SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Neupro 6 mg/24 h transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Neupro 6 mg/24 h transdermal patch
Each patch releases 6 mg of rotigotine per 24 hours. Each patch of 30 cm^2 contains 13.5 mg of rotigotine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.
Thin, matrix-type, square-shaped with rounded edges, consisting of three layers.

Neupro 6 mg/24 h transdermal patch
The outside of the backing layer is tan-coloured and imprinted with ‘Neupro 6 mg/24 h’.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Posology

The dose recommendations made are in nominal dose.

Dosing in patients with early-stage Parkinson's disease:
A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximum 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 maximum dose is 8 mg/24 h.

Dosing in patients with advanced stage Parkinson's disease with fluctuations:
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 maximum 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 combination of a 6 mg/24 h and a 4 mg/24 h patch.

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.

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 (see section 4.4).

Special populations

Hepatic 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 the hepatic impairment.

Renal 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 at acute worsening of renal function (see section 5.2).

Paediatric population

There is no relevant use of Neupro in the paediatric population in Parkinson's disease.

Method of administration

Neupro is for transdermal use.

The patch should be applied to clean, dry, intact healthy skin on the abdomen, thigh, hip, flank, shoulder, or upper 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 (see section 4.4).

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 release liner should be removed and the sticky side should be applied and pressed firmly to 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 30 seconds, so that it sticks well.

The patch should not be cut into pieces.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Magnetic resonance imaging or cardioversion (see section 4.4).

4.4 Special warnings and precautions for use

If a Parkinson's disease patient is insufficiently controlled while on treatment with rotigotine switching to another dopamine agonist might provide additional benefit (see section 5.1)

Magnetic resonance imaging and cardioversion

The backing layer of Neupro contains aluminium. To avoid skin burns, Neupro should be removed if the patient has to undergo magnetic resonance imaging (MRI) or cardioversion.

Orthostatic hypotension

Dopamine agonists are known to impair the systemic regulation of the blood pressure resulting in postural/orthostatic hypotension. These events have also been observed during treatment with rotigotine, but the incidence was similar to that observed in placebo-treated patients.
It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of orthostatic hypotension associated with dopaminergic therapy.

Syncope

In clinical studies with rotigotine, syncope has been observed at a rate that was similar to that observed in patients treated with placebo. Because patients with clinically relevant cardiovascular disease were excluded in these studies, patients with severe cardiovascular disease should be asked about symptoms of syncope and pre-syncope.

Sudden onset of sleep and somnolence

Rotigotine has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness of any warning signs, has been reported. Prescribers should continually reassess patients for drowsiness or sleepiness, as patients may not acknowledge drowsiness or sleepiness until directly questioned. A reduction of dosage or termination of therapy should be carefully considered.

Impulse control and other related disorders

Patients should be regularly monitored for the development of impulse control disorders and related disorders including dopamine dysregulation syndrome. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathologic gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive

eating can occur in patients treated with dopamine agonists, including rotigotine. In some patients, dopamine dysregulation syndrome was observed under the treatment with rotigotine. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Neuroleptic malignant syndrome

Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore, it is recommended to taper treatment (see section 4.2).

Dopamine agonist withdrawal syndrome

Symptoms suggestive of dopamine agonist withdrawal syndrome (for example, pain, fatigue, depression, sweating, and anxiety) have been reported with abrupt withdrawal of dopaminergic therapy, therefore, it is recommended to taper treatment (see section 4.2).

Abnormal thinking and behaviour

Abnormal thinking and behaviour have been reported and can consist of a variety of manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behaviour, disorientation, aggressive behaviour, agitation, and delirium.

Fibrotic complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when treatment is discontinued, complete resolution does not always occur.
Although these adverse reactions are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.

Neuroleptics

Neuroleptics given as antiemetic should not be given to patients taking dopamine agonists (see also section 4.5).

Ophthalmologic monitoring

Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur.

Heat application

External heat (excessive sunlight, heating pads and other sources of heat such as sauna, hot bath) should not be applied to the area of the patch.

Application site reactions

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, as exposure could lead to changes in the skin color.
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.

Peripheral oedema

In clinical studies in Parkinson's patients, the 6 month-specific rates of peripheral oedema remained at about 4% through the entire observation period up to 36 months.

Dopaminergic adverse reactions

The incidence of some dopaminergic adverse reactions, such as hallucinations, dyskinesia, and peripheral oedema generally is higher when given in combination with L-dopa in Parkinson's patients. This should be considered when prescribing rotigotine.

