HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

31 January 2007

NEUPRO 2 mg/24 h transdermal patch
Single dose pack, B/30: 377 209-7
Single dose pack, B/90: 570 143-4

NEUPRO 4 mg/24 h transdermal patch
Single dose pack, B/30: 377 211-1
Single dose pack, B/90: 570 148-6

NEUPRO 6 mg/24 h transdermal patch
Single dose pack, B/30: 377 213-4
Single dose pack, B/90: 570 154-6

NEUPRO 8 mg/24 h transdermal patch
Single dose pack, B/30: 377 215-7
Single dose pack, B/90: 570 158-1

NEUPRO 2 mg/24 h + 4 mg/24 h + 6 mg/24 h + 8 mg/24 h transdermal patch
Single dose pack, B/7 transdermal patches of 2 mg/24 H + 7 transdermal patches of 4 mg/24 H + 7 transdermal patches of 6 mg/24 H + 7 transdermal patches of 8 mg/24 H: 373 295-6

Applicant: SCHWARZ PHARMA

Rotigotine

List I

Marketing Authorisation (MA) Date (centralised): March 24, 2006

Reason for application: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Rotigotine

1.2. Background

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

1.3. Indications

NEUPRO is indicated for the treatment of signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. without Levodopa).

1.4. Dosage

NEUPRO is applied once daily. 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.

Dosage

The dose recommendations made are expressed in nominal dose.
Treatment should be initiated with a single daily dose of 2 mg/24 h and then titrated upwards in weekly increments of 2 mg/24 h to the effective dose up to a maximal dose of 8 mg/24 h.
4 mg/24 h may be an effective dose in some patients. For most patients an effective dose is reached within 3 or 4 weeks at doses of 6 mg/24 h or 8 mg/24 h, respectively.
The maximal dose is 8 mg/24 h.

Hepatic and renal impairment: No dose adjustment is necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis.

Treatment discontinuation

NEUPRO should be discontinued gradually. The daily 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 red, irritated or damaged skin.

Use and handling

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the protective liner should be removed and the sticky side should be applied and pressed firmly on the skin. Then, the patch is fold back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch

should be pressed down firmly with the palm of the hand for about 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 24 hour dosing interval.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification 2005

N : Nervous system
04 : Antiparkinsonian
B : Dopaminergic
C : Dopamine agonist
09 : Rotigotine

2.2. Medicines in the same therapeutic category

Dopamine receptor agonists indicated as monotherapy:
- Bromocriptine: BROMOKIN, PARLODEL
- Lisuride: DOPERGINE
- Piribedil: TRIVASTAL
- Pergolide: CELANCE
- Pramipexole: SIFROL
- Ropinirole: REQUIP

2.3. Medicines with a similar therapeutic aim

Anti-Parkinson medicinal products:
- Levodopa/dopa decarboxylase inhibitor
- COMTI: entacapone, tolcapone (in patient not responding or who are intolerant to other COMT inhibitors)
- Anticholinergics
- MAO-B inhibitors: selegiline

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Seven studies have been carried out: 5 phase II studies (4 studies versus placebo: parts 1 and 2 of SP 534, SP535 and SP506, and a single-blind study SP540) and 2 comparative phase III studies versus placebo (SP512) and versus ropinirole (SP513).
Only the phase III studies will be discussed in this document.

Study SP512
The objective was to compare the efficacy and safety of rotigotine with that of placebo in 273 patients Parkinson's disease patients. This 27-week study had a randomised, double-blind design.

Enrolled patients presented at least two cardinal signs and symptoms of the disease (bradykinesia, resting tremor, rigidity and postural instability) and were in Hoehn & Yahr stage ≤III[1].

Patients had a 3-week dose titration phase to attain the effective optimal dose (dose which allows a maximum reduction in Parkinson's disease symptoms with a safety profile deemed acceptable by the investigator and patient). Patients then entered a 24-week stable-dose maintenance phase.

