTREL, tablets (ropinirole) *GLAXOSMITHKINE*	Yes	Symptomatic treatment of moderate to severe idiopathic RLS in adults	30 March 2011	insufficient	not applica ble	no
NEUPRO 2 mg/24 h, transdermal device (rotigotine) *UCB Pharma*			No application for registration made	not applicable	not applic-able	no

For information, the medicines used off-label for the treatment of RLS include in particular:

- levodopa[5] (SINEMET, MODOPAR),
- Other rye ergot derived-dopaminergic agonists: cabergoline (DOSTINEX), bromocriptine (PARLODEL) and lisuride (DOPERGINE). These medicinal products carry a risk of valve disease and systemic fibrosis.
- a benzodiazepine, oral clonazepam (RIVOTRIL),[6,7]
- antiepileptics: gabapentin (NEURONTIN) and pregabalin (LYRICA),
- opiodes such as oxycodone (OXYCONTIN), tramadol, methadone and morphine.

◗ Conclusion:

ADARTREL and NEUPRO are the relevant comparators for SIFROL although none are refundable.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Four medicines have obtained Marketing Authorisation from the FDA in the United States of America (USA), for the treatment of moderate to severe RLS: pramipexole (MIRAPEX, MIRAPEXIN, SIFROL), ropinirole (ADARTREL and its generics), rotigotine (NEUPRO) and since 6 April 2011, gabapentin enacarbil (HORIZANT).

[5] Six clinical studies which compared levodopa to placebo and three studies which compared it to a dopaminergic agonist have been analysed recently in a Cochrane meta-analysis. These studies included 521 patients and lasted 1 to 8 weeks. The symptom severity score (score on a scale of 0 to 10) fell by 1.34 points ([95% CI: -2.18 to -0.5], p=0.002) on L-DOPA in two placebo-controlled studies, periodic leg movements during the sleep were reduced by 26.3/hour of sleep compared with placebo ([95% CI: -30.53 to -22.02], p<0.00001). In two of the placebo-controlled studies, sleep quality (SMD: 0.92 [95% CI: 0.52 to 1.33], p<0.00001) and quality of life (3.23 mm on a 50 mm visual analogue scale [95% CI: 1.64 to 4.82], p<0.0001)) also improved on levodopa.

[6] Matthews WB. Treatment of the restless legs syndrome with clonazepam. Br Med J 1979; 1 (6165): 751.

[7] Clonazepam has been included on the list of toxic substances since January 2012, because of its misappropriation for addictive purposes and now requires dispensing on secure prescription for periods not exceeding one month.

08 SUMMARY OF PREVIOUS ASSESSMENTS

CF Appendix 1

Date of opinion	28 February 2007 (registration)
Indication	Symptomatic treatment of moderate to severe restless legs syndrome.
AB (wording)	- Substantial in very severe forms of idiopathic RLS. - Insufficient in other forms of RLS
IAB (wording)	The SIFROL proprietary medicinal products offer the same minor improvement in actual benefit (level IV) as the ADARTREL proprietary medicinal products (ropinirole) in the management of patients with very severe idiopathic RLS
Studies requested	The Transparency Committee would like the company to carry out a study in order to assess the difference between the target population in RLS and the population actually treated, particularly because of the potential existence of: - medicalisation of patients whose severity has been poorly assessed. - inappropriate medical treatment of patients whose complaint represents the somatic expression of a psychiatric problem requiring specific treatment. It would be desirable for this data collection to be repeated in order to describe changes in practices. The Committee would like to re-examine these proprietary medicinal products in light of the results obtained at the end of the first year of this study.

09 ANALYSIS OF NEW AVAILABLE DATA

The new clinical data presented by the company are based on the results of three post-marketing studies (phase IV) which compared pramipexole with placebo in patients with idiopathic restless legs syndrome (cf Appendix 2):

- A double-blind, randomised, controlled study, the objective of which was to compare the efficacy and adverse effects of oral pramipexole after treatment for 26 weeks at a dose of 0.125 to 0.75 mg/d with placebo in patients with moderate to severe RLS (study 248.629).[8]
- A double-blind, randomised, controlled study, the objective of which was to compare the efficacy of pramipexole at a dose of 0.125 mg/d to 0.75 mg/d with placebo after 12 weeks on symptoms of RLS (based on the IRLS scale), mood disturbances (based on item 10 of IRLS scale) and depressive symptoms (based on the BDI-II - Beck Depression Inventory-II) in ambulatory patients with RLS of unstated severity (study 248.604).[9]
- A double-blind, randomised, controlled study, the objective of which was to compare the efficacy of pramipexole at a dose of 0.125 to 0.75 mg/d with that of placebo over 12 weeks on symptoms of RLS (based on the IRLS) and on disturbed sleep (based on the MOS – Medical Outcome Study sleep scale in ambulatory patients with moderate to severe RLS (study 248.615).[10]

Other data: a Cochrane meta-analysis[11,12] assessed the efficacy of dopaminergic agonists in the treatment of RLS.

