HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

18 September 2013

NEUPRO 1 mg/24 hours, transdermal patch

Single-dose sachet – box of 7 transdermal patches (CIP: 34009 267 967 4 7)
Single-dose sachet – box of 30 transdermal patches (CIP: 34009 267 968 0 8)

NEUPRO 2 mg/24 hours, transdermal patch

Single-dose sachet – box of 7 transdermal patches (CIP: 34009 373 285 0 0)
Single-dose sachet – box of 30 transdermal patches (CIP: 34009 377 209 7 7)

NEUPRO 3 mg/24 hours, transdermal patch

Single-dose sachet – box of 30 transdermal patches (CIP: 34009 267 970 5 8)

Applicant: UCB PHARMA SA

INN	**rotigotine**
ATC code (2013)	**N04BC09 (dopamine agonist)**
Reasons for the review	**- Submission by the Directorate-General for Health and the Social Security Directorate on the justification for reimbursement of NEUPRO in idiopathic restless legs syndrome pursuant to ARTICLE R-163-19 of the Social Security Code.** **- Inclusion: NEUPRO 1 and 3 mg/24 hours** **- Extension of the indication: NEUPRO 2 mg/24 hours**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"NEUPRO is indicated in the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults."**

Actual Benefit:	**Moderate in patients with very severe idiopathic RLS.**
Improvement in Actual Benefit	**NEUPRO, like SIFROL, offers 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	**The Committee would like the initial medical prescription to be issued by a neurologist or a specialist doctor working at a sleep centre.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (European centralised procedure)	Dosages of 1 and 3 mg/24 hours Initial in RLS: 29 August 2008 Dosage of 2 mg/24 hours: - Initial Marketing Authorisation in Parkinson's disease: 15 February 2006. - Extension of indication to RLS: 29 August 2008 Current European Risk Management Plan (RMP)[1]
Prescribing and dispensing conditions / special status	List I

ATC Classification	2013	
	N	Central nervous system
	N04	Anti-Parkinson drugs
	N04B	Dopaminergic agents
	N04BC	Dopamine agonists
	N04BC09	Rotigotine

02 BACKGROUND

NEUPRO 2 mg/24h transdermal patch (rotigotine), a dopamine agonist, has been reimbursable in the symptomatic treatment of Parkinson's disease since August 2010[2] (substantial Actual Benefit, no IAB in comparison with REQUIP, opinion of 31 January 2007, and later in comparison with SIFROL, opinion of 30 April 2008).

NEUPRO subsequently obtained Marketing Authorisation in restless legs syndrome (2008). The Directorate-General for Health and the Social Security Directorate approached the Transparency Committee for an opinion on the justification for the reimbursement of NEUPRO in the treatment of idiopathic restless legs syndrome (RLS).[3] Indeed, the applicant had not hitherto applied for reimbursement in this indication.
Two other dopamine agonists are also indicated in the symptomatic treatment of RLS (moderate to severe forms): ADARTREL (ropinirole) and SIFROL (pramipexole). The former was withdrawn in March 2012. SIFROL, which also has an indication in Parkinson's disease, was recently reassessed by the Committee in RLS[4]: Moderate Actual Benefit only in very severe forms and AIB IV in the management of this syndrome, but it is not included.

[1] Version of the RMP valid as of 19 July 2012.
[2] Decree of 30 July 2010 published in the Official Gazette of 04 August 2010 for the presentation in a box of 30 transdermal patches and Decree of 28 January 2011 published in the Official Gazette of 3 February 2011 for its presentation in a box of 7 transdermal patches.
[3] Letter of submission to the Committee by the DSS and DGS of 30 November 2012.
[4] Cf. opinion re-assessing SIFROL of 18 December 2012.

03 THERAPEUTIC INDICATIONS

"- Restless Legs Syndrome: NEUPRO is indicated in the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults."

Only for the 2 mg/24h dosage:

"- Parkinson's disease: NEUPRO is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. 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)."

04 DOSAGE

"NEUPRO is applied once a day. The patch should be applied at approximately the same time of day, every day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different site of application. If the patient forgets to apply the patch at the usual time of day or if the patch becomes detached, another patch should be applied for the remainder of the day.

Restless legs syndrome
Treatment should start with a single daily dose of 1 mg/24 h. Depending on individual patient response, the dose may be increased in weekly increments of 1 mg/24 h to a maximal dose of 3 mg/24 h.
The need for treatment continuation should be reconsidered every 6 months.

Treatment discontinuation:
NEUPRO should be discontinued gradually. The daily dose should be reduced in steps of 1 mg/24 h with a dose reduction preferably every other day, until complete withdrawal of NEUPRO. Following this procedure, rebound (worsening of symptoms beyond initial intensity after discontinuation of treatment) was not observed.

Dosage in cases of hepatic and renal impairment:
- Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment. Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Rotigotine has not been investigated in this patient group. A dose reduction might be needed in case of worsening of hepatic impairment.
- Adjustment of the dose is not necessary in patients with mild to severe renal impairment, including those requiring dialysis. Unexpected accumulation of rotigotine levels may also occur with acute worsening of renal function."

05 THERAPEUTIC NEED

Restless legs syndrome (RLS) is a sporadic or hereditary neurological condition comprising a set of sensorimotor symptoms made up of unpleasant sensations preferentially affecting mainly the lower limbs and characterised by an irresistible urge to move. Symptoms are more severe at the end of the day; they are exacerbated by prolonged immobility and relieved, partially and temporarily, by movement.

A distinction is made between primary or idiopathic forms and secondary forms (end-stage chronic renal failure, pregnancy, peripheral neuropathy and iron deficiency, given that iron deficiency exacerbates idiopathic forms).[5]
In 2003, the International Restless Legs Study Group approved a rating scale used mainly in therapeutic trials to assess symptoms and their progression.[6] The scale consists of 10 items scored from 1 to 4 according to symptom severity (0 = no symptoms; 4 = very severe symptoms); the maximum score is 40. This scale is also used for epidemiological studies and allows patients to be classified as follows:

- mild form: IRLS score > 0 and ≤ 10
- moderate form: IRLS score > 10 and ≤ 20
- severe form: IRLS score > 20 and ≤ 30
- very severe form: IRLS score > 30

In doubtful cases (people who have difficulty in expressing themselves, people with dementia, children, confusion with other related pains or comorbidities), polysomnography helps to clarify the diagnosis by observing the patient's behaviour at night during an awakening (continuous restlessness with numerous voluntary movements in 100% of cases, more rarely periodic involuntary movements) and while asleep (periodic involuntary movements in at least 60% of cases).

Patients complain of sensory disturbances (electrical discharge, stinging, tingling, tension, burning sensation) and affective disorders (exhausting, distressing, unbearable, irritating and depressing). Pain is frequent (60% of patients in hospitalised populations; Allen, Arch Intern Med 2005; Karroum, Sleep Med 2011). Sleep disturbances may also occur. They are characterised by insomnia with hyper-wakefulness, distressing, painful, with sleep periods of less than 4 hours. Daytime somnolence is reported in a third of patients.