Dystonic reactions

Dystonic reactions including dystonia, abnormal posture, torticollis and pleurothotonus (Pisa Syndrome) have occasionally been reported in patients with Parkinson's disease following initiation or incremental dose increase of rotigotine. Although dystonic reactions may be a symptom of Parkinson's disease, the symptoms in some of these patients have improved after reduction or withdrawal of rotigotine. If a dystonic reaction occurs, the dopaminergic medication regimen should be reviewed and an adjustment in the dose of rotigotine considered.

Sulphite sensitivity

Neupro contains sodium metabisulphite, a sulphite that may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people.

4.5 Interaction with other medicinal products and other forms of interaction

Because rotigotine is a dopamine agonist, it is assumed that dopamine antagonists, such as neuroleptics (e.g. phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of Neupro, and co-administration should be avoided. Because of possible additive effects, caution should be advised when patients are taking sedating medicinal products or other CNS (central nervous system) depressants (e.g. benzodiazepines, antipsychotics, antidepressants) or alcohol in combination with rotigotine.

Co-administration of L-dopa and carbidopa with rotigotine had no effect on the pharmacokinetics of rotigotine, and rotigotine had no effect on the pharmacokinetics of L-dopa and carbidopa.

Co-administration of domperidone with rotigotine had no effect on the pharmacokinetics of rotigotine.

Co-administration of omeprazole (inhibitor of CYP2C19), in doses of 40 mg/day, had no effect on the pharmacokinetics and metabolism of rotigotine in healthy volunteers.

Neupro may potentiate the dopaminergic adverse reaction of L-dopa and may cause and/or exacerbate pre-existing dyskinesia, as described with other dopamine agonists.

Co-administration of rotigotine (3 mg/24 h) did not affect the pharmacodynamics and pharmacokinetics of oral contraceptives (0.03 mg ethinylestradiol, 0.15 mg levonorgestrel).
Interactions with other forms of hormonal contraception have not been investigated.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential, contraception in females

Women of childbearing potential should use effective contraception to prevent pregnancy during treatment with rotigotine.

Pregnancy

There are no adequate data from the use of rotigotine in pregnant women. Animal studies do not indicate any teratogenic effects in rats and rabbits, but embryo-toxicity was observed in rats and mice at materno-toxic doses (see section 5.3). The potential risk for humans is unknown. Rotigotine should not be used during pregnancy.

Breast-feeding

Because rotigotine decreases prolactin secretion in humans, inhibition of lactation is expected. Studies in rats have shown that rotigotine and/or its metabolite(s) are excreted in breast milk. In the absence of human data, breast-feeding should be discontinued.

Fertility

For information on fertility studies, please see section 5.3.

4.7 Effects on ability to drive and use machines

Rotigotine may have major influence on the ability to drive and use machines. Patients being treated with rotigotine and presenting with somnolence and/or sudden sleep episodes must be informed not to drive or engage in activities (e.g. operating machines) where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved (see also sections 4.4 and 4.5).

4.8 Undesirable effects

Summary of the safety profile

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 1,307 Neupro- and 607 placebo-treated patients, 72.5% of the patients on Neupro and 58.0% of patients on placebo reported at least one adverse reaction.

At the beginning of therapy dopaminergic adverse reactions such as nausea and vomiting may occur. These are usually mild or moderate in intensity and transient even if treatment is continued.

Adverse drug reactions (ADRs) reported in more than 10% of patients treated with Neupro transdermal patch are nausea, vomiting, application site reactions, somnolence, dizziness and headache.

In trials where the application sites were rotated as reflected in the instructions provided in SmPC and package leaflet, 35.7% of 830 patients using the Neupro transdermal patch, experienced application site reactions. The majority of application site reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of treatment with Neupro in only 4.3% of all subjects receiving Neupro.