No efficacy or safety studies have compared pramipexole with ropinirole or rotigotine in RLS. On the other hand there is a study which compared pramipexole with L-DOPA. In addition, one study compared ropinirole to lisuride (cf. Cochrane analysis of controlled studies with levodopa[13]).

09.1 Efficacy

9.1.1 Pramipexole versus placebo

In study 248.629, conducted between May 2007 and July 2008 (42 centres from 9 European countries), 331 patients were randomised and 329 were given treatment: 166 in the pramipexole group and 163 in the placebo group. The primary efficacy endpoint was change in the total IRLS score after treatment for 26 weeks compared with baseline.

Primary efficacy endpoint: after treatment for 26 weeks the mean adjusted IRLS score fell by 13.7 in the pramipexole group and by 11.1 points in the placebo group, i.e. a mean difference in favour of pramipexole of 2.6 points, p=0.0077.

The secondary endpoints included the following:

- the percentage of IRLS responders (defined by a ≥ 50% fall in the score) was higher in the pramipexole group (58.6%) than in the placebo group (42.8%), p = 0.0044.

[8] B. Högl et al. Efficacy and augmentation during 6 months of double-blind pramipexole for restless-leg syndrome. Sleep Med. 2011; 12 (4): 351-60.
[9] P. Montagna et al. Randomized trial of pramipexole for patients with restless legs syndrome (RLS) and RLS-related impairment of mood. Sleep Med 2011; 12 (1): 34-40.
[10] L. Ferini-Strambi et al. Effect of pramipexole on RLS symptoms and sleep: a randomized, double-blind, placebo controlled trial. Sleep Med 2008;9 (8): 874-81.
[11] Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Dopamine agonists for restless legs syndrome. Cochrane Database Syst Rev. 2011 Mar 16; (3): CD006009.
[12] Hornyak M, Trenkwalder C, Kohnen R, Scholz H. Efficacy and safety of dopamine agonists in restless legs syndrome. Sleep Med. 2012 Mar;13(3):228-36. Epub 2012 Jan 27.
Hornyak M, Trenkwalder C, Kohnen R, Scholz H.
[13] Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Levodopa for restless legs syndrome. Cochrane Database Syst Rev. 2011 Feb 16; (2): CD005504.

- the percentage of responders according to the CGI-I (Clinical Global Impression-Improvement scale/improved, greatly improved) was higher in the pramipexole group (68.5%: 111 out of 162) than in the placebo group (50.3%: 80 out of 159), p=0.001.

The results of this post-marketing study were incorporated into the SIFROL SPC.

In study 248.604, conducted between July 2006 and June 2007 in 9 countries (Italy, United Kingdom, Ireland, Spain, Germany, Sweden, Finland, France and Korea), 404 patients were randomised and 403 were given treatment: Two-hundred in the placebo group and 203 in the pramipexole group. The intention-to-treat population was made up of 199 patients in the placebo group and 203 in the pramipexole group.
The results (intention-to-treat analysis) after 12 weeks of treatment are shown below:

- the mean adjusted change in total IRLS score was greater in the pramipexole group (-14.2 ± 0.7) than in the placebo group (-8.1 ± 0.7), p < 0.0001.
- the mean adjusted change in the BDI-II scale was greater in the pramipexole group (-7.3 ± 0.4) than in the placebo group (-5.8 ± 0.5), p = 0.0199.
- The responder rate (reduction towards slight or no problems, item 10 of the IRLS), was greater in the pramipexole group (75.9%) than in the placebo group (57.3%), p < 0.0001.

