HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMISSION**

OPINION

30 April 2008

**NEUPRO 2 mg/24 h transdermal patch**
**Single-dose sachet, B/30 (CIP: 377 209-7)**
**Single-dose sachet, B/90 (CIP: 570 143-4)**

**NEUPRO 4 mg/24 h transdermal patch**
**Single-dose sachet, B/30 (CIP: 377 211-1)**
**Single-dose sachet, B/90 (CIP: 570 148-6)**

**NEUPRO 6 mg/24 h transdermal patch**
**Single-dose sachet, B/30 (CIP: 377 213-4)**
**Single-dose sachet, B/90 (CIP: 570 154-6)**

**NEUPRO 8 mg/24 h transdermal patch**
**Single-dose sachet, B/30 (CIP: 377 215-7)**
**Single-dose sachet, B/90 (CIP: 570 158-1)**

**NEUPRO 2 mg/24 h + 4 mg/24 h + 6 mg/24 h + 8 mg/24 h transdermal patch (titration kit)**
**Single-dose sachet, B/7 x 2 mg/24 h transdermal patches + 7 x 4 mg/24 h transdermal patches + 7 x 6 mg/24 h transdermal patches + 7 x 8 mg/24 h transdermal patches (CIP: 373 295-6)**

**Applicant: UCB PHARMA**

rotigotine

List I

ATC code: N04BC09

Date of marketing authorisation (centralised): 24 March 2006
Date of extension to indication (centralised procedure): 9 January 2007

Reason for request: inclusion on the list of medicines approved for use by National Insurance and hospitals for the extension of indication: “treatment of the signs and symptoms of late-stage idiopathic Parkinson’s disease 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’ motor fluctuations)”.

Medical, Economic and Public Health Assessment Division

## 1. CHARACTERISTICS OF MEDICINAL PRODUCT

### 1.1. Active ingredient
rotigotine

### 1.2. Background
Rotigotine is a non-ergolinic dopamine agonist in the form of a transdermal system designed to permit continuous plasma diffusion for permanent stimulation of the dopaminergic receptors.

### 1.3. Indication
"Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. without levodopa).

**Indication applied for:**
**Treatment of the signs and symptoms of late-stage idiopathic Parkinson's disease 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' motor fluctuations)."**

### 1.4. Dosage
"Neupro is applied once a day. The patch should be applied at approximately the same time 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 the day or if the patch becomes detached, another patch should be applied for the remainder of the day.

*Dosing in patients with advanced stage Parkinson's disease with fluctuations:*
The dose recommendations made are expressed in nominal dose.
A single daily dose should be initiated at 4 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 16 mg/24 h.
4 mg/24 h or 6 mg/24 h may be effective doses in some patients. For most patients an effective dose is reached within 3 to 7 weeks at doses of 8 mg/24 h up to a maximum dose of 16 mg/24 h.
For doses higher than 8 mg/24 h, multiple patches may be used to achieve the final dose, e.g. 10 mg/24 h may be reached by combining a 6 mg/24 h and a 4 mg/24 h patch.

*Hepatic and renal impairment:* adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment, including those requiring dialysis.

*Children and adolescents:* Neupro is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

*Treatment discontinuation:* NEUPRO should be discontinued gradually. The weekly dose should be reduced in steps of 2 mg/24 h with a dose reduction preferably every other day, until complete withdrawal of NEUPRO.

*Method of administration:* the patch should be applied to clean, dry, intact healthy skin on the abdomen, thigh, hip, flank, shoulder, or arm. Reapplication to the same site within 14 days should be avoided. NEUPRO should not be placed on skin that is red, irritated or damaged.

*Use and handling:* each patch is packed in a sachet and should be applied directly after the sachet has been opened. Remove half of the protective liner and apply the sticky side of the patch on the skin by pressing firmly. Then, fold back the patch and remove the other half of the protective liner. Do not touch the sticky side of the patch. Press the patch down firmly with the palm of the hand for 20 to 30 seconds, so that it sticks well.

In the event that a patch should fall off, a new patch should be applied for the remainder of the day."