Patients previously treated with carbidopa/levodopa during the 28 days before the visit were excluded.

The primary efficacy endpoints differed according to geographical location:

- In Europe: 20 % responder rates (patients with a reduction of at least 20% in the UPDRS II + III score from inclusion to the end of the maintenance phase at 27 weeks)
- In the United States: improvement in UPDRS II+III score at the end of the maintenance phase relative to baseline.

Secondary endpoints included the change in the UPDRS II + III score from inclusion to the end of maintenance phase, the 30% responder rate (reduction of at least 30 % of UPDRS II + III score), improvement in the UPDRS II score and UPDRS III score were also evaluated.

Results:

273 patients, with an average age of 63 years, were randomised to two groups according to a 2/1 ratio:

- rotigotine (N=177)
- placebo (N= 96)

91% of patients were treated with the maximum dose per patch of rotigotine of 13.5 mg/24h, i.e. a maximum delivered daily dose of 6 mg/24h.

For the primary endpoints:

At baseline, the UPDRS II + III scores were 30.0 ± 10.7 in the placebo group and 29.9 ± 12.2 in the rotigotine group.

In Europe, after 27 weeks of treatment, the ITT analysis showed that the 20% responder rate for the UPDRS II + III score was 48% (84 patients) in the rotigotine group and 19% (18 patients) in the placebo group, i.e. an absolute difference of 28.8% (95% CI [0.18; 0.39]) in favour of rotigotine ($p<0.0001$).

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

Table 1: UPDRS II +III score (USA) at 27 weeks

	Rotigotine N=177	Placebo N=96
Baseline value	29.9 (12.2)	30.0 (10.7)
Value at the end of the stable dose phase (27 weeks)	-3.98	1.31
95% CI difference versus placebo	-5.28 [-7.6 ;-2.96]	

In the United States, a significant difference of 5.28 points was observed between placebo (1.3 point) and the rotigotine group (- 3.98 points) for the UPDRS II -III score ($p<0.0001$).

For the secondary endpoints:
The 30% responder rate for the UPDRS II +III score was 37% (66 patients) with rotigotine and 13% (12 patients) with placebo, i.e. an absolute difference of 24,8% ($p<0.0001$).

Safety
57 cases of drowsiness (31%) were reported in the rotigotine group and 16 (17%) in the placebo group.
2 cases of sleep attacks were reported in the rotigotine group and 0 in the placebo group.
6% (6/95) of patients in the placebo group and 14% (25/181) of those in the rotigotine group reported 6 adverse events and 42 adverse events respectively and stopped treatment for safety reasons.
For the rotigotine group, most treatment discontinuations were due to application site reactions: 10 events for 9 subjects (5%).
Other adverse events responsible for treatment discontinuation were those observed in patients with Parkinson's disease and/or treated by other dopamine agonists (hypotension, hypokinesia, tremor, dizziness, asthenia, headache, confusion, nausea, drowsiness, palpitations) with incidences <1% in each case.

Study SP513
The objective of this study was to compare the efficacy and safety of rotigotine with those of ropinirole in 561 Parkinson's disease patients.
This 37-week, randomised, non-inferiority study enrolled patients with at least two of the cardinal signs and symptoms of the disease (bradykinesia, resting tremor, rigidity and postural instability) and in Hoehn & Yahr stage ≤III. Rotigotine was considered to be non-inferior to ropinirole if the lower limit of the 95% CI of the difference between the success rates[2] of the 2 treatments (rotigotine less ropinirole) was less than - 15%.

The primary endpoints differed according to geographical location:
- In Europe: 20% responder rates (patients with a reduction of at least 20% in the UPDRS II +III score from baseline visit to the end of the maintenance phase)
- In the United States: improvement in UPDRS II +III score at the end of the maintenance phase compared to the baseline value.