In study 248.615, conducted between August 2006 and May 2007 in 49 centres from 9 countries (Italy, Germany, United Kingdom, Ireland, Spain, Sweden, Finland, Denmark and Norway), 369 patients were randomised and treated: 187 in the placebo group and 182 in the pramipexole group. The intention-to-treat population (main analysis) was made up of 357 patients, 179 patients in the placebo group and 178 in the pramipexole group.
After treatment for 12 weeks:

- IRLS score: the mean adjusted change from baseline was higher in the pramipexole group (-13.4 ± 0.7) than in the placebo group (-9.6 ± 0.7), p ≤ 0.0001.
- MOS sleep disturbance score: the mean adjusted change from baseline was higher in the pramipexole group (-25.3 ± 1.5) than in the placebo group (-16.8 ± 1.5), p ≤ 0.0001.

9.1.2 Cochrane meta-analysis

The Cochrane meta-analysis included controlled randomised studies available in December 2008 for lisuride, pergolide and cabergoline (rye ergot derived agonists), ropinirole (ADARTREL), pramipexole (SIFROL), rotigotine (NEUPRO) and sumanirole (non-rye ergot derived agonists). The results of 38 randomised studies were included: 35 placebo-controlled studies (6,954 patients included) and 3 studies against L-DOPA, i.e. a total of 7,365 adult patients suffering from moderate to severe RLS. The majority of placebo-controlled studies lasted for 12 weeks. Only four studies examined the efficacy and adverse effects of the dopaminergic agonists for up to 7 months. In particular, two studies lasting 26 weeks (one with pramipexole and the other with ropinirole) and two studies lasting 7 months (with rotigotine) were included.

Results of the comparisons against placebo (primary objective of the meta-analysis):
Overall, the dopaminergic agonists were more effective than placebo except for sumanirole. The results supporting the dopaminergic agonists were identified from the following criteria:

- Symptom severity:
  - IRLS severity score (33 studies): mean fall in score -5.74 [95% CI: -6.74 to -4.74], p < 0.00001. This comparison showed very considerable heterogeneity (I^2 = 75%).
  - Percentage of responders according to clinical global impression (CGI-I): RR = 1.44 ([95% CI: 1.34-1.54], I^2=49%).
- Periodic leg movement: mean reduction of - 22.4/hour of sleep ([95% CI: - 27.8 to -16.9], I2 = 73%).

In terms of the evaluation of sleep quality, the scores were improved more by the dopaminergic agonists, with a standard mean difference (SMD) of 0.40 [95% CI: 0.33 to 0.47]; the same applied to the quality of life score results (SMD: 0.34 [95% CI: 0.23 to 0.44]).

Results against an active comparator (L-DOPA or lisuride):

- cabergoline and pramipexole produced a greater fall in symptom severity than L-DOPA, with a mean fall in the IRLS score of -5.25 points [95% CI: -8.4 to -2.10]. There were no differences between the pramipexole and L-DOPA groups in terms of reduced periodic leg movement during sleep, percentage responders to the CGI-I, quality of sleep and quality of life.
- lisuride reduced the IRLS more than ropinirole with a mean reduction of - 3.00 points [95% CI: -5.7 to -0.3] and improved quality of life score (MD: -4.50 [95% CI: -8.12 to 0.88]).

Analysis of results by active substance

- Symptom severity: from the sub-group analyses (indirect comparisons), the most effective agonists on IRLS score symptoms were the ergot agonists with a mean additional fall of -11.5 points [95% CI: -15.1 to -7.8] for cabergoline (two studies) and -11.7 [95% CI: -14.8 to -8.6] for pergolide (one study). A significant effect was also found for lisuride patches (-8.0 95% CI: -10.3 to - 5.7]). Except for rotigotine patches (-6.98 [95% CI: -8.99 to -4.96], I^2=44%), the magnitude of the effect of the different non rye ergot-derived dopaminergic agonists appeared to be lower and similar to placebo (except for sumanirole which was identical in efficacy to the placebo): the average fall in IRLS symptom scale was -5.16 ([95% CI: -6.88 to -3.43], I^2=76%) for pramipexole, -4.19 ([95% CI: - 5.40 to -2.97], I^2=58%) for ropinirole and only -1.8 points for sumanirole.
  From a visual examination of the Forest plot, the maximum effects on the IRLS score was found with cabergoline and pergolide (rye ergot-derived dopaminergic agonists): an intermediary effect was seen with rotigotine and a lesser effect with pramipexole and ropinirole.

- Periodic leg movements during sleep: from the sub-group analysis, pergolide, pramipexole and rotigotine appeared to be the most effective in reducing these.

- Sleep quality: pramipexole, rotigotine, cabergoline and ropinirole were no different from the placebo; pergolide appeared to be more effective than placebo although results varied greatly between the studies.

No effects were found depending on severity of the IRLS.