## 2. COMPARABLE DRUGS

### 2.1. ATC Classification (2008)

N: Nervous system
N04: Anti-parkinson drugs
N04B: Dopaminergic
N04BC: Dopamine agonist
N04BC09: rotigotine

### 2.2. Medicines in the same therapeutic category

Dopamine agonists indicated in combination with L-dopa treatment:

- ergot dopamine agonists:

- BROMOKIN, PARLODEL (bromocriptine)
- DOPERGINE (lisuride)
- CELANCE (pergolide)

- non-ergot dopamine agonists:

- TRIVASTAL (piribedil)
- SIFROL (pramipexole)
- REQUIP (ropinirole)

### 2.3. Medicines with a similar therapeutic aim

- Levodopa associated with a catechol-o-methyltransferase inhibitor (COMTI) : STALEVO
- COMTI: COMTAN (entacapone), TASMAR (tolcapone) in patients who are unresponsive to or intolerant of other COMT inhibitors
- MAOI B: DEPRENYL, OTRASEL (selegiline), AZILECT (rasagiline)
- APOKINON injectable solution (apomorphine hydrochloride)

## 3. ANALYSIS OF AVAILABLE DATA

The company submitted the results of 3 trials: 2 phase III comparative trials (trials SP 650 and SP 515) and a phase III exploratory non-comparative trial (trial SP 826) (to evaluate the effect of rotigotine on the quality of sleep and morning motor scores).
Only trials SP 650 and SP 515 are described in this document.

### 3.1. Efficacy results

#### 3.1.1. Trial SP 650

Objective: to compare the efficacy and safety of rotigotine with those of the placebo as an adjuvant treatment to L-dopa in 351 patients suffering from late-stage Parkinson's disease pre-treated with and poorly controlled by L-dopa

Methodology: phase III randomised, double-blind, comparative, placebo-controlled, parallel groups trial

Inclusion criteria:
- idiopathic Parkinson's disease for over 3 years
- at least two of the cardinal signs of the disease (bradykinesia, tremor at rest, rigidity and structural instability)
- stage II, III or IV of the Hoehn and Yahr classification [1]
- mean 'off' time: at least 2.5 h/day
- MMSE score ≥ 25
- Stable dose of L-dopa (minimum dose of 200 mg/day) or anticholinergics or MAOI-B or NMDA for at least 28 days

Dosing regimen:
The protocol required an initial 5-week dose titration stage to determine the effective optimal dose (dose which causes the maximum reduction in Parkinson's disease symptoms with a safety profile deemed acceptable by the investigator and patient), followed by a 6-month dose stability stage.
The patients were randomised to the placebo (n=120) or rotigotine at the dosage of 8 mg (n=120) or 12 mg/24h (n=111) for 6 months.

Primary endpoint: 30% responder rate (patients with at least a 30% reduction in 'off' time from randomisation until the end of the stable dose stage over a 24-hour period) [2]

Secondary endpoints:
- absolute reduction in 'off' time, assessed over a 24-hour period, from randomisation to the end of the stable dose stage
- variation in 'on' time, with or without painful dyskinesia, from baseline to the end of the stable dose stage

[1] Hoehn and Yahr staging (Stage I-V) - M. Hoehn and MD Yahr, Neurology 17, 427 (1967). The Hoehn and Yahr scale scores the stage of Idiopathic Parkinson's Disease from 0 to 5 (0 = normal, 5 = disabled)

[2] The primary endpoint used for both trials, ie. variation in 'off' time, was analysed in two ways, depending on the registration authority. For EMEA, the analysis was based on the 30% responder rate, and this criterion served to calculate the number of subjects required. For the FDA, the evaluation was based on a continuous variable: the absolute reduction in 'off' time. This criterion was considered as a secondary endpoint for EMEA, as stated in the report on the trials.

- variation in the number of 'off' periods per day from baseline to the end of the stable dose stage
- variation in patient's on/off status on waking
- variation in UPDRS II, III and IV score from baseline to the end of the stable dose stage

Results: (ITT population[3])
The mean duration of treatment was 173 days in the placebo group, 174 days in the rotigotine 8 mg/24h group and 175 days in the rotigotine 12 mg/24h group.