Treatment of idiopathic forms relies on lifestyle discipline and medicinal treatments. According to the SFRMS (French society for sleep research and sleep medicine), patients are recommended to avoid coffee, tea and white wine, and to go to bed at a fixed time, but these recommendations are not based on any scientific evidence of efficacy. Cutting out medicines known to exacerbate RLS (including neuroleptics and antidepressants), whenever this is medically feasible, can sometimes be enough to relieve the sensations, as well as correcting any hypoferritinaemia.

Several medicines may be prescribed, in the knowledge that their efficacy relies on clinical data of variable levels of proof; specifically, levodopa and dopamine agonists, benzodiazepines, opioids and anticonvulsants. Only three medicines – non-ergot dopamine agonists for the treatment of Parkinson's disease – have so far received Marketing Authorisation in France: ropinirole (ADARTREL) and pramipexole (SIFROL), which are administered orally, and rotigotine (NEUPRO), administered transcutaneously. According to the wording of their Marketing Authorisation, their indication is restricted to moderate to severe idiopathic RLS.

[5] Ekbom K, Ulfberg J. Restless legs syndrome. J Intern Med 2009;266(5):419-31.
[6] Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4(2):121-32.

Sedatives like benzodiazepines (including clonazepam) are also prescribed for insomnia and for the relief of nocturnal symptoms. If the symptoms are unbearable and accompanied by pain, medicines may be offered for the pain (codeine, oxycodone). If sleep is disturbed by involuntary leg movements, (off-label) treatment with an anticonvulsant such as gabapentine may be considered.

Particularly in severe and very severe forms, there is a poorly-satisfied therapeutic need inasmuch as the three non-ergot dopamine agonists are of limited efficacy (poor to moderate effect size that seems to diminish with time), unproven efficacy (weak effects, short duration of follow-up lasting up to 7 months) and may lead to a paradoxical exacerbation of the RLS or be the cause of serious adverse effects (impulse control disorders, psychotic disorders), or ones affecting quality of life (psychotic disorders, digestive disorders, sudden onset of sleep).

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

In France, two other dopamine agonists have Marketing Authorisation in the treatment of idiopathic restless legs syndrome: pramipexole and rotigotine.

NAME INN *Company*	Same pharmaco-therapeutic category? Yes / No	Indication	Date of opinion	Actual benefit	Improvement in Actual Benefit	Reimbursement
ADARTREL, tablets (ropinirole) *GLAXOSMITHKLINE*	Yes	Symptomatic treatment of moderate to severe idiopathic RLS in adults	30 March 2011	Insufficient	Not applicable	No
SIFROL, tablets Dosages: 0.088 mg/0.125 mg, tablets 0.18 mg/0.25 mg, tablets 0.35 mg/0.5 mg, tablets 0.7 mg/1.0 mg, tablets (pramipexole) *BOEHRINGER INGELHEIM FRANCE*			19 December 2012 (opinion on re-assessment)	Moderate* in patients with very severe idiopathic RLS	Minor (IAB IV) in the management of patients with very severe idiopathic restless legs syndrome.	No

*: other Transparency Committee recommendations: A post-inclusion study should be carried out. This study will enable an assessment to be made of the disparity between the population targeted in very severe RLS and the population actually reached. The Committee would like the initial medical prescription to be issued by a neurologist or a specialist doctor working at a sleep centre.

By way of information, the medicines used off-label in the treatment of RLS are:
- levodopa[7] (SINEMET, MODOPAR),
- other dopamine agonists derived from rye ergot: cabergoline (DOSTINEX), bromocriptine (PARLODEL) and lisuride (DOPERGINE). These medicines expose patients to the risk of heart valve disease and systemic fibrosis,
- a benzodiazepine, clonazepam per os (RIVOTRIL),[8,9]

[7] Six clinical studies comparing levodopa with placebo and three studies with a dopamine agonist were recently analysed in a Cochrane meta-analysis. These studies included 521 patients and lasted from 1 to 8 weeks. With L-DOPA, the symptom severity score (on a scale of 0 to 10) fell by 1.34 points ([95% CI: -2.18 to -0.5], p = 0.002) in two trials versus placebo; periodic leg movements while asleep were reduced by 26.3/h of sleep in comparison with placebo ([95% CI:-30.53 to -22.02], p < 0.00001). In two studies versus placebo, 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)) were also improved with levodopa.

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

- antiepileptics: gabapentine (NEURONTIN) and pregabaline (LYRICA),
- opioids such as oxycodone (OXYCONTIN), tramadol, methadone and morphine.

◗ Conclusion:

ADARTREL and SIFROL are relevant comparators for NEUPRO.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

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

08 ANALYSIS OF AVAILABLE DATA

In moderate to severe restless legs syndrome (RLS), the clinical data presented by the Applicant for NEUPRO (rotigotine) are based on the results of the following three comparative studies:

- two controlled, randomised, double-blind, parallel-group studies whose main objective was to compare the efficacy of rotigotine administered transcutaneously with that of placebo after a 6-month treatment, performed in patients with a moderate to very severe form of RSL (studies SP790[10] and 792).
- a randomised, double-blind, parallel-group, phase III study (SP794) whose main objective was to evaluate the efficacy of transcutaneous rotigotine, in comparison with placebo, on the structural elements of sleep by recording the polysomnographic parameters after 4 weeks of treatment in patients with a moderate to severe form of RLS.

In addition, the Applicant presented the data from three open studies:

- two 1-year extension studies, studies SP790 and SP792: studies SP791 and SP793.
- a 5-year extension study to a dose-finding study (SP710).

Only the tolerability results of these three non-comparative studies are reported.

Other data: A Cochrane meta-analysis[11,12] evaluated the efficacy of dopamine agonists in the treatment of RLS.

[9] The inclusion of clonazepam in the list of toxic products since January 2012, owing to its misuse as a recreational drug, now requires that it be dispensed against an *'ordonnance sécurisée'* (secure prescription) for a period not exceeding one month.

[10] Trenkwalder C et al. SP790 Study group. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomized, double-blind, placebo-controlled trial. Lancet Neurol 2008; 7(7):595-604.

[11] Scholz H, Trenkwalder C, Kohnen R, et al. 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.

There were no efficacy or tolerability studies comparing rotigotine with pramipexole or ropinirole in RLS. On the other hand, there is a study comparing pramipexole with L-DOPA. In addition, one study compared ropinirole with lisuride (cf. Cochrane meta-analysis of controlled studies with levodopa[11]). The Applicant performed an indirect comparison in the form of a multi-treatment meta-analysis of the efficacy of rotigotine with other medicines, including pramipexole and ropinirole, after 12 weeks of treatment.

08.1 Efficacy

8.1.1 Rotigotine versus placebo

Two studies with similar methodologies (study design, endpoint, study duration, choice of comparator) were performed, one in Europe (**SP790**), the other in the USA (**SP792**). The rotigotine doses evaluated were 1 mg/24 h, 2 mg/24 h and 3 mg/24 h. A fourth dosage (0.5 mg/24 h) was also evaluated in study SP792, but this dosage is off-label. Given that the results of these two studies are similar, only the results of the European study at the dosages approved by a Marketing Authorisation are presented below.

In study SP790, conducted between May 2005 and August 2006 (49 centres in 8 European countries), 458 patients were randomised: 341 into the rotigotine group (115 at the dosage of 1 mg/24 h, 112 at 2 mg/24 h and 114 at 3 mg/24 h) and 117 into the placebo group. The included patients, with a mean age of 57.6 years, were predominantly women (69% on placebo and 74% in the rotigotine groups). Patients were included at a moderate to very severe stage, 85% of them at a severe (216 patients, 48%) or very severe stage (166 patients, 37%). There was no difference between treatment groups on inclusion, either in their demographic characteristics or in severity stage.