Secondary endpoints included the absolute difference in the change in the UPDRS II + III score from the baseline visit to the end of maintenance phase, the improvement in UPDRS II score, improvement in UPDRS III score and the 30% responder rate.

[2] Success rate : 20% responder rates and improvement in UPDRS II+III score at the end of the maintenance phase compared to baseline

Patients had a dose titration phase of less than 13 weeks during which the effective optimal dose was determined (dose which allowed a maximum reduction in the symptoms of Parkinson's disease with a safety deemed acceptable by the investigator and patient). Patients then entered in a 24-week maintenance phase, during which the dose of rotigotine or ropinirole was stable (maximum 8 mg/24 h and 24 mg/24h).

Results:
561 patients, with an average age of 61.1 years, were randomised to three groups:
- Rotigotine group: rotigotine patch + placebo tablet (N=213)
- Ropinirole group: ropinirole tablet + placebo patch (N=227)
- Placebo group (N=117)

93% of patients with a rotigotine patch were treated with the maximum dose of 8 mg/24h.
38% of patients with ropinirole tablets received doses less than or equal to 9 mg/day; 62% of patients with ropinirole received doses of between 12 and 24 mg/day (26% received doses of 24mg/day).

For primary endpoints:
At baseline, the UPDRS II + III scores were 31.3 ± 12.6 in the placebo group, 33.0 ± 12.6 in the rotigotine group and 32.2 ± 12.4 in the ropinirole group.

Table 2: Number of 20% responder patients according to UPDRS II +III score from baseline to the end of the maintenance phase (Europe)

	Rotigotine N=145	**Ropinirole** N=157	Placebo N=77
20 % Improvement	80 (55%)	118 (75%)	30 (39 %)
95% CI difference versus placebo	16.2 % [2.6 ; 29.8]	36 % [23.4; 49.0]	
95% CI difference versus ropinirole	-20 % [-30,5 ; -9,4]		

Per protocol analysis
In Europe, per protocol analysis did not demonstrate the non-inferiority of rotigotine to ropinirole for the 20% responder rate.

In the United States, per protocol analysis did not demonstrate the non-inferiority of rotigotine to ropinirole in terms of improvement in UPDRS-II+III score (23% with rotigotine versus 39% with ropinirole i.e. a difference of - 16%).

The ITT results confirmed the per protocol analysis.

For secondary endpoints:
The 30% response rate for the UPDRS II +III score was higher with rotigotine (42%) and ropinirole (59%) than with placebo (24%).

Note:
According to EPAR, the effect of rotigotine corresponds to what is expected from a dopamine agonist.
The 20% responder rate in the ropinirole group (75%) was higher than usually reported in the literature. This may be explained by a dosage of 24 mg/day for one third of patients instead of 8.3 mg and 16 mg/day for the data published in early-stage Parkinson’s disease.

Safety:
At 6 months, 17% of patients taking rotigotine (37/215) discontinued treatment because of adverse events (including 8% for an application site reaction), 13% in the ropinirole group (29/228) and 5% in the placebo group.
There was no difference in the incidence of adverse effects between the rotigotine and ropinirole groups.

Follow-up data
The two phase III studies (SP512 and SP513) were the object of an open label follow-up study for a period of three years. The study consisted of data relative to the long-term efficacy of NEUPRO (evaluation of the variation in UPDRS II/III score, compliance, quality of life, and of any recourse to treatment with dopamine). These descriptive results do not allow for a conclusion to be drawn regarding the long-term efficacy of NEUPRO.

3.2. Adverse events

For all the clinical studies (a total of 649 patients on rotigotine, 228 patients on ropinirole and 289 patients on placebo), 75.5% of patients on rotigotine, 70% patients on ropinirole and 57.1% of patients on placebo reported at least one adverse event.
Transient dopaminergic adverse effects, such as nausea and vomiting were observed at the start of treatment.
Other adverse effects were described in more than 10% of patients in the rotigotine arm: dizziness, drowsiness and application site reactions.
During trials where the application site was alternated, 40.4% of the 396 patients who used rotigotine presented application site reactions. Most of these reactions were mild to moderate. Discontinuation of treatment was observed in 7% of patients treated with rotigotine.