Characteristics of patients at baseline:

| | Placebo group (n=120) | Rotigotine 8 mg/24h group (n=118) | Rotigotine 12 mg/24h group (n=111) |
|---|---|---|---|
| Mean age | 66.3 | 66.5 | 64.5 |
| < 65 years (%) | 37 | 40 | 50 |
| 65-75 years | 43 | 35 | 32 |
| > 75 years | 20 | 25 | 18 |
| Disease duration (years) | 7.7 (± 4.0) | 7.7 (± 4.3) | 7.8 (± 4.6) |
| 'Off' time (h) | 6.4 | 6.7 | 6.3 |
| Hoehn-Yahr (%) | | | |
| Stage I | 0 | < 1 | 3 |
| Stage II | 62 | 63 | 57 |
| Stage III | 34 | 31 | 35 |
| Stage IV | 4 | 5 | 5 |
| Stage V | 0 | 0 | 0 |
| UPDRS II score | 13 | 13.3 | 13.6 |
| UPDRS III score | 26.7 | 27.2 | 27.5 |
| Mean dose of L-dopa (mg/day) | 753 | 760 | 741 |

Primary endpoint results:

30% responder rate:

| | Placebo group (n=119) | Rotigotine 8 mg/24h group (n =113) | Rotigotine 12 mg/24h group (n=109) |
|---|---|---|---|
| 30% responder rate | 34% | 57% | 55% |
| Difference vs. placebo | | 22.2 | 20.6 |
| 95% CI difference vs. placebo | | [9.7 ; 34.7] | [7.9 ; 33.3] |
| p | | < 0.001 | < 0.001 |

After 6 months' treatment, a statistically significant difference in the 30% responder rate endpoint was observed in favour of the 2 rotigotine treatment groups compared with the placebo group.

Secondary endpoint results:

The reduction in 'off' time was 0.9 h in the placebo group, 2.7 h in the rotigotine 8 mg/24h group and 2.1 h in the rotigotine 12 mg/24h group. The differences observed compared with the placebo (- 1.8 95% CI [-2.6; -1.0] in the rotigotine 8 mg/24h group; -1.2 95% CI [-2.0; -0.4] in the rotigotine 12 mg/24h group) were statistically significant.
As no statistical analysis was conducted for the other secondary endpoints, they are presented by way of information only.

[3] Defined as all patients who received at least one dose of rotigotine and underwent a valid examination after inclusion

| | Placebo group (n=119) | Rotigotine 8 mg/24h group (n=113) | Rotigotine 12 mg/24h group (n=109) |
|---|---|---|---|
| Variation in 'ON' time (h) | | | |
| baseline | 9.6 | 9.2 | 10.1 |
| end of stable dose | 10.7 | 12.3 | 12.4 |
| Variation | 1.1 | 3.1 | 2.3 |
| Variation in 'ON' time with dyskinesia (h) | | | |
| baseline | 1.2 | 1.2 | 1.1 |
| end of stable dose | 1.2 | 0.8 | 1.2 |
| Variation | -0.1 | -0.4 | 0.1 |
| Variation in 'ON' time without dyskinesia (h) | | | |
| baseline | 8.4 | 8.0 | 9.0 |
| end of stable dose | 9.5 | 11.5 | 11.2 |
| Variation | 1.1 | 3.5 | 2.2 |
| Change in number of daily 'OFF' periods | -0.7 | -1.5 | -1.3 |
| Change in ON / OFF status on waking (% of patients) | | | |
| 'OFF' | -9.1 | -28.8 | -22.6 |
| 'ON' without dyskinesia | 8.5 | 27.0 | 20.9 |
| 'ON' with dyskinesia | 0.6 | 1.8 | 1.7 |
| UPDRS-II score | | | |
| baseline | 13.1 | 13.4 | 13.6 |
| variation | -0.5 | -3.1 | -3.2 |
| UPDRS-III score ON | | | |
| baseline | 26.7 | 27.4 | 27.7 |
| variation | -3.4 | -6.8 | -8.7 |

### 3.1.2. Trial SP 515

Objective: to compare the efficacy and safety of rotigotine as an adjuvant to L-dopa with those of the placebo and pramipexole (SIFROL) in 506 patients suffering from late-stage Parkinson's disease pre-treated with and poorly controlled by L-dopa

Methodology: phase III randomised, double-blind, parallel groups, placebo-controlled trial of non-inferiority vs pramipexole.