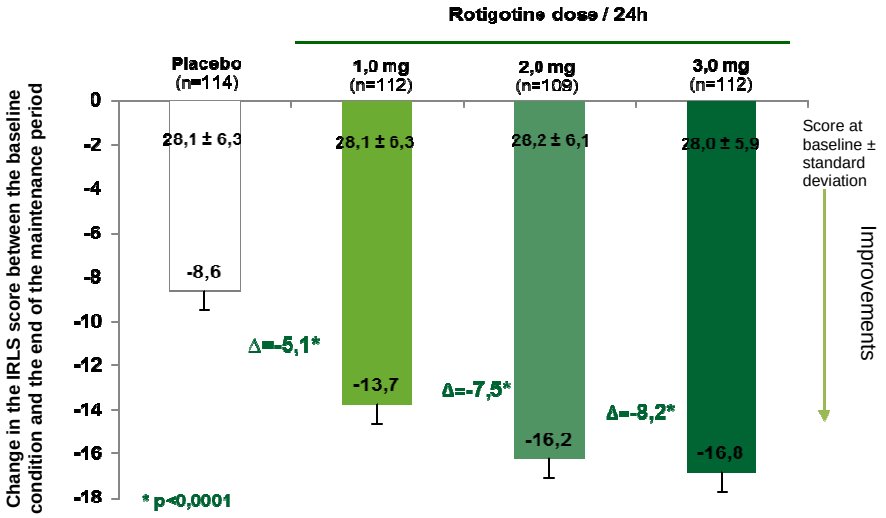
The primary efficacy endpoints were the changes with respect to baseline values in the IRLS score[13] and in item 1 of the CGI scale[14] evaluating the symptomatology and RLS severity, respectively. A 4-point decrease in the IRLS score and a 0.75-point decrease in item 1 of the CGI score were considered to be clinically relevant.[15] Several secondary efficacy endpoints were evaluated, including the percentage responders according to the IRLS score (patients showing a reduction in the IRLS score ≥ 50%) and to item 1 of the CGI scale (patients showing a minimum decrease of ≥ 50% in item 1 of the CGI scale) and the percentage of patients in remission, defined as those showing an IRLS score ≤ 10.In addition, a post-hoc analysis was performed in the subgroup of patients at a very severe stage of the condition.

Results:
After a 6-month maintenance treatment, the results favour rotigotine at the three dosages in comparison with placebo.

As regards the primary efficacy endpoints:
- Symptom progression according to the IRLS score (results for the three rotigotine dosages in Figure 1).

[13] The International Restless Legs Syndrome (IRLS) Rating Scale is used to assess RLS severity. Patients rate various aspects of their symptoms (10 items scored from 0 to 4). They assess the intensity, duration and frequency of fidgeting and its impact on their ability to sleep at night, their alertness during the day and on their quality of life. The score assigned to each item results in a total IRLS rating between 0 and 40. RLS is considered mild with a score between 0 and 10, moderate with a score between 11 and 20, severe with a score between 21 and 30, and very severe with a score between 31 and 40.
[14] Item 1 of The Clinical Global Impression Scale (CGI), severity, is used to assess the severity of RLS. The score can vary from 0 to 7 (the most severe stage).
[15] With a total of 95 patients per group it was possible to show a difference for rotigotine 3 mg/24 h versus placebo with a power of 85% and a (unilateral) α-risk of 0.025.

Figure 1: Change in the IRLS score in study SP790 after a 6-month maintenance treatment (LOCF*)



*LOCF: Last observation carried forward

The IRLS score showed a mean change from 30.7 to 20.7 in the placebo group and from 30.2 to 13.8 in the rotigotine group, i.e. a mean adjusted difference in favour of rotigotine of -6.5 points (95% CI –8.7; –4.4, p < 0.0001).

- RLS severity, evaluated according to item 1 of the CGI scale, was less great in patients receiving rotigotine than those receiving placebo. The mean difference between the rotigotine and placebo groups – greater than the expected difference of 0.75 – was between -0.8 and -1.2 points. The mean change with respect to the baseline value was -2.09 (0.14) in the 1 mg/24 h group, -2.41 (0.14) in the 2 mg/24 h group, -2.55 (0.14) in the 3 mg/24 h group and -1.34 (0.14) with placebo. The differences between each of the three rotigotine groups and placebo were significant (p < 0.0001).

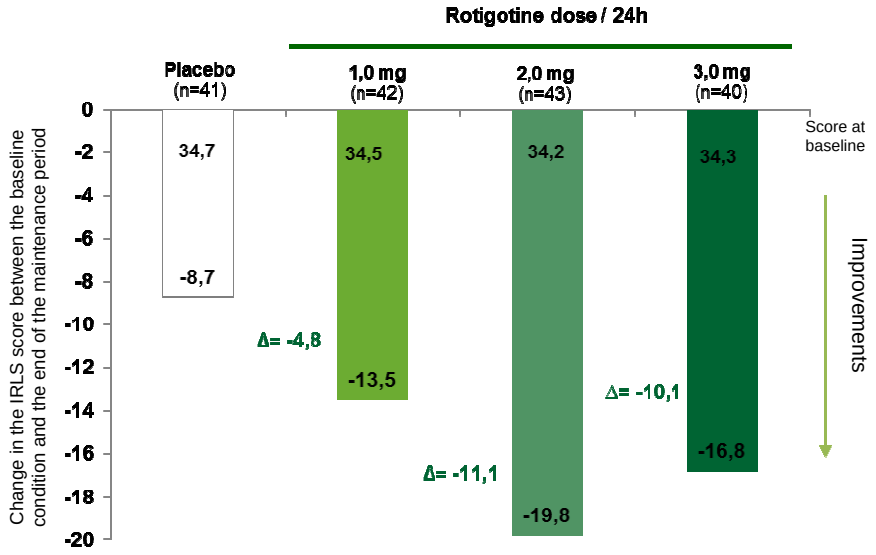
Among the secondary endpoints:

- The percentage of IRLS responders was greater in the rotigotine groups (51.8% at 1 mg/24 h, 57.8% at 2 mg/24 h and 55.4% at 3 mg/24 h) than on placebo (25.4%), p < 0.0001. The difference with respect to placebo was 26.3% in the rotigotine 1 mg/24 h group, 32.4% in the 2 mg/24 h group (p = 0.0011) and 29.9% in the 3 mg/24 h group (p < 0.0001).
- The percentage of responders according to item 1 of the CGI scale was greater in the rotigotine groups (50.9% at 1 mg/24 h, 53.2% at 2 mg/24 h and 61.6% at 3 mg/24 h) than with placebo (31.6%). The difference with respect to placebo was 19.3% in the rotigotine 1 mg/24 h group (p = 0.0032), 21.6% in the 2 mg/24 h group (p = 0.0011) and 30% in the 3 mg/24 h group (p < 0.0001).
- The percentage of patients in remission was greater in the rotigotine groups (41.1% at 1 mg/24 h, 45.9% at 2 mg/24 h and 47.3% at 3 mg/24 h) than with placebo (22.8%). The difference with respect to placebo was 18.3% at 1 mg/24 h, 23.1% at 2 mg/24 h and 24.5% at 3 mg/24 h.