Tabulated list of adverse reactions

The following table covers adverse drug reactions from the pooled studies mentioned above in patients with Parkinson's disease and from post-marketing experience. Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System/organ classes acc. to MedDRA	**Very common**	**Common**	**Uncommon**	**Rare**	**Not known**
Immune system disorders			Hypersensitivity, which may include angioedema, tongue oedema and lip oedema		

Psychiatric disorders		Perception disturbances[a] (incl. hallucination, hallucination visual, hallucination auditory, illusion), insomnia, sleep disorder, nightmare, abnormal dreams, impulse-control disorders[a,d] (incl. pathological gambling, stereotypy/ punding, binge eating/eating disorder[b], compulsive shopping[c])	Sleep attacks/sudden onset of sleep, paranoia, sexual desire disorders[a] (incl. hypersexuality, libido increased), confusional state, disorientation[d], agitation[d]	Psychotic disorder, obsessive-compulsive disorder, aggressive behaviour/ aggression[b], delusion[d], delirium[d]	Dopamine dysregulation syndrome[c]
Nervous system disorders	Somnolence, dizziness, headache	Disturbances in consciousness NEC[a] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia, dizziness postural, lethargy		Convulsion	Dropped head syndrome[c]
Eye disorders			Vision blurred, visual impairment, photopsia		

Ear and labyrinth disorders		Vertigo			
Cardiac disorders		Palpitations	Atrial fibrillation	Supraventricular tachycardia	
Vascular disorders		Orthostatic hypotension, hypertension	Hypotension		
Respiratory, thoracic and mediastinal disorders		Hiccups			
Gastrointestinal disorders	Nausea, vomiting	Constipation, dry mouth, dyspepsia	Abdominal pain		Diarrhoea[c]
Skin and subcutaneous tissue disorders		Erythema, hyperhidrosis, pruritus	Pruritus generalised, skin irritation, dermatitis contact	Rash generalised	
Reproductive system and breast disorder			Erectile dysfunction		
General disorders and administration site conditions	Application and instillation site reactions[a] (incl. erythema, pruritus, irritation, rash, dermatitis, vesicles, pain, eczema, inflammation, swelling, discolouration, papules, exfoliation, urticaria, hypersensitivity)	Oedema peripheral, asthenic conditions[a] (incl. fatigue, asthenia, malaise)		Irritability	

Investigations		Weight decreased	Hepatic enzyme increased (incl. AST, ALT, GGT), weight increased, heart rate increased, CPK increased[d]		
Injury, poisoning and procedural complications		Fall			
Musculoskeletal and connective tissue disorders					Rhabdomyolysis[c]

[a] High Level Term
[b] Observed in open-label studies
[c] Observed during post-marketing
[d] Observed in 2011 data pool of double-blind placebo-controlled studies

Description of selected adverse reactions

Sudden onset of sleep and somnolence

Rotigotine has been associated with somnolence including excessive daytime somnolence and sudden sleep onset episodes. In isolated cases "sudden onset of sleep" occurred while driving and resulted in motor vehicle accidents (see also sections 4.4 and 4.7).

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 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

The most likely adverse reactions would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hypotension, involuntary movements, hallucinations, confusion, convulsions and other signs of central dopaminergic stimulation.

Management

There is no known antidote for overdose of dopamine agonists. In case of suspected overdose, removal of the patch(es) should be considered because after removal of the patch(es) the active substance input is stopped and the plasma concentration of rotigotine decreases rapidly. The patient should be monitored closely, including heart rate, heart rhythm and blood pressure. Treatment of overdose may require general supportive measures to maintain the vital signs. Dialysis would not be expected to be beneficial as rotigotine is not eliminated by dialysis.

If it is necessary to discontinue rotigotine, this should be done gradually to prevent neuroleptic malignant syndrome.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-parkinson drugs, dopamine agonists; ATC code: N04BC09

Rotigotine is a non-ergolinic dopamine agonist for the treatment of signs and symptoms of Parkinson’s disease and Restless Legs Syndrome.

Mechanism of action

Rotigotine is believed to elicit its beneficial effect on Parkinson’s disease by activation of the D_3, D_2 and D_1 receptors of the caudate-putamen in the brain.

The precise mechanism of action of rotigotine as a treatment of RLS is unknown. It is thought that rotigotine may exert its activity mainly via dopamine receptors.

Pharmacodynamic effects

Regarding the functional activity at the various receptor subtypes and their distribution in the brain, rotigotine is a D_2 and D_3 receptor agonist acting also on D_1, D_4 and D_5 receptors. With non-dopaminergic receptors, rotigotine showed antagonism at alpha2B and agonism at 5HT1A receptors, but no activity on the 5HT2B receptor.

Clinical efficacy and safety

The effectiveness of rotigotine in the treatment of the signs and symptoms of idiopathic Parkinson's disease was evaluated in a multinational drug development program consisting of four pivotal, parallel, randomized, double-blind placebo controlled studies and three studies investigating specific aspects of Parkinson's disease.