09.2 Adverse effects

9.2.1 Data from clinical studies and the Cochrane meta-analyses

Study 248.629 (26 weeks): an increasing symptom effect was seen in 11.8% of patients in the pramipexole group (N=152) and in 9.4% of patients in the placebo group (N=149). The incidence of confirmed cases was 9.2% in the pramipexole group and 6.0% in the placebo group. This percentage increased with duration of treatment with pramipexole, but not with placebo. The Kaplan-Meier analysis showed no significant difference in time to onset of the increasing symptom effect between the pramipexole and placebo groups. A higher percentage of patients dropped out of the study in the placebo group (36.8%) than in the pramipexole group (21.1%).

Studies 248.604 and 248.615 (12 weeks): in view of their short duration and limited sample size, the contribution of these studies in improving knowledge about the safety profile of pramipexole in RLS is limited and contributes little.

Cochrane meta-analysis of dopaminergic agonists: more patients on dopaminergic agonists stopped treatment because of adverse effects (66 per 1000 patients) than on placebo (33 per 1,000 patients): OR: 1.82 ([95% CI: 1.35 to 2.45], I^2=45%) and had more adverse effects OR: 1.82 [95% CI: 1.59 to 2.08], I^2=24%). According to the subgroup analysis and compared with the placebo group, there were no more discontinuations of treatment because of adverse effects in patients receiving cabergoline, pergolide, pramipexole or rotigotine. On the other hand a difference was found in patients in groups receiving lisuride and ropinirole. In terms of adverse effects, there

were no more adverse effects compared with placebo in the lisuride, pergolide and cabergoline groups. On the other hand, the risk of adverse effects increased in the rotigotine (OR: 2.41, I^2=2%), ropinirole (OR: 2.07, I^2=12%) and pramipexole (OR: 1.48, I^2=0%) groups. The increasing symptom effect could not be assessed reliably in these studies.

Levodopa meta-analysis: Few patients stopped treatment because of adverse effects in the levodopa group although these patients had more adverse effects than those on placebo (OR: 2.61 [95% CI: 1.35 to 5.04, p=0.004).
In the meta-analysis of the three studies which compared levodopa to a dopaminergic agonist, no differences were seen in terms of adverse effects between the two groups. The sub-group analysis suggests that patients receiving pramipexole have slightly fewer adverse effects than those receiving levodopa. The increasing or worsening symptom effect cannot be assessed or quantified from these short term studies and they are of limited relevance in assessing the safety profile of the different medicines.

9.2.2 Update of pharmacovigilance data

According to the international pharmacovigilance data during the last PSUR (*Periodic Safety Update Report*) covering the period from 7 April 2009 to 6 April 2010, exposure during this period was estimated to be approximately 856,846 patient-years for the indication RLS.

To recap, apart from the adverse effects already known about (particularly, nausea, vomiting, hypotension, hallucinations, drowsiness or sudden episodes of falling asleep), the SIFROL SPC refers to the following information in the "Warnings and adverse effects" section.

Included amongst the adverse effects considered to be "expected" which could occur during treatment with SIFROL are: "abnormal dreams, amnesia, behavioural symptoms, constipation, dizziness, dyskinesia, dyspnoea, fatigue, headaches, hiccups, hyperkinesia, hyperphagia, insomnia, visual impairment including diplopia, vision blurred and visual acuity reduced, vomiting, weight decrease including decreased appetite, weight increase."

"**Augmentation of symtoms: Restless Legs Syndrome**: Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medicinal products can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. Augmentation was specifically investigated in a controlled clinical trial [study 248.629] over 26 weeks. Augmentation was observed in 11.8% of patients in the pramipexole group (N = 152) and 9.4% of patients in the placebo group (N = 149). Kaplan-Meier analysis of time to augmentation showed no significant difference between pramipexole and placebo groups."

"Impulse control disorder and compulsive behaviour: Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including SIFROL. Furthermore, patients and caregivers should be aware of the fact that other behavioural symptoms of impulse control disorders and compulsions such as binge eating and compulsive shopping can occur. Dose reduction/tapered discontinuation should be considered."

Psychotic reactions (other than hallucinations) including agitation, delusions, illusions and paranoia have been reported. The SPC states that "patients with psychotic disorders should only be treated with dopaminergic agonists if the potential benefits outweigh the risks. Co-administration of anti-psychotic medicinal products with pramipexole should be avoided."