The analysis results in the very severe patient subgroup, representing 37% of included patients, remained in favour of rotigotine:

- In the 1 mg/24 h, 2 mg/24 h and 3 mg/24 h rotigotine groups, the difference in the reduction in the IRLS scores versus placebo was, respectively, -4.8, -11.1 and -10.1 (cf. Figure 2):

Figure 2: Change in the IRLS score in very severe patients in study SP790 (LOCF*)



- The percentage of patients still at a very severe stage (IRLS score ≥ 31) at the end of the study period was 29% in the rotigotine 1 mg/24 h group, 9% in the rotigotine 2 mg/24 h group and 12% in the rotigotine 3 mg/24 h group, as against 51% among patients in the placebo group.

In study SP794, 67 patients, predominantly women, with a mean age of 59.1 years, were randomised: 21 into the placebo group and 46 into the rotigotine group. On inclusion, the patients had moderately severe RLS.[16] Patients treated for RLS had undergone treatment for a mean 3.6 years, but 42% of patients had never previously received any treatment. Patients could receive rotigotine at a dosage of 1 mg/24 h, 2 mg/24 h, 3 mg/24 h (titration phase) or placebo. The primary efficacy endpoint was the change between the two groups in the Periodic Limb Movement Index, or PLMI,[17] at the end of treatment.

Results: After 7 weeks of treatment (4 weeks preceded by a 3-week titration period), there was a greater reduction in the rotigotine group (the value of this index fell from 50.9 to 7.7) than with placebo (37.4 to 32.7), $p < 0.0001$. Among the many secondary efficacy endpoints in this study, it will be noted that the number of movements leading to an arousal per hour of sleep showed a greater reduction in the rotigotine than in the placebo group, with a difference of 3.12 in favour of rotigotine compared with placebo ($p = 0.01$), with the PLMSAI value falling from 8.57/h to 2.47/h in the rotigotine group.[18] In contrast, there was no evidence of any difference between the two groups in terms of sleep efficiency (being the time spent sleeping expressed as a percentage of the time in bed), sleep latency, total sleep time or according to the MOS Sleep Scale.[19] In addition, the motor symptoms of RLS showed a greater improvement during sleep in patients belonging to the rotigotine group: the IRLS score fell by 16.38 points in the rotigotine group versus 10.29 points in the placebo group ($p = 0.01$); the score for item 1 of the CGI scale fell by 2.68 points in the

[16] On inclusion, patients had a mean IRLS score of 25.4 [15-39] in the placebo group and 26.3 [15-39] in the rotigotine group, and a mean score for item 1 of the CGI scale ("severity of illness") of 4.8 for patients in the placebo group and 5.0 in the rotigotine group.
[17] The PLMI (Periodic Limb Movement Index) is defined as the number of periodic limb movements divided by the total time spent in bed. The term Periodic Limb Movements refers to involuntary movements caused by muscle contraction with a frequency of at least 4 muscle contractions lasting from 0.5 to 5 seconds.
[18] This assessment is based on changes in the PLMSAI (Periodic Limb Movements during Sleep Arousal Index). This index is defined by the number of periodic movements during sleep and with arousals, divided by the total sleep time. It reflects the influence of periodic leg movements on sleep continuity. The threshold defining the clinically normal level of PLMSAI is ≤ 2.
[19] The 12-item MOS Sleep Scale Adequacy Subscale seeks to assess the various aspects of sleep.

rotigotine group versus 1.79 points in the placebo group, i.e. a difference in favour of the rotigotine group of 0.89 points (p = 0.02).

8.1.2 Cochrane meta-analysis

A Cochrane meta-analysis included controlled and 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 taken into account: 35 studies versus placebo (6954 patients included) and 3 studies versus L-DOPA, i.e. a total of 7365 adult patients with moderate to severe RLS. Most of the studies versus placebo were over 12 weeks. Only 4 studies examined the efficacy and adverse effects of dopamine agonists for up to 7 months. Two 26-week studies in particular (one with pramipexole and the other with ropinirole) and two 6-month studies with rotigotine were considered.

Results of the comparisons with placebo (primary endpoint of this meta-analysis):
Overall, the dopamine agonists were more effective than placebo, with the exception of sumanirole. Results favourable to the dopamine agonists were revealed in relation to the following endpoints:

- Symptom severity:
    - IRLS severity score (33 studies): mean reduction in the score by -5.74 [95% CI: - 6.74 to -4.74], p < 0.00001. This comparison shows a very great heterogeneity (I^2 = 75%).
    - Percentage of responders according to the Clinical Global Impression scale (CGI-I): RR = 1.44 ([95% CI: 1.34-1.54], I^2 = 49%).
- Periodic leg movement: mean reduction in the score by -22.4/hour of sleep ([95% CI: - 27.8 to -16.9], I^2 = 73%).

As regards the sleep quality assessment, scores were further improved by the dopamine agonists, with a standard mean difference (SMD) of 0.40 [95% CI: 0,33 to 0.47]; the same applied to the results for the quality-of-life score (SMD: 0.34 [95% CI: 0.23 to 0.44]).

Results versus active comparator (L-DOPA or lisuride):

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

Analysis of the results by active substance

- Symptom severity: according to the subgroup analyses (indirect comparisons), the agonists most active on the symptoms in the IRLS score are ergot-derived agonists with a mean additional reduction of -11.5 points [95% CI: -15.1 to -7.8] for cabergoline (2 studies) and -11.7 [95% CI: -14.8 to -8.6] for pergolide (1 study). One notable effect also occurred with lisuride in patch form (-8.0 [95% CI: -10.3 to -5.7]). Apart from rotigotine in patch form (-6.98 [95% CI: -8.99 to -4.96], I^2 = 44%), the amplitude of the effect of the various non-rye-ergot-derived dopamine agonists appears smaller and similar compared with the placebo (except for sumanirole, whose efficacy was the same as that of the placebo): the mean reduction in symptoms on the IRLS scale was -5.16 ([95% CI: -6.88 to -3.43], I^2 = 76%) with pramipexole, -4.19 ([95% CI: -5.40 to -2.97], I^2 = 58%) with ropinirole and only -1.8 points with sumanirole.

    According to the visual examination of the Forest plot: the maximum effect on the IRLS score is observed with cabergoline and pergolide (dopamine agonists derived from rye ergot); it is intermediate with rotigotine and weaker with pramipexole and ropinirole.

- Periodic leg movements during sleep: according to the subgroup analysis, pergolide, pramipexole and rotigotine seemed the most effective in reducing them.

- Sleep quality: there was no difference between pramipexole, rotigotine, cabergoline and ropinirole and placebo; pergolide seemed more effective than placebo, but the results between studies are very heterogeneous.

There was no identification of the effect according to the severity of the RLS.

8.1.3 Indirect comparison

The Applicant proposes to introduce elements of indirect efficacy comparison in relation to RLS for rotigotine versus ropinirole (ADARTREL) and pramipexole (SIFROL) with the aid of a multiple-treatments network meta-analysis based on controlled studies.