Rotigotine was considered to be non-inferior to pramipexole if the lower limit of the 95% confidence interval of the difference in 30% responder rate between the two treatments (rotigotine less pramipexole) was less than 15% in terms of absolute score[4].

Inclusion criteria:

- idiopathic Parkinson's disease for over 3 years
- at least two of the cardinal signs of the disease (bradykinesia, tremor at rest, rigidity and structural instability)
- stage II, III or IV of the Hoehn and Yahr classification[5]
- mean 'off' time: at least 2.5 h/day
- MMSE score ≥ 25
- stable dose of L-dopa (minimum dose of 300 mg/day) or anticholinergics or MAOI-B or NMDA for at least 28 days

Dosing regimen:

The protocol required an initial titration stage of ≤ 7 weeks to determine the optimal effective dose (dose which causes the maximum reduction in Parkinson's disease symptoms with a safety profile deemed acceptable by the investigator and patient), plus a 16-week dose stability stage.

The patients were randomised 2:2:1 to receive the placebo (n=101) or rotigotine at the maximum dosage of 16 mg/24h (n=204) or pramipexole at the maximum dosage of 4.5 mg/day (n=201) for 6 months.

Primary endpoint: 30% responder rate (patients with at least a 30% reduction in 'off' time from randomisation until the end of the stable dose stage over a 24-hour period)

Secondary endpoints:

- absolute reduction in 'off' time, assessed over a 24-hour period, from randomisation to the end of the stable dose stage [6]
- variation in 'on' time, with or without painful dyskinesia, from baseline to the end of the stable dose stage
- variation in the number of 'off' periods per day from baseline to the end of the stable dose stage
- variation in patient's on/off status on waking
- variation in UPDRS II, III and IV score from baseline to the end of the stable dose stage

[4] According to the EPAR, the relevance of the non-inferiority limit set is controversial. In practice, this limit was chosen on the assumption of a 50% loss of efficacy with pramipexole.

[5] Hoehn and Yahr staging (Stage I-V) - M. Hoehn and MD Yahr, Neurology 17, 427 (1967). The Hoehn and Yahr scale scores the stage of Idiopathic Parkinson's Disease from 0 to 5 (0 = normal, 5 = disabled)

[6] Rotigotine was considered to be non-inferior to pramipexole if the lower limit of the 95% confidence interval of the difference between the two treatments (rotigotine less pramipexole) was less than 1.2 h in terms of the absolute reduction in OFF time.

Results:

Characteristics of patients at baseline:
The mean duration of treatment was 139 days in the placebo group, 151 days in the rotigotine group and 144 days in the pramipexole group.
The mean dose of rotigotine was 12.4 mg/24h, and that of pramipexole was 2.95 mg/day.

| | Placebo group (n=99) | Rotigotine group (n=205) | Pramipexole group (n=202) |
|---|---|---|---|
| Mean age<br>< 65 years no. (%)<br>≥ 65 years<br>< 75 years<br>≥ 75 years | 64.7<br>45 (45.5)<br>54 (54.5)<br>83 (83.8)<br>16 (16.2) | 64.3<br>94 (45.9)<br>111 (54.1)<br>184 (89.8)<br>21 (10.2) | 63.3<br>98 (48.5)<br>104 (51.5)<br>183 (90.6)<br>19 (9.4) |
| Disease duration (years) | 8.3 (± 4.9) | 8.8 (± 4.4) | 8.4 (± 4.7) |
| 'Off' time (h) | 6.4 | 6.2 | 6.0 |
| 'On' time (h) | 9.5 | 9.8 | 10.0 |
| Hoehn-Yahr (%)<br>Stage I<br>Stage II<br>Stage III<br>Stage IV<br>Stage V | <br>0<br>18.2<br>51.5<br>30.3<br>0 | <br>0.5<br>19.5<br>57.6<br>22<br>0.5 | <br>0<br>18.8<br>58.4<br>22.3<br>0.5 |
| Mean UPDRS II score | 12.7 (±6.0) | 12.5 (±6.0) | 11.7 (±6.1) |
| Mean UPDRS III score | 27.3 (±12.0) | 25.8 (±11.8) | 26.1 (±11.7) |
| Mean dose of L-dopa (mg/day) | 814 | 795 | 813 |