Two pivotal trials (SP512 Part I and SP513 Part I) investigating the effectiveness of rotigotine in the treatment of the signs and symptoms of idiopathic Parkinson's disease were conducted in patients who were not receiving concomitant dopamine agonist therapy and were either L-dopa naïve or previous L-dopa treatment was ≤ 6 months. The primary outcome assessment was the score for the Activities of Daily Living (ADL) component (Part II) plus the Motor Examination component (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS).
Efficacy was determined by the subject's response to therapy in terms of responder and absolute points improvement in the scores of ADL and Motor Examination combined (UPDRS part II+III).

In the double blind study SP512 Part I, 177 patients received rotigotine and 96 patients received placebo. The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 6 mg/24 h. Patients in each treatment group were maintained at their optimal dose for 6 months.
At the end of the maintenance treatment in 91% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 6 mg/24 h. An improvement of 20% was seen in 48% of the subjects receiving rotigotine and in 19% of the subjects receiving placebo (Difference 29%, $CI_{95\%}$ 18%; 39%, $p<0.0001$). With rotigotine, the mean improvement in the UPDRS score (Parts II + III) was -3.98 points (baseline 29.9 points) whereas in the placebo-treated arm a worsening of 1.31 points was observed (baseline 30.0 points). The difference was 5.28 points and statistically significant ($p<0.0001$).

In the double-blind study SP513 Part I, 213 patients received rotigotine, 227 received ropinirole and 117 patients received placebo. The patients were titrated to their optimal dose of rotigotine in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 8 mg/24 h over 4 weeks. In the

ropinirole group, patients were titrated to their optimal dose up to a maximum of 24 mg/day over 13 weeks. Patients in each treatment group were maintained for 6 months.
At the end of the maintenance treatment in 92% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 8 mg/24 h. An improvement of 20% was seen in 52% of the subjects receiving rotigotine, 68% of the subjects receiving ropinirole and 30% of the subjects receiving placebo (Difference rotigotine *versus* placebo 21.7%, $CI_{95\%}$ 11.1%; 32.4%, difference ropinirole *versus* placebo 38.4%, $CI_{95\%}$ 28.1%; 48.6%, difference ropinirole *versus* rotigotine 16.6%, $CI_{95\%}$ 7.6%; 25.7%). The mean improvement in the UPDRS score (Parts II + III) was 6.83 points (baseline 33.2 points) in the rotigotine arm, 10.78 points in the ropinirole arm (baseline 32.2 points) and 2.33 points in the placebo arm (baseline 31.3 points). All differences between the active treatments and placebo were statistically significant. This study failed to demonstrate non-inferiority of rotigotine to ropinirole.

In a subsequent open-label study (SP824), a multicenter, multinational study, the tolerability of overnight switching from ropinirole, pramipexole or cabergoline to rotigotine transdermal patch and its effect on symptoms in subjects with idiopathic Parkinson's disease have been studied. 116 patients were switched from previous oral therapy to receive up to 8 mg/24 h of rotigotine, among these were 47 who had been treated with ropinirole up to 9 mg/day, 47 who had been treated with pramipexole up to 2 mg/day and 22 who had been treated with cabergoline up to 3 mg/day. Switching to rotigotine was feasible, with minor dose adjustment (median 2 mg/24 h) being necessary in only 2 patients switching from ropinirole, 5 patients from pramipexole and 4 patients from cabergoline. Improvements were seen in UPDRS Parts I - IV scores. The safety profile was unchanged from that observed in previous studies.

In a randomized, open-label study (SP825) in patients with early stage Parkinson's disease, 25 patients were randomized to rotigotine treatment and 26 to ropinirole. In both arms treatment was titrated to optimal or maximum dose of 8 mg/24 h or 9 mg/day, respectively. Both treatments showed improvements in early morning motor function and sleep. Motor symptoms (UPDRS Part III) improved by 6.3 ± 1.3 points in rotigotine-treated patients, and by 5.9 ± 1.3 points in the ropinirole-group after 4 weeks of maintenance. Sleep (PDSS) improved by 4.1 ± 13.8 points for rotigotine-treated patients, and by 2.5 ± 13.5 points for ropinirole-treated patients. The safety profile was comparable, with the exception of application site reactions.