Methodology
The data from fifteen placebo-controlled studies lasting 12 weeks or more and including 4413 patients were analysed; two studies were carried out with gabapentine enacarbil, which does not have Marketing Authorisation in France in RLS (cf. Table 1 in the appendix, which shows the design of these studies and the characteristics of the included patients). Although 6-month data are also available for ropinirole and pramipexole, the indirect comparison was carried out on the primary endpoint “change in the IRLS score after 12 weeks of treatment” (12 studies). For rotigotine, the results for the change in the IRLS score after 12 weeks have been extracted from reports on the two pivot studies SP790 and SP792.

Results
After 12 weeks of treatment, and in comparison with placebo, the mean additional reduction in the IRLS score observed with the three dopamine agonists is shown in Table 3.
As regards this criterion, the indirect comparison suggests that (cf. Table 4):
- rotigotine was more effective than ropinirole (REQUIP),
- with no difference in efficacy between rotigotine and pramipexole (SIFROL) being apparent.

Table 3: Mean reduction in IRLS score in comparison with placebo after 12 weeks for the three dopamine agonists

	Relative effect of the reduction in the IRLS score in comparison with placebo after 12 weeks (mean, 95% confidence interval)
Ropinirole	-2.92 (-4.13; -1.67)*
Pramipexole	-4.40 (-5.89; -2.93)*
Rotigotine	-5.44 (-7.24; -3.69)*

*statistically significant difference versus placebo

Table 4: Comparison between dopamine agonists in terms of the reduction in the IRLS score after 12 weeks of treatment

A \ B	B versus A (95% CI)	
	Pramipexole	Rotigotine
Ropinirole	-1.48 (-3.44; 0.45)	-2.52 (-4.74; -0.40)*
Pramipexole		-1.04 (-3.40; 1.25)

*statistically significant difference for rotigotine versus ropinirole

08.2 Adverse effects

8.2.1 Data from clinical studies and from the Cochrane meta-analysis

Data from pooled studies SP790 and SP792 versus placebo (6 months): 748 patients were treated with rotigotine and 214 patients with placebo, with a mean rotigotine treatment duration of 167.2 ± 69.49 days. An adverse effect (AE) was reported in 65.2% of patients on rotigotine and 33.2% of patients on placebo. The most common (i.e. those occurring in at least 5% of patients) were application and instillation site reactions (34% versus 4% with placebo), nausea (19% versus 10% with placebo) and headache (17% versus 11% with placebo).

A serious adverse effect (AE) was reported in 17% of patients on rotigotine and 10% of patients on placebo. Discontinuation was associated with application and instillation site reactions (2.8% with rotigotine versus 0% with placebo), nausea (1.5% versus 0.5%) and headache (1.3% versus 0%).

There were more cases of AE-related treatment discontinuation with rotigotine (18%) than with placebo (6%), and in the rotigotine groups in patients receiving the highest dosages with a frequency of 16% at the 1 mg/24 h dosage, 18% at 2 mg/24 h and 25% at 3 mg/24 h. The AEs in question were mainly application and instillation site reactions (7% versus 0% in the placebo group). When application sites were rotated, 34.2% of the 748 patients on NEUPRO had application site reactions, for the most part mild to moderate, with NEUPRO being discontinued in 7.2% of subjects.

Symptom augmentation phenomenon according to pooled data from studies SP790 and SP792:
- an augmentation score > 1 was reported in 4.9% of patients (32/688) on rotigotine and in 6.2% (12/201) of those on placebo,
- a clinically significant augmentation phenomenon was observed in 1.5% of patients on rotigotine and in 0.5% of patients on placebo.

Impulse control disorders: These were observed in 2/217 (< 1%) of patients on placebo and in 21/745 (3%) of patients on rotigotine, according to pooled data from studies SP790 and SP792. These mostly related to increased libido, sexual arousal disorders and erectile dysfunction. None of these events was considered serious or led to treatment discontinuation.

Data from pooled open studies SP710 (5-year), SP791 and SP793 (1-year): 914 patients received rotigotine with a mean treatment duration of 418.1 ± 368.5 days. Of these:
- 703 (77%) had at least one adverse event. The most common were application and instillation site reactions (34%), nausea (10%), headache (7%) and fatigue (7%).
- 150 patients (16%) had at least one event considered serious, most commonly application and instillation site reactions (6%).
- 173 patients (19%) had to discontinue treatment due to an adverse effect, mainly because of an application and instillation site reaction.

Symptom augmentation phenomenon:
- In the two open studies with a 12-month additional follow-up, the rate was 2.9%. None of these patients had to discontinue treatment on account of the augmentation phenomenon.
- In the 5-year open study, the augmentation score did not show any significant progression during the course of the study. The augmentation phenomenon occurred in 11.9% of patients treated with validated doses (1-3 mg/day) of rotigotine, in the knowledge that 5.1% of the exacerbations were considered to be clinically significant. The majority of augmentation episodes occurred during the first two years of treatment. This study also allowed the use of a 4 mg/24 h dose, with which a higher rate of augmentations was observed. The 4 mg/24 h dose has not been approved for the treatment of RLS (cf. SPC).

Impulse control disorders: These were observed in 4/914 (< 1%) of patients according to pooled data from studies SP710, SP791 and SP793.

Data from study SP794: In view of the short duration (7 weeks) of the study and the small size of the study populations included (only 46 patients received rotigotine), this study's contribution to an understanding of the tolerability of rotigotine in RLS is limited and has little to offer.

Cochrane meta-analysis of dopamine agonists: Patients on dopamine agonists had more treatment discontinuations due to adverse effects (66 per 1000 patients) than those on placebo (33 per 1000 patients): OR: 1.82 ([95% CI: 1.35 to 2.45], I^2 = 45%) and had more AEs (OR: 1.82 [95% CI: 1.59 to 2.08], I^2 = 24%). According to the subgroup analysis and in comparison with the placebo group, there were no further treatment discontinuations due to adverse effects in patients on cabergoline, pergolide, pramipexole or rotigotine. On the other hand, a difference was found in patients from the lisuride and ropinirole groups. As regards the onset of adverse effects, there were no more adverse effects in the lisuride, pergolide and cabergoline groups compared with the placebo group. On the other hand, the risk of having an adverse effect increased in the rotigotine group (OR: 2.41, I^2 = 2%), ropinirole (OR: 2.07, I^2 = 12%) and pramipexole (OR: 1.48, I^2 = 0%). The symptom augmentation phenomenon could not be reliably evaluated in these studies.

Meta-analysis of levodopa: There were few cases of treatment discontinuation due to adverse effects, but patients in the levodopa group had more adverse effects than those on placebo (OR: 2.61 [95% CI: 1.35 to 5.04], p = 0.004). As regards the meta-analysis of the three studies comparing levodopa with a dopamine agonist, there was no difference between the two groups in terms of the occurrence of adverse effects. The sub-group analysis suggests that patients on pramipexole had slightly fewer side effects than those on levodopa. In these short-term trials it was not possible to evaluate or quantify the phenomenon of exacerbation or of symptom augmentation and they are therefore of little relevance for judging the tolerability profile of the various medicines. There are no data allowing a comparison between levodopa and rotigotine.