Primary endpoint results:

30% responder rate:

| | placebo group n = 73 | rotigotine group n = 177 | pramipexole group n = 165 |
|---|---|---|---|
| 30% responder rate | 41% | 63% | 70% |
| 95% CI difference vs. placebo | | 22.2 % [8.8 ; 35.5]<br>p<0.001 | 28.6% [15.3 ; 41.9] |
| 95% CI difference vs. pramipexole | | **-6.4% [-16.4 ; 3.6]** | |

Per-protocol analysis

The per-protocol analysis did not demonstrate that rotigotine was non-inferior to pramipexole in terms of the 30% responder rate. These results are confirmed in the ITT population.

Secondary endpoint results:

In the per-protocol population, the mean reduction in 'off' time was 2.6 h in the rotigotine group and 3.0 h in the pramipexole group, ie. a difference of 0.44 h (95% CI [-0.15; 1, 03]). As the lower limit of the confidence interval of the difference was below the non-inferiority threshold (1.2 h) in terms of absolute score, non-inferiority was demonstrated.

As no statistical analysis was conducted for the other secondary endpoints, they are presented by way of information only.

| | Placebo group (n=100) | Rotigotine group (n=201) | Pramipexole group (n=200) |
|---|---|---|---|
| Variation in 'ON' time (h) | | | |
| baseline | 9.4 | 9.8 | 10.0 |
| end of stable dose | 10.3 | 12.2 | 12.7 |
| Variation | 0.9 | 2.4 | 2.6 |
| Variation in 'ON' time with dyskinesia (h) | | | |
| baseline | 1.2 | 1.4 | 1.5 |
| end of stable dose | 0.7 | 1.0 | 1.5 |
| Variation | -0.5 | -0.4 | 0.0 |
| Variation in 'ON' time without dyskinesia (h) | | | |
| baseline | 8.2 | 8.4 | 8.5 |
| end of stable dose | 9.5 | 11.2 | 11.2 |
| Variation | 1.4 | 2.8 | 2.7 |
| Change in number of 'OFF' periods | -0.6 | -1.4 | -1.1 |
| Change in ON / OFF status on waking (% of patients) | | | |
| 'OFF' | -10.7% | -22.6% | -21.1% |
| 'ON' without dyskinesia | 11.1% | 23.3% | 21.6% |
| 'ON' with dyskinesia | -0.4% | -0.7% | -0.5% |
| UPDRS-II score | | | |
| baseline | 12.8 | 12.3 | 12.1 |
| Variation | -2.0 | -4.2 | -4.6 |
| UPDRS-III score ON | | | |
| baseline | 26.8 | 26.3 | 26.4 |
| Variation | -4.3 | -8.7 | -10.3 |

### 3.2. Adverse events

In all the clinical trials (total: 434 patients treated with rotigotine, 202 patients with pramipexole and 219 patients with placebo), 73.0% of the patients treated with rotigotine, 70.3% of the patients treated with pramipexole and 62.6% of the patients with the placebo reported at least one adverse event.

The main adverse events observed were nausea and vomiting (22.6% of patients in the rotigotine group, 12.9% of patients in the pramipexole group, and 17.4% of patients in the placebo group), application site reactions (31.3%; 8.4%; 11.9%), drowsiness (22.8%; 11.9%; 18.7%), dyskinesia (13.6%; 15.3%; 5.0%) and vertigo (14.7%; 10.9% ; 12.8%).

Treatment was discontinued due to adverse events in the case of 8% of patients in the placebo groups, 7% of patients in the pramipexole group and 11% of patients treated with rotigotine.

### 3.3. Conclusion

The efficacy and safety of rotigotine as an adjuvant to L-dopa were analysed in two phase III trials, SP 650 and SP 515, with a total of 857 patients suffering from late-stage Parkinson's disease, pre-treated with and poorly controlled by L-dopa.