Cardiac failure: "In clinical studies and post-marketing experience cardiac failure has been reported in patients with pramipexole. In a pharmacoepidemiological study pramipexole use was associated with an increased risk of cardiac failure compared with non-use of pramipexole (observed risk ratio 1.86; 95% CI: 1.21-2.85)."

Hypersensitivity reactions (including urticarial, angio-oedema, skin rash and pruritus) have been described for pramipexole.

9.2.3 Data from the European RMP

The dopaminergic agonists, which are indicated principally in Parkinson's Disease or RLS, appeared in a letter distributed by Afssaps to prescribers in July 2009 about a common adverse effect of the dopaminergic agonist class: impulse control disorder.[14] Behavioural disorders (compulsive gaming, repetitive behaviour, compulsive shopping, hypersexuality) have been reported in patients treated with dopaminergic medicinal products indicated principally for Parkinson's Disease. By 1st December 2008, around a hundred cases of pathological gaming (addiction to gaming, particularly gambling, and resulting in inappropriate, persistent, repeated gaming), repeated purposeless behaviour ("punding"), increased libido and hypersexuality, had been reported in France in patients treated with one or more dopaminergic medicinal products. From the analysis of these cases it appears that:

- the majority of cases occurred in patients treated for Parkinson's Disease. Cases were rarer in treatment of restless legs syndrome and very rare during treatment for endocrine disorders.
- the majority of the cases reported were pathological gaming and "punding". The other problems reported were sexual (increased libido, hyper-sexuality, exhibitionism) and more occasionally, behavioural disorders which could result for example in compulsive shopping.

An evaluation of these adverse effects was also carried out on a European scale for all of the dopaminergic medicinal products. This evaluation indicates that the adverse effects are so-called "class" adverse effects, i.e. they involve all of the medicinal products belonging to this therapeutic class. These adverse effects can have serious consequences, particularly on social, occupational and family life. In addition, the great majority are reported in Parkinsonian patients treated with high doses of the dopaminergic medicinal product or when several dopaminergic medicinal products are co-prescribed. These disorders generally resolve after doses are reduced or the dopaminergic treatment is stopped.

Following this evaluation, the "Warnings and special precautions for use" and "Undesirable effects" sections of the summaries of product characteristics (SPC) for dopaminergic medicinal products with a Marketing Authorisation in France were amended in order to include the risk of these types of adverse effects occurring. The leaflets in the medicine packs intended for patients have also been amended in order to inform patients and their friends and family about this risk.
A European Risk Management Plan (RMP) has been set up for proprietary medicinal products containing pramipexole, ropinirole and rotigotine. An information leaflet was released on 11 April 2011. Monitoring in this RMP has been continued (28 October 2011).

09.3 Summary & discussion

Since the previous Committee opinion, three controlled studies have been submitted by the company:

- in one study including 44.2% of patients with severe to very severe RLS, pramipexole was more effective than placebo after treatment for 12 weeks on symptoms of restless legs syndrome (based on the IRLS) on mood disturbance (based on item 10 of the IRLS scale) and on depressive symptoms (based on the BDI-II). The effect size was modest.
- in one study which did not include severe to very severe RLS, pramipexole was more effective than a placebo after treatment for 12 weeks on symptoms of restless legs syndrome (based on the IRLS), and on disturbed sleep (based on the MOS – Medical Outcome Study sleep scale). The effect size was modest.
- in one study, after treatment for 26 weeks, the benefit of pramipexole over placebo if present was small and its clinical relevance was debatable. Compared with the effect size in the short-term studies, the 26-week results suggest that this benefit also falls over time.

[14] Levodopa, dopaminergic agonists and impulse control disorders. Afssaps – letter to health professionals – pharmacovigilance – 29 July 2009

These studies confirm the efficacy of pramipexole compared with placebo over a limited period of 12 weeks but do not confirm the utility of the medicinal product in the most severe patients beyond 26 weeks.
The Cochrane meta-analysis on dopaminergic agonists showed them to be more effective than placebo up to 29 weeks of treatment. The effect size was described by the authors as moderate in terms of reducing the IRLS severity score. It was greater with ergot derivatives than with non-ergot derivatives and was the same between the non-ergot derivatives. Cabergoline (ergot derivative) and pramipexole (a non-ergot derivative) were however more effective than an L-DOPA on some endpoints. The authors concluded that longer studies against an active comparator were still needed. Larger scale studies are needed to identify the most efficient treatments in patients with RLS.