8.2.2 Pharmacovigilance data

Rotigotine has had Marketing Authorisation in Europe in the indication of treatment for Parkinson's disease since February 2006. In France, NEUPRO has been marketed in dosages of 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h since January 2011 and is only refundable in the Parkinson's disease indication. According to international pharmacovigilance data from Periodic Safety Update Reports (PSURs) covering the period from 16 August 2008 to 15 August 2012, exposure to rotigotine was estimated at around 336,152 patients/year (taking all indications together). But exposure to rotigotine in the sole indication of RLS is not available given that exposure in this indication represents a small proportion on account of the prevalence of this syndrome and because this indication was obtained more recently than the indication relating to Parkinson's disease. As regards the two most recent PSURs (period from 16 August 2011 to 15 August 2012), on the basis of the sales data and medical data from IMS, the distribution has been estimated as follows: RLS: 10.69% – 16.8% and Parkinson's disease: 83.2%-89.31%. By 15 August 2012, a total of 2179 adverse events had been reported in patients treated for RLS, 177 (8%) of them being considered as serious.

The PSUR data over a 7-year period are consistent with the tolerability profile for rotigotine observed in clinical studies. Nothing new stood out.

8.2.3 Other data

It is worth recalling that, apart from the already known adverse effects (including nausea, vomiting, hypotension, hallucinations, somnolence and sudden onset of sleep), the SPC for NEUPRO gives the following information under the heading "Special warnings" and "Undesirable effects".

Augmentation of symptoms (of restless legs syndrome):

“Augmentation may occur in restless legs syndrome patients. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in severity of symptoms, and spread of symptoms to involve other body parts.”

Impulse control disorders:
“Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including rotigotine.” … “Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including rotigotine. Dose reduction/tapered discontinuation should be considered if such symptoms develop."

Effects associated with the administration of rotigotine by transdermal patch.
- Reactions at the application site of the transdermal patch: According to the SPC, “Application site skin reactions may occur and are usually mild or moderate in intensity. It is recommended that the application site should be rotated on a daily basis (e.g. from the right side to the left side and from the upper body to the lower body). The same site should not be used within 14 days. If application site reactions occur which last for more than a few days or are persistent, if there is an increase in severity, or if the skin reaction spreads outside the application site, an assessment of the risk/benefit balance for the individual patient should be conducted. If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin colour. If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of NEUPRO is observed, NEUPRO should be discontinued.”
- Sulfite sensitivity: “NEUPRO contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.”
- Dosage adjustment and differences in bioavailability: According to the SPC, “The absolute bioavailability after transdermal application is approximately 37%. Rotating the site of patch application may result in day-to-day differences in plasma levels. Differences in bioavailability of rotigotine ranged from 2% (upper arm *versus* flank) to 46% (shoulder versus thigh). However, there is no indication of a relevant impact on the clinical outcome.”

8.2.4 Data from the European RMP

“Increased monitoring” of dopamine agonists
Dopamine agonists, indicated essentially in Parkinson’s Disease or RLS, were the subject of an Afssaps letter to prescribers in July 2009 concerning an adverse effect common to the class of dopamine agonists: impulse control disorder.[20] Behavioural disorders (gambling addiction, repetitive behaviours, compulsive buying, hypersexuality) have been reported in patients treated with dopaminergic agents indicated essentially in Parkinson’s disease. In France, by 1 December 2008, a hundred or so cases of the kind involving pathological gaming (addiction to games, especially games of chance and gambling for money resulting in inappropriate persistent and repeated playing of the game), punding, increased libido or hypersexuality, had been reported in patients treated with one or more dopaminergic agents. From an analysis of these observations it transpires that:

- Most cases occurred in patients undergoing treatment for Parkinson’s disease. Observations are more infrequent in the context of treatment for restless legs syndrome, and they are the exception in patients under treatment for hormonal disorders.
- The majority of these observations report cases of pathological gaming and punding; other observed disorders are of a sexual nature (increased libido, hypersexuality, exhibitionism) and more rarely behavioural disorders possibly leading, for example, to compulsive buying.

[20] Lévodopa, agonistes dopaminergiques et troubles du contrôle des impulsions. Afssaps – letter to healthcare professionals – pharmacovigilance – 29 July 2009

An assessment of these adverse effects was also conducted at European level for all dopaminergic agents as a whole. It emerges from this assessment that these adverse effects are so-called "class" adverse effects, i.e. they concern all medicinal products in this therapeutic category. These adverse effects can have serious consequences, including social, occupational and family consequences. Moreover, they are very widely reported in Parkinson's disease patients treated with high doses of dopaminergic agents or with a combination of several dopaminergic agents. They are generally reversible after reduction of the dose or discontinuation of the dopaminergic treatment.

Following this assessment, the sections "Special warnings and precautions for use" and "Undesirable effects" (SPC) for dopaminergic medicinal products holding Marketing Authorisation in France have been modified[21] to include a reference to the risk of occurrence of this type of adverse effects. Package leaflets aimed at patients have also been modified in order to give patients and their carers the fullest possible information.

European Risk Management Plan

A European Risk Management Plan (RMP) has been introduced for proprietary medicinal products based on pramipexole, ropinirole and rotigotine. An information leaflet was released on 11 April 2011. Monitoring within the framework of this RMP was maintained (28 October 2011).

The European Risk Management Plan specifically for NEUPRO (version 2 of 19.07.12) contained a provision for carrying out two post-Marketing Authorisation studies in relation to its use in Parkinson's disease:

- An observational study under conditions of actual clinical practice relying on a registry of patients followed up long-term (TRUST study: Transdermal Rotigotine User Surveillance Study, PASS SP854) in early-stage patients. The study should in particular allow the follow-up of cases of sudden onset sleep and somnolence, as well as fibrosis-related complications (heart valve disease). The participating countries are Germany, Austria, Spain, the United States, Italy and Mexico. The study began on 30 June 2006. The study is planned to last 33 months per patient. The study report is expected in March 2015.
- A prospective comparative study conducted in Germany[22] to evaluate the prevalence of heart valve disease treated with both ergot and non-ergot-derived dopamine agonists. Six hundred patients (300 taking ergot-derived and 300 taking non-ergot derived dopamine agonists) were to be followed up for 2 years. According to an interim analysis, no fibrotic heart valve damage was observed in ultrasound scans carried out in patients on rotigotine in November 2009. However, the study was terminated prematurely owing to recruitment problems. A new study was started by the academic sponsor in January 2011, using the same study design. According to the applicant, the final report should be available in late 2014.

08.3 Summary & discussion

Two double-blind randomised studies over 6 months comparing transcutaneous rotigotine with placebo were presented by the Applicant (SP790 and SP792).
In one study (SP790), rotigotine was used at the dosages approved in the Marketing Authorisation (1, 2 or 3 mg/24 h) in patients with moderate to very severe RLS (severe 48% and very severe 37%). After 6 months of treatment, rotigotine was superior to placebo in its effects on symptom severity (measured by the IRLS rating scale) and seriousness (on the basis of item 1 of the CGI scale). The percentages of responder patients according to the IRLS scale, to item 1 of the CGI scale and patients in remission on the IRLS scale were higher in patients receiving rotigotine (at all three dosages) than in those on placebo. The effect size was slight:

- The IRLS score showed a mean change from 30.7 to 20.7 in the placebo group and from 30.2 to 13.8 in the rotigotine group, i.e. a mean adjusted difference in favour of rotigotine of -6.5 points (95% CI –8.7; –4.4, $p < 0.0001$).