Three hundred and fifty one (351) patients were included in trial SP 650, a comparative, placebo-controlled, randomised, double-blind trial (120 in the placebo group, 120 in the rotigotine 8 mg/24h group and 111 in the rotigotine 12 mg/24h group). At baseline, the characteristics of the patients in each treatment group were comparable.
After 6 months' treatment, a statistically significant difference in the 30% responder rate endpoint was observed in favour of the 2 groups treated with rotigotine compared with the placebo group.

Five hundred and six (506) patients were included in trial SP 515, a randomised, double-blind, parallel groups, placebo-controlled non-inferiority trial vs. pramipexole (101 in the placebo group, 204 in the rotigotine group, and 201 in the pramipexole group). At baseline, the characteristics of the patients in each treatment group were comparable.
The difference observed in the per-protocol population for the primary endpoint (30% responder rate) between the two treatments was -6.4% [-16.4; 3.6]. As the lower limit of the 95% confidence interval of the difference (rotigotine less pramipexole) was above the non-inferiority threshold set (15%), the non-inferiority of rotigotine to pramipexole was not demonstrated.
There are no data versus another dopamine agonist such as ropinirole.

The main adverse events observed in the patients treated with rotigotine with a higher frequency than in the placebo or pramipexole group were nausea and vomiting, application site reactions, drowsiness and vertigo. There are no available data relating to quality of life, but treatment discontinuations were more frequent in the patients treated with rotigotine than in those treated with pramipexole or the placebo.

The Committee wishes to point out that the transdermal administration method of NEUPRO would allow the management of certain clinical situations where the continuity of oral treatment is compromised (patients with swallowing difficulties or gastric malabsorption of medicinal products, patients who have undergone digestive surgery, and patients who are unconscious due to general anaesthesia or coma). However, these populations have not been subjected to a specific evaluation, and are not included in the present marketing authorisation indication.

## 4. TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Parkinson's disease is characterised by tremors at rest, rigidity, bradykinesia or akinesia and loss of postural reflexes. As the disease progresses, neurovegetative disturbances, painful sensory complaints and mental disorders are associated with these motor disorders. The onset of Parkinson's disease is usually insidious, with a slow and progressive clinical course characterized by progressive disability and a marked reduction in quality of life. It is life-threatening.
NEUPRO is a symptomatic anti-parkinsonian treatment.
Its efficacy/adverse effects ratio is moderate.
There are numerous alternative treatments.

Public health benefit:
Parkinson's disease represents a major public health burden.
Improving the global management of affected persons and, in particular, delaying the onset of disabling symptoms and improving quality of life, constitutes a public health need falling within an identified priority area (public health law and the National Technical Objective Definition Group (GTNDO))[7].
Having regard to the available data, NEUPRO is not expected to have any additional impact compared with other dopamine agonists in reducing the morbidity/mortality associated with the Parkinson's disease, improving the quality of life of these patients or improving the compliance which could be expected in view of the innovative administration methods of NEUPRO.
The proprietary drug NEUPRO is therefore unlikely to provide a supplementary response to the identified public health need.
Accordingly, NEUPRO is not expected to have an impact on public health for this indication.

However, the actual benefit is substantial.

### 4.2. Improvement in actual benefit

NEUPRO provides no improvement in actual benefit (IAB level V) compared with SIFROL in late-stage Parkinson's disease patients.
It is the only available agonist for transdermal administration, for continuous and non-pulsatile dopaminergic stimulation, and therefore provides an additional means of management of late-stage Parkinson's disease.

### 4.3. Therapeutic use[8] [9] [10]

In late-stage Idiopathic Parkinson's Disease, after a variable stabilisation period ("honeymoon"), the clinical situation deteriorates due to the onset of motor complications associated with dopaminergic treatment (motor fluctuations, on/off effects, dyskinesia) and the appearance or worsening of specific signs of non-dopa-dependant Idiopathic Parkinson's Disease (disorders associated with impairment of the sympathetic nervous system).