The safety profile of pramipexole appears to be superimposable to that of the other non-ergot dopaminergic agonists, with two severe adverse effects in particular: behavioural disorders (pathological gaming, repetitive behaviour, compulsive shopping, hypersexuality) and paradoxical worsening of the RLS.

The main points for discussion from these findings are the evaluation of the effect size and ability to extrapolate findings:
- clinical data suggest that the efficacy of pramipexole on symptom severity is modest but greater than placebo for up to 26 weeks. There are as yet no clinical data supporting the clinical utility of pramipexole in patients with very severe RLS and the risk of aggravation has not been correctly assessed during long-term treatment.
- no studies have compared the efficacy of the medicinal products indicated in RLS (Marketing Authorisation) (pramipexole, ropinirole, rotigotine).
- clinical evaluation is limited to 6 months whereas pramipexole therapy is liable to be prescribed long-term in some patients.

010 THERAPEUTIC USE

RLS must only be treated after its diagnosis has been established unequivocally (exclusion of intermittent limb movements during sleep) and assessing its severity (symptom frequency, resultant disability).

According to international guidelines the dopaminergic agonists are a first-line medical treatment of moderate to severe RLS impacting on quality of life[15,16,17,]. However, their long term utility has not been demonstrated and their efficacy does not appear to be maintained[18] (except it appears for rotigotine[19]). No studies have compared dopaminergic agonists between each other or with active medicinal products from other classes.

Some adverse effects may limit their use. All of the dopaminergic agonists therefore expose patients to risks of serious adverse effects and/or effects which may significantly reduce patients'

[15] Vignatelli L, Billiard M, Clarenbach P, Garcia-Borreguero D, Kaynak D, Liesiene V, Trenkwalder C, Montagna P; EFNS Task Force. EFNS guidelines on management of restless legs syndrome and periodic limb movement disorder in sleep. Eur J Neurol. 2006; 13 (10): 1049-65.
[16] Garcia-Borreguero D, Stillman P, Benes H, Buschmann H, Chaudhuri KR, Gonzalez Rodríguez VM, Högl B, Kohnen R, Monti GC, Stiasny-Kolster K, Trenkwalder C, Williams AM, Zucconi M. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurol. 2011; 27; 11:28.
[17] Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, O'Keeffe S, Trenkwalder C, Högl B, Benes H, Jennum P, Partinen M, Fer D, Montagna P, Bassetti CL, Iranzo A, Sonka K, Williams AM. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. Eur J Neurol. 2012 Sep 3. doi: 10.1111/j.1468-1331.2012.03853.x. [Epub ahead of print]
[18] Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med. 2011; 12 (5): 440-4. Epub 2011 Jan 15.
[19] Oertel W, Trenkwalder C, Beneš H, Ferini-Strambi L, Högl B, Poewe W, Stiasny-Kolster K, Fichtner A, Schollmayer E, Kohnen R, García-Borreguero D; SP710 study group. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol. 2011 Aug;10 (8): 710-20. Epub 2011 Jun 24.

quality of life. Behavioural disorders (particularly failure of impulse control) described initially for the treatment of Parkinson's Disease, also appear to be worrying in RLS.[20,21]

A 2012 review[22] recalls that medicinal products may worsen symptoms (symptoms occurring during the day, increased severity and affecting other parts of the body). This increase appears to be associated particularly with high doses and the duration of treatment. For this reason, if symptoms worsen, treatment with the dopaminergic agonist should be reassessed or stopped.

No studies are available which have assessed the different medicinal products beyond 6 months. The appropriateness of treatment with a dopaminergic agonist must therefore be regularly reassessed. These treatments should be stopped promptly if serious adverse effects develop.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual Benefit

◗ Restless Legs Syndrome (RLS) is classified as a chronic organic insomnia. In approximately 80% of cases, the periodic leg movements occur during sleep and are associated with insomnia. The disorder is not life-threatening, does not cause serious complications or disability but may very significantly reduce quality of life. RLS is usually associated with paraesthesiae and dysaesthesiae of the legs combined with motor agitation. These difficulties worsen at rest and are improved by activity. They generally occur in the evening at bedtime. Severe to very severe RLS causes a pronounced deterioration in quality of life.

◗ Pramipexole is a symptomatic treatment.

◗ The efficacy/adverse effect ratio of SIFROL is still modest in short term use. It has not been established beyond treatment for 6 months and at the very severe stage of RLS.

◗ Non-medical alternatives, particularly sleeping habit advice apply to all forms of the condition and are generally sufficient for non-serious cases. In severe cases, medical alternatives are available although none is currently refundable. No studies have compared pramipexole to its therapeutic alternatives, particularly ropinirole.