[21] The NEUPRO SPC and Package Leaflet were updated on 14 January 2013.
[22] This study was conducted by an independent group, the German Parkinson Study Group.

- RLS severity, evaluated on item 1 of the CGI scale, was less great in patients receiving rotigotine than those on placebo. The mean difference between the rotigotine and placebo group – greater than the expected difference of 0.75 – was between -0.8 and -1.2 points. The mean change with respect to the baseline value was -2.09 (0.14) in the 1 mg/24 hours group, -2.41 (0.14) in the 2 mg/24 hours group and -2.55 (0.14) in the 3 mg/24 hours group and -1.34 (0.14) under placebo. The differences between the three rotigotine groups and placebo were significant ($p < 0.0001$).

The results in the subgroup of very severe patients are of the same order as those obtained in the population as a whole (the difference in the reduction in the IRLS scores versus placebo were, respectively, -4.8, -11.1 and -10.1 in the 1 mg/24 h, 2 mg/24 h and 3 mg/24 h rotigotine groups).
In the second study (SP792) the results are of the same order as in the previous study.
A 3rd double-blind, randomised, controlled, parallel-group phase III study (SP794) was conducted in the moderate to severe forms of RLS. Its main objective was to evaluate the efficacy of transcutaneous rotigotine in comparison with placebo on the structural elements of sleep by recording the polysomnographic parameters after 7 weeks of treatment. The reduction in the Periodic Limb Movement Index (PLMI, primary efficacy endpoint) after 7 weeks of treatment was greater with rotigotine (from 50.9 to 7.7) than with placebo (from 37.4 to 32.7) ($p < 0.0001$), with a PLMI < 5 being considered as normal.

These three studies show the efficacy of rotigotine compared with placebo over a period ranging from 7 weeks to 6 months in patients with mostly a severe to very severe form of RLS.

The Cochrane meta-analysis of dopamine agonists including rotigotine showed dopamine agonists to have a greater efficacy than placebo up to 29 weeks of treatment. The reduction in the IRLS severity score is classed as moderate by the authors. It is greater with ergot derivatives than with non-ergot derivatives and of the same order of magnitude between non-ergot derivatives. The authors conclude that large-scale long-term studies are necessary to identify the most effective treatments for RLS.

The tolerability profile of rotigotine appears overall to match that of other non-ergot dopamine agonists with, in particular, severe adverse effects:
- behavioural disorders (gaming addiction, repetitive behaviours, compulsive buying, hypersexuality),
- paradoxical exacerbation of RLS.

The transdermal patch may provoke severe application and instillation site reactions, which represent the main reason for discontinuation of treatment.
Observational data suggest that the tolerability profile of rotigotine is similar in the short and in the long term (up to 5 years).

The main points of discussion as regards these data relate to estimation of the effect size and its transferability:
- The clinical data suggest that the efficacy of rotigotine on symptom severity is modest but superior to placebo in the short term (6 months). A subgroup analysis in one of the studies (SP790) shows rotigotine to be equally effective against the very severe form of RLS.
- The risk of paradoxical symptom exacerbation should be taken into account.
- There have been no studies making a comparison between medicinal products with Marketing Authorisation in RLS (pramipexole, ropinirole, rotigotine).
- Clinical assessment of the efficacy of rotigotine is limited to 6 months, despite the fact that this medicinal product is liable to be prescribed for much longer than that.

09 THERAPEUTIC USE

RLS should not be treated until the diagnosis has been firmly established (exclusion of periodic leg movements during sleep) and its severity assessed (symptom frequency, resultant disability).

According to international guidelines, dopamine agonists are the first-line medicinal treatment for moderate to severe RLS impacting on quality of life.[23,24,25] However, the benefits of their longer-term use have yet to be demonstrated and their efficacy does not seem to be lasting[26] (except perhaps in the case of rotigotine[27]). There are no studies available comparing dopamine agonists among themselves or with other classes of active medicines.

Certain adverse effects may limit their use: all dopamine agonists expose patients to serious adverse effects and/or can significantly affect patients' quality of life. Behavioural disorders (including uncontrolled impulses) described initially as forming part of the treatment for Parkinson's disease, seem to be as great a matter of concern in RLS.[28,29]

A review in 2012[30] recalls that these agents can exacerbate symptoms (onset of symptoms during the daytime, increased severity and affecting other parts of the body). This exacerbation seems to be associated with high doses and treatment duration in particular. That is why in the event of symptom exacerbation, treatment with dopamine agonists should be reassessed or stopped.

There are no studies available in which the various agents are evaluated over a period longer than 6 months. The relevance of dopamine agonist treatment therefore needs to be reassessed on a regular basis. In the event of serious adverse effects occurring, these treatments should be promptly suspended in accordance with discontinuation procedure described in the SPC.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

[23] Vignatelli L, Billiard M, Clarenbach P, et al. 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.
[24] Garcia-Borreguero D, Stillman P, Benes H, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurol. 2011; 27;11:28.
[25] Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, et al. 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]
[26] 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.
[27] Oertel W, Trenkwalder C, Beneš H, et al. 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.
Oertel W, Trenkwalder C, Beneš H, et al. D; SP710 study group
[28] Cornelius JR, Tippmann-Peikert M, et al. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. Sleep. 2010;33(1):81-7.
[29] Voon V, Schoerling A, Wenzel S, et al. Frequency of impulse control behaviours associated with dopaminergic therapy in restless legs syndrome. BMC Neurol 2011; 28;11:117.
[30] Leschziner G, Gringras P. Restless legs syndrome. Review. BMJ 2012;344:e3056. doi: 10.1136/bmj.e3056.

010.1 Actual benefit

◗ Restless legs syndrome (RLS) is a condition classified as a form of organic chronic insomnia. In about 80% of cases, these periodic leg movements during sleep are associated with insomnia. This condition is not life-threatening, nor does it cause serious complications, or any disability, or any marked deterioration in quality of life. It is typically characterised by paraesthesia and dysaesthesia in the legs associated with motor agitation. These disorders get worse when resting and are improved by physical exercise. They generally occur in the evening on going to bed. Severe to very severe RLS results in marked deterioration in the quality of life.

◗ NEUPRO is intended as a symptomatic treatment.

◗ The efficacy/adverse effects ratio of rotigotine in the very severe stage of RLS is modest. This was established versus placebo and in the short term, i.e. up to 6 months of treatment. In the longer term, the efficacy/adverse effects ratio has yet to be confirmed.

◗ Non-medicinal alternatives, including advice on ways of improving sleep, are appropriate for all forms of the condition and are generally adequate for dealing with the mildest forms. In the severe forms, medicinal alternatives do exist (ADARTREL, SIFROL). No studies are available in which rotigotine has been compared to its medicinal alternatives.
◗ NEUPRO is a first-line medicine in the very severe forms.