[7] Loi de santé publique du 9 Août 2004. GTNDO : Groupe Technique National de Définition des Objectifs (DGS-2003)
[8] La Maladie de Parkinson : critères diagnostiques et thérapeutiques Conférence de consensus - 3 mars 2000 – ANAES / Fédération Française de Neurologie
[9] Diagnosis and Initial Management of Parkinson's Disease. New Engl J Med 2005;353:1021-7.
[10] HAS Guide ALD : Syndromes parkinsoniens dégénératifs ou secondaires non réversibles. Avril 2007

Treatment of motor complications involves continual and individually tailored adjustment of the dose and dosing regimen according to changes in the patient's motor status from month to month.
These readjustments must also take into account the non-motor signs of the disease, and in particular fluctuations in mood, treatment-related behavioural disorders, fatigue, sensory disorders and pain.

Before any readjustment of treatment, it is necessary:
- to consider the role played by:
    - the quality of medical prescription (accuracy of doses and dosing schedule) and compliance by the patient (importance of how treatment is explained and understood by patients and the main caregivers),
    - combined medication which may worsen the motor and non-motor complications
- to keep an on/off diary to carefully record motor fluctuations and to evaluate in particular the response to the first morning dose of L-dopa;
- then to optimize L-dopa therapy in order to obtain regular dopaminergic stimulation (division of the daily dose by increasing the number of doses and by reducing the unit dose and titration to the minimum effective dose, adjustment of dosing times, prescription of different pharmaceutical forms).

Other treatments may then be combined with L-dopa:
- dopamine agonists:
    - ergot-derived dopamine agonists ("ergopeptins") which require annual cardiac monitoring by echocardiography (as they may cause cardiac valve disease): bromocriptine, lisuride, and especially pergolide, prescribed only after failure of treatment with other dopamine agonists,
    - non ergot-derivative agonists: ropinirole, piribedil, pramipexole, apomorphine and rotigotine.

Off-times may be reduced by combining L-dopa with an agonist administered at effective doses.
Subcutaneous injection of apomorphine may be used to rapidly terminate an 'off' period in highly fluctuating patients in motor block.
In patients with severe fluctuations and dyskinesias, in the absence of an indication for deep brain stimulation, these may be improved by treatment with apomorphine administered by a continuous subcutaneous infusion pump and levodopa/carbidopa (enteral administration by a permanent transabdominal tube).

- Catechol-O-methyl transferase inhibitors (COMTI):
    - entacapone, which is useful as it significantly increases "on" time, and often allows a reduction in the dose of L-dopa;
    - tolcapone, if entacapone is insufficiently effective or poorly tolerated. The duration of tolcapone treatment should not exceed 3 weeks in the event of inefficacy, due to its toxicity, especially to the liver.

- MAO-B inhibitors (selegiline, rasagiline)

Rotigotine (NEUPRO), a dopamine agonist administered transdermally, therefore represents an additional means of treating late-stage Parkinson's disease as an adjuvant to L-dopa.

### 4.4. Target population

The target population of NEUPRO, in this extension to the indication, is represented by patients suffering from late-stage Parkinson's disease.

This population may be estimated from the following data:
- NEUPRO can be used in monotherapy at an early stage of Parkinson's disease or at a late stage in combination with L-dopa if motor complications arise. NEUPRO can therefore be used for all patients suffering from Parkinson's disease, with the exception of those who are well controlled by L-dopa alone.
- The number of patients suffering from Parkinson's disease is estimated at between 110,000 and 145,000; 80-90% of them are treated with L-dopa, including approximately 30% of cases treated with monotherapy.
- The number of patients controlled by L-dopa alone is therefore between approximately 26,000 and 40,000.
- Thus the total population liable to receive treatment with NEUPRO is between 84,000 and 105,000 patients.
- among this population, some 25,000 [11] patients are at an early stage of the disease, and could be treated with NEUPRO.

Thus the target population of NEUPRO for the treatment of late-stage Parkinson's disease is estimated at between 59,000 and 80,000 patients.

### 4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication extension and at the dosage specified in the marketing authorisation.

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 65%

[11] Transparency Committee's opinion, NEUPRO – 31 January 2007