◗ SIFROL is a first-line medicinal product.

◗ Public health benefit:

In view of the benign nature of idiopathic RLS in the great majority of cases and its expected moderate consequences on quality of life except in the most severe cases, the burden of the disease is considered to be low (very severe cases being a minority). In view of the available clinical data, the expected benefit of SIFROL on morbidity is low overall. A negative impact in some patients cannot be excluded because of the potential adverse effects (particularly, paradoxical worsening of symptoms and impulse control disorders).

[20] Cornelius JR, Tippmann-Peikert M, Slocumb NL, Frerichs CF, Silber MH. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. Sleep. 2010; 33 (1): 81-7.
[21] Voon V, Schoerling A, Wenzel S, Ekanayake V, Reiff J, Trenkwalder C, Sixel-Döring F. Frequency of impulse control behaviours associated with dopaminergic therapy in restless legs syndrome. BMC Neurol. 2011; 28; 11: 117.
[22] Leschziner G, Gringras P. Restless legs syndrome. Review. BMJ 2012; 344: e3056. doi: 10.1136/bmj.e3056.

It is not certain whether the study results can be extrapolated to a real-life situation particularly because of difficulties in identifying the patients who may benefit from medical treatment and the under-use of the IRLS scale in usual clinical practice.
As a result, SIFROL does not have a public health benefit in moderate to severe idiopathic RLS.

As a result/in view of these new findings the Committee considers that the actual benefit of SIFROL is moderate in idiopathic restless legs syndrome but only in patients at a very severe stage. Because of the severity of some adverse effects, less severe cases should not be exposed to this medicinal product.

The Committee confirms its recommendation for inclusion on the list of medicines reimbursable by National Health Insurance and/or on the list of medicines approved for hospital use in very severe forms of RLS. The Committee considers that initial medical prescription should be performed by a neurologist or a specialist practitioner working in a sleep centre.

- **Reimbursement rate: 30%.**

011.2 Improvement in actual benefit

SIFROL offers a minor improvement in actual benefit (IAB IV) in the management of patients with very severe idiopathic restless legs syndrome.

011.3 Target population

The target population for SIFROL is defined as adult patients with very severe idiopathic restless legs syndrome.
According to the study by Allen et al., [23] patients with a confirmed diagnosis of moderate to severe restless legs syndrome with the symptoms occurring at least twice weekly leading them to consult a doctor are believed to represent 0.14% of the general population. By extrapolating these prevalence data to the French population over 18 years old, an estimate can be made that there are no more than 70,000 patients in France.[24] The proportion of patients with very severe RLS is unknown but is less than the 70,000 patients.

[23] Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005; 165 (11): 1286-92.
[24] i.e. approximately 49 million people.

Packaging

These are appropriate for the prescription conditions according to the indication, dosage and duration of treatment.

Specific request inherent to reimbursement.

The Transparency Committee reiterates its request of 2007 for a study to allow an evaluation of the possible difference between the target population in very severe RLS and the population actually treated, particularly because of the potential existence of:
- medicalisation of patients whose severity has been poorly evaluated.
- inappropriate medical treatment of patients whose complaint represents the somatic expression of a psychiatric problem requiring specific treatment.

The Committee recalls that it is in the public health interest for this study to be carried out with proprietary medicinal products containing pramipexole. It would like to re-assess this proprietary medicinal product[25] in light of the results obtained at the end of the first year of the study.

[25] **According to current regulations, the generics have the same AB as the branded medicines for investigation procedures (Art. R163-3 CSS).**

APPENDICES

Appendix 1: Review of the conclusions of the previous opinion

"The efficacy of pramipexole in the treatment of moderate to severe idiopathic restless legs syndrome has been demonstrated against placebo in short term studies (maximum 12 weeks). The benefit observed against placebo was modest, in the region of 4 to 6 points on the IRLS scale (0 to 40). The percentage of greatly improved or very greatly improved responders ranged from 60 to 70% on pramipexole compared with 30 to 50% on placebo. There are no efficacy data for treatment durations beyond 12 weeks. Maintenance of the efficacy of pramipexole remains to be assessed and continuation of treatment must be reconsidered at 3 months. The Committee regrets that there are no direct comparative studies against ropinirole.
A meta-analysis based on five studies (two pramipexole studies, n=677, three ropinirole studies, n=930) which evaluated the efficacy of treatments over a maximum of 12 weeks showed pramipexole to be non-inferior to ropinirole (2.3 IRLS points difference). The efficacy results in favour of pramipexole's superiority are not robust. The analysis of the adverse events which occurred on pramipexole in RLS have shown dopaminergic agonist adverse effects. The most commonly seen on pramipexole during the product development phase were nausea, headaches, asthenia and drowsiness. Pramipexole must be administered using a period when the treatment is started gradually. The CHMP has requested a 6-month placebo-controlled study in order to assess the symptom aggravation effects on treatment and the rebound effect on discontinuation. "