◗ Public health benefit:

In view of the mild nature of idiopathic RLS in the vast majority of cases and the moderate impact on quality of life except in the more severe cases, the burden of the condition may be considered to be slight (the very severe forms affecting small patient numbers). In light of the available clinical data, the expected impact of NEUPRO on morbidity is generally slight. A negative impact in some patients cannot be ruled out in view of the potential adverse effects (paradoxical aggravation of symptoms and impulse control disorders in particular).
The transferability of the results of trials to real-life situations is not guaranteed, especially in view of the problems in identifying patients likely to benefit from the medicinal treatment and of the underuse of the IRLS rating scale in current clinical practice.
Consequently, NEUPRO does not offer any public health benefit in moderate to very severe idiopathic RLS.

In consequence, the Committee considers that the actual benefit provided by NEUPRO is moderate in idiopathic restless legs syndrome, but only at the very severe stage, and insufficient in all other cases. Indeed, the serious nature of some of the adverse effects makes it imperative to avoid exposing patients with a less severe form of RLS to this medicine.

The Committee recommends inclusion of NEUPRO on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in very severe forms of RLS.

◗ Proposed reimbursement rate: 30%.

010.2 Improvement in actual benefit (IAB)

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

010.3 Target population

The target population for NEUPRO is defined as adult patients with very severe idiopathic restless legs syndrome.

According to the study by Allen et al.,[31] patients with a confirmed diagnosis of moderate to severe restless legs syndrome, with symptoms occurring at least twice a week and causing them to see their doctor, probably account for 0.14% of the general population. Extrapolating these prevalence data to the French population of over 18-year-olds, i.e. around 49 million people, suggests that there are at most 70,000 patients in France.

The proportion of patients with a very severe form of RLS is not known with any accuracy, but is less than 70,000 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescription conditions according to the indication, dosage and treatment duration.

◗ Specific requests inherent to reimbursement

The Committee would like the initial medical prescription to be by a neurologist or a specialist doctor working at a sleep centre.

◗ Request for further data

The Transparency Committee would like the applicant to provide data from which it could be ascertained that patients with very severe RLS are the ones that are actually being treated with NEUPRO. A search of existing databases could be performed to meet this request within a maximum period of 1 year.

[31] Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005;165(11):1286-92.

APPENDICES

Table 1: Study design and characteristics of patients included in studies used for carrying out indirect comparisons

INN	Study reference	Study design	Study duration (weeks)	Type/severity stage of WED[1]	Comparator	Dosages
Rotigotine	SP790	Double-blind, parallel	27	IRLS ≥ 15	Placebo	1 | 2 | 3 mg/day
	SP792	Double-blind, parallel	28	IRLS ≥ 15	Placebo	0.5 | 1 | 2 | 3 mg/day
Ropirinole	ROP101892	Double-blind, parallel	12	moderate to severe	Placebo	0.25-4 mg/day
	ROR104836	Double-blind, parallel	26	IRLS ≥ 24	Placebo	0.25-4 mg/day
	RRL106721	Double-blind, parallel	12	IRLS ≥ 15	Placebo	0.25-4.0 mg/day
	SKF-101468-190	Double-blind, parallel	12	IRLS ≥ 15	Placebo	0.25-4.0 mg/day
	SKF-101468-191	Double-blind, parallel	12	IRLS ≥ 15	Placebo	0.25-4.0 mg/day
	SKF-101468-194	Double-blind, parallel	12	IRLS ≥ 15	Placebo	0.25-4.0 mg/day
	SKF-101468-249	Double-blind, parallel	12	IRLS ≥ 15	Placebo	0.25-4.0 mg/day
Pramipexole	248.543	Double-blind, parallel	12	IRLS > 15	Placebo	0.25 | 0.50 | 0.75 mg/day
	248.604	Double-blind, parallel	12	IRLS > 15	Placebo	0.25-0.75 mg/day
	248.615	Double-blind, parallel	12	IRLS > 15	Placebo	0.125-0.75 mg/day
	248.629	Double-blind, parallel	26	IRLS > 15	Placebo	0.125-0.75 mg/day
Gabapentine enacarbil	XP053	Double-blind, parallel	12	IRLS ≥ 15	Placebo	1200 | 600 mg/day
	XP081	Double-blind, parallel	12	IRLS ≥ 15	Placebo	2400 | 1800 | 1200 | 600 mg/day

[1] WED: Willis-Ekbom Disease. This is another name for Restless Legs Syndrome.

Table 2: Change in the IRLS score after 12 weeks between two treatment groups in each of the studies used for carrying out indirect comparisons

Study	Assessed/control medicinal product	Sample size	IRLS score baseline value (assessed/control medicinal product)	Change in IRLS score after 12 weeks
ROR104836	Ropinirole	196	27.7 (3.62)	-14.2 (0.71)
	Placebo	205	27.5 (3.92)	-12.1 (0.70)
RRL106721	Ropinirole	171	28.5 (4.5)	-14.6 (0.7)
	Placebo	60	29.0 (4.6)	-10.2 (1.4)
SKF-101468-190	Ropinirole	146	24.4 (5.75)	-11.0 (0.72)
	Placebo	138	25.2 (5.63)	-8.0 (0.74)
SKF-101468-191	Ropinirole	32	Not available	-10.7 (1.45)
	Placebo	33		-9.6 (1.41)
SKF-101468-194	Ropinirole	131	23.6 (5.86)	-11.2 (0.76)
	Placebo	136	24.8 (5.42)	-8.7 (0.75)
SKF-101468-249	Ropinirole	187	22.0 (4.99)	-13.5 (0.60)
	Placebo	192	21.6 (4.79)	-9.8 (0.60)
XP053	Gabapentine enacarbil 1200 | 600 mg/day	114	23.2 (5.32)	-13.8 (0.76)
			23.1 (4.93)	-9.8 (0.78)
	Placebo	96	23.8 (4.58)	
XP081	Gabapentine enacarbil 2400 | 1800 | 1200 | 600 mg/day	47	23.3 (5.70)	-13.8 (1.38)
			23.6 (4.25)	-9.3 (1.29)
			23.9 (5.49)	
	Placebo		23.9 (5.33)	
		40	22.5 (5.32)	
248.543	Pramipexole 0.25 Pramipexole 0.50 Pramipexole 0.75 mg/day	87	23.4 (4.9)	-14.0 (1.0)
			22.9 (5.1)	-9.4 (0.99)
	Placebo		24.1 (5.2)	
		85	23.5 (5.2)	
248.604	Pramipexole	202	25.9 (5.2)	-14.2 (0.7)
	Placebo	196	25.9 (5.5)	-8.1 (0.7)
248.615	Pramipexole	178	24.2 (5.2)	-13.7 (0.7)
	Placebo	179	24.6 (5.7)	-9.6 (0.7)
248.629	Pramipexole	162	23.9 (5.3)	-13.7 (0.8)
	Placebo	159	23.5 (5.4)	-11.1 (0.8)
SP790	Rotigotine 1 mg	112	28.1 (6.3)	-14.4 (0.9)
	Rotigotine 2 mg	109	28.2 (6.1)	-16.5 (0.9)
	Rotigotine 3 mg	112	28.0 (5.9)	-16.3 (0.9)
	Placebo	114	28.1 (6.3)	-9.2 (0.9)
SP792	Rotigotine 1 mg	99	23.1 (5.0)	-12.6 (0.8)
	Rotigotine 2 mg	95	23.2 (5.3)	-13.7 (0.8)
	Rotigotine 3 mg	103	23.3 (4.6)	-15.2 (0.8)
	Placebo	99	23.6 (5.0)	-9.3 (0.8)