3.3. Conclusion
In a comparative phase III study (study SP512) evaluating the efficacy and safety of rotigotine versus placebo, in 273 Parkinson's disease patients at early stage with at least two of the cardinal signs and symptoms of the disease (bradykinesia, resting tremor, rigidity and postural instability) and a Hoehn & Yahr stage ≤ III, a significant improvement in the UPDRS II +III score of more than 20% was observed in the rotigotine group compared to placebo, after 27 weeks of treatment (48% versus 19% $p<0.0001$). A significant difference of 5.28 points was also observed between the two groups on the UPDRS II +III score ($p<0.0001$), this difference was clinically relevant.

A non-inferiority study (study SP513) (threshold of non-inferiority of - 15%) in Parkinson's disease patients, did not demonstrate the non-inferiority of rotigotine compared to ropinirole. In Europe, the 20% responder rate was 55% with rotigotine *versus* 75% with ropinirole. In the United States, the improvement in the UPDRS-II+III score was 23% with rotigotine *versus* 39% with ropinirole.

Safety: the most frequent adverse event was an application site reaction in patients receiving rotigotine (observed in approximately 40% of cases).
In one study, 17% of patients receiving rotigotine discontinued treatment because of adverse effects compared to 13% in the ropinirole group and 5% in the placebo group.
Most of the other adverse effects were those usually observed in Parkinson’s disease patients treated by other dopamine agonists (hypotension, hypokinesia, tremor, dizziness, (asthenia, headache, confusion, nausea, drowsiness, palpitations).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Parkinson's disease is associated with resting tremor, rigidity, bradykinesia or akinesia and loss of postural reflexes. As the disease progresses, neurovegetative disturbances, sensory painful 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 characterised by a progression of disability over time and a marked reduction in quality of life. It is life-threatening.

This proprietary drug is a symptomatic anti-parkinsonian treatment.

The efficacy/adverse effects ratio is moderate.

It provides symptomatic treatment.

There are numerous alternative treatments.

Public health benefit:

Parkinson's disease represents a considerable public health burden.

Improving the global management of affected people and, particularly, delaying the onset of disabling symptoms and improving quality of life, constitutes a public health need falling within an established priority area (public health law and GTNDO).

Compared to other dopamine agonists, NEUPRO is not expected to provide an additional impact on the reduction in morbidity and mortality related to Parkinson's disease or the improvement in quality of life, taking into account:

- The lack of demonstration of any real impact of continuous dopaminergic stimulation in terms of prevention of motor complications;
- The results of the study versus ropinirole which did not show non-inferiority for a reduction of at least 20% in the UPDRS II +III score;
- The lack of data regarding an expected improvement in adherence because of the innovative method of administration of NEUPRO
- The lack of quality of life data compared to other dopamine agonists.

Accordingly, NEUPRO is not expected to have an impact on public health.

The medical benefit of NEUPRO is substantial.

4.2. Improvement in actual benefit

NEUPRO was not found to be non-inferior to ropinirole (REQUIP); it provides no improvement in actual benefit (IAB 5) compared to ropinirole in early-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 early management in Parkinson's disease.

4.3. Therapeutic use[3, 4]

The age of onset and degree of functional discomfort are the two factors guiding the choice of therapy during the initial stage of the disease:

o In the absence of motor impact, antiparkinsonian medication is not essential;

o The following agents may be prescribed when the functional impairment is minor: dopamine agonist, MAO-B inhibitor or anticholinergic. The choice depends on the predominant symptom and the patient's age;

o When there is a more severe functional impairment, treatment depends on the patient's age:

. In young patients, dopamine agonists should be preferred as long as possible. The use of L-dopa therapy is justified in the event of adverse events or an insufficient therapeutic response. The dose of levodopa must remain as low as possible.
. In elderly patients, L-dopa may be used as first-line treatment. The minimum effective dose should be used if the patient develops cognitive impairment.