NB. The Transparency Committee, which released opinions for ADARTREL in 2004 and SIFROL in 2007, considered that initial prescription of these medicinal products should be restricted to specialists to ensure the diagnosis is made (stage of severity, differential diagnosis) and that their clinical utility was restricted to the management of patients suffering from very severe RLS. In the case of ADARTREL, following this advice and from the findings about conditions of use of ropinirole from a sample of general practitioners, more than a third of initial prescriptions are not written by a neurologist or a doctor practising in a sleep centre.

Appendix 2: Tabulated summary of new studies

Summary of studies							
Study no. Dates	Methodological design	Patients randomised	Treatment groups	Duration of treatment	Inclusion criteria	Primary endpoint Result	Secondary endpoints
248.629 May 2007 – July 2008	Phase IV Double-blind, randomised placebo-controlled 42 centres, 9 countries	N = 331	Pramipexole (ppx) (= 166) Placebo (plc) (N = 163)	26 weeks	- Ambulatory patients between 18 and 85 years old. - Diagnosed with idiopathic RLS according to IRLSSG clinical criteria. - Symptoms of RLS present for at least 2-3 days per week during the last 3 months before baseline (V2) - Total IRLS score > 15 at baseline (V2)	Δ total IRLS score: Ppx -13.7 (SE 0.8) versus plc -11.1 (SE 0.8) (p=0.0077)	IRSL responder rate: ppx 58.6% versus plc 42.8% (p=0.0044) CGI-I responder rate: ppx 68.5% versus plc 50.3% (p=0.0010) PGI responder rate: ppx 62.3% versus plc 44.0% (p=0.0011) Rate of increase: ppx 9,2% versus plc 6.0% Rebound rate: ppx 10.4%
248.604 July 2006 – June 2007	Phase IV Double-blind, randomised placebo-controlled 52 centres, 9 countries	N = 404	Pramipexole (ppx) (= 203) Placebo (plc) (N = 200)	12 weeks	- 18-85-year-old ambulatory patients - Diagnosed with idiopathic RLS according to IRLSSG clinical criteria. - Symptoms of RLS present for at least 2-3 days per week during the last 3 months before baseline (V2) - Total IRLS score > 15 at baseline (V2) and score ≥ 2 for the IRLS item 10 at baseline	Δ total IRLS score: Ppx -14.2±0.7 versus plc -8.1±0.7 (p<0.0001) Δ BDI-II: Ppx -7.3±0.4 versus plc -5.8±0.5 (p=0.0199) IRLS responder rate item 10: Ppx 75.9% versus plc 57.3% (p<0.0001)	IRLS responder rate: ppx 59.9% versus plc 32.7% (p<0.0001) BDI-II responder rate: Ppx 57.4% versus plc 52.7% (p=0.3821) CGI-I responder rate : ppx 69.3% versus plc 36.9% (p<0.05) PGI responder rate: ppx 62.9% versus plc 38% (p<0.05)
248.615 August 2006 – May 2007	Phase IV Double-blind, randomised placebo-controlled 49 centres, 9 countries	N = 369	Pramipexole (ppx) (= 182) Placebo (plc) (N= 187)	12 weeks	- 18-85-year-old ambulatory patients - Diagnosed with idiopathic RLS according to IRLSSG clinical criteria. - Symptoms of RLS present for at least 2-3 days per week during the last 3 months before baseline (V2) - Total IRLS score > 15 at baseline (V2)	Δ total IRLS score: Ppx -13.4±0.7 versus plc -9.6±0.7 (p ≤ 0.0001 ANCOVA) MOS score: Ppx -25.3±1.5 versus plc -16.8±1.5 (p≤0.0001 ANCOVA)	IRLS responder rate: ppx 59.6% versus plc 39.7% (p=0.0003) PGI responder rate: ppx 62.9% versus plc 38% (p<0.001) CGI-I Responder rate: ppx 66.3% versus plc 40.2% (p<0.001)