After a "honeymoon" phase of good symptom control by treatment, the patient's health status worsens with the onset of dopa-induced motor disorders (motor fluctuations and dyskinesia) and the specific signs of the disease (dysautonomic cognitive impairment, psycho-behavioural signs) which are generally dopa-resistant.

Because these motor complications are caused by dopaminergic treatment, drugs should be sought that worsen the "off" periods and dyskinesias and L-dopa therapy should then be optimised (splitting of daily dose, adjustment of dosing schedule, prescription of different pharmaceutical forms).

The therapeutic management of these complications may also justify the combination of other drugs with levodopa:

- Dopamine agonist
- COMT inhibitor
- MAO-B inhibitor (selegiline, rasagiline).

Rehabilitation plays a considerable role in the management of Parkinson's disease patients. Rehabilitation procedures must be adjusted, even in the short term, to the risks and fluctuations of the disease.

Stereotactic surgery is an effective method of treatment of severe motor disorders in advanced Parkinson's disease and intractable tremor.

The following agents may be prescribed when the functional impairment is minor: a dopamine agonist, MAO-B inhibitor or anticholinergic. The choice depends on the predominant symptom and the patient's age.
When the functional discomfort is greater, in the young subject, dopamine agonists should be preferred as long as possible in order to delay the use of L-dopa therapy.
The choice between levodopa+ decarboxylase or a dopamine agonist as initial therapy remains controversial[5]. On the one hand, this combination seems to be more effective and better tolerated than dopamine agonists whereas on the other hand, it may be toxic for dopaminergic neurons and may cause more akinesia fluctuations and dyskinesia.

1. Parkinson's disease: diagnostic and therapeutic criteria.
2. Consensus conference -3 March, 2000
3. Diagnosis and Initial Management of Parkinson's Disease. New Engl J Med 2005;353:1021-7.
4. EPAR

Role of NEUPRO in treatment strategy:
NEUPRO, a dopamine agonist in a transdermal patch form, represents an additional therapeutic mean in the management of early-stage Parkinson's disease. Its method of administration allows for a more constant stimulation of the dopaminergic receptor, conforming to the current treatment recommendations for Parkinson's disease.

4.4. Target population

Apart from the incidence and prevalence data for Parkinson's disease, the target population was extrapolated from international epidemiological data and hypotheses made about this data.

Hence, according to the following data and hypotheses:

- The incidence of Parkinson's disease in France is approximately 10,000 new cases per year[6],
- The number of incident cases is stable over time,
- Dopamine agonists are indicated at early stage of Parkinson's disease, in patients aged less than 70 years[7],
- 70% of Parkinson's disease patients are aged under 70 years[8],
- 100% of patients receive dopamine agonists during the first 2 years of the disease though only 40% still receive this treatment after 3 to 5 years and 20% after 6-10 years of disease progression[9],
- Annual mortality is taken into account by using survival curves (according to the age of onset of the disease) of Parkinson's disease patients[10], in order to correct the estimates made from the incidence data and the duration of the clinical course of the disease.

The population of early-stage Parkinson's disease patients who may benefit from NEUPRO is no more than 25,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals and various public services in the Marketing Authorisation.

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 65 %

[6] GTNDO, March 2003
[7] Consensus conference - Parkinson's disease: diagnostic and therapeutic criteria – 3 March 2000
[8] Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1990. Neurology 1999;52:1214-1220
[9] Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 2000;342(20):1484-1491.
[10] Elbaz A, Bower JH, Peterson BJ, Maraganore D, McDonnell SK, Aslskog JE, Schaid DJ et al. Survival study of Parkinson Disease in Olmsted County, Minnesota. Arch Neurol 2003;60:91-96