In studies SP824 and SP825 conducted since the initial comparative trial, rotigotine and ropinirole at equivalent doses were shown to have comparable efficacy.

Two additional pivotal trials (SP650DB and SP515) were conducted in patients who were receiving concomitant levodopa therapy. The primary outcome assessment was the reduction in "off" time (hours). Efficacy was

determined by the subject's response to therapy in terms of responder and absolute improvement in the time spent "off".

In the double blind study SP650DB, 113 patients received rotigotine up to a maximum dose of 8 mg/24 h, 109 patients received rotigotine up to a maximum dose of 12 mg/24 h and 119 patients received placebo. The patients were titrated to their optimal doses of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 4 mg/24 h. Patients in each treatment group were maintained at their optimal dose for 6 months. At the end of the maintenance treatment an improvement of at least 30% was seen in 57% and 55% of the subjects receiving rotigotine 8 mg/24 h and 12 mg/24 h, respectively and in 34% of the subjects receiving placebo (Differences 22% and 21%, respectively, $CI_{95\%}$ 10%; 35% and 8%; 33%, respectively, $p<0.001$ for both rotigotine groups). With rotigotine, the mean reductions in "off" time were 2.7 and 2.1 hours, respectively whereas in the placebo-treated arm a reduction of 0.9 hours was observed. The differences were statistically significant ($p<0.001$ and $p=0.003$, respectively).

In the double-blind study SP515, 201 patients received rotigotine, 200 received pramipexole and 100 patients received placebo. The patients were titrated to their optimal dose of rotigotine in weekly increments of 2 mg/24 h starting at 4 mg/24 h to a maximum dose of 16 mg/24 h. In the pramipexole group, patients received 0,375 mg in the first week, 0.75 mg in the second week and were titrated further in weekly increments of 0.75 mg to their optimal dose up to a maximum of 4.5 mg/day. Patients in each treatment group were maintained for 4 months.
At the end of the maintenance treatment an improvement of at least 30% was seen in 60% of the subjects receiving rotigotine, 67% of the subjects receiving pramipexole and 35% of the subjects receiving placebo (Difference rotigotine *versus* placebo 25%, $CI_{95\%}$ 13%; 36%, difference pramipexole *versus* placebo 32%, $CI_{95\%}$ 21%; 43%, difference pramipexole *versus* rotigotine 7%, $CI_{95\%}$ -2%; 17%). The mean reduction in the "off" time was 2.5 hours in the rotigotine arm, 2.8 hours in the pramipexole arm and 0.9 hours in the placebo arm. All differences between the active treatments and placebo were statistically significant.

A further multinational double-blind study (SP889) was conducted in 287 patients with early or advanced stages of Parkinson's disease who had unsatisfactory early morning motor symptom control. 81.5% of these patients were on concomitant levodopa therapy. 190 patients received rotigotine, and 97 placebo. The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 16 mg/24 h over 8 weeks, followed by a maintenance period of 4 weeks. Early morning motor function, assessed by UPDRS part III, and nocturnal sleep disturbances, measured by the modified Parkinson's Disease Sleep Scale (PDSS-2), were co-primary outcome measures. At the end of maintenance, the mean UPDRS part III score had improved by 7.0 points in rotigotine-treated patients (baseline 29.6), and by 3.9 points in the placebo-group (baseline 32.0). Improvements in the mean PDSS-2 total score were 5.9 (rotigotine, baseline 19.3) and 1.9 points (placebo, baseline 20.5). Treatment

differences for the coprimary variables were statistically significant ($p=0.0002$ and $p<0.0001$).

5.2 Pharmacokinetic properties

Absorption

Following application, rotigotine is continuously released from the transdermal patch and absorbed through the skin. Steady-state concentrations are reached after one to two days of patch application and are maintained at a stable level by once daily application in which the patch is worn for 24 hours. Rotigotine plasma concentrations increase dose-proportionally over a dose range of 1 mg/24 h to 24 mg/24 h.

Approximately 45% of the active substance within the patch is released to the skin in 24 hours. 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.

Distribution

The *in vitro* binding of rotigotine to plasma proteins is approximately 92%. The apparent volume of distribution in humans is approximately 84 l/kg.

Biotransformation

Rotigotine is metabolised to a great extent. Rotigotine is metabolised by N-dealkylation as well as direct and secondary conjugation. *In vitro* results indicate that different CYP isoforms are able to catalyse the N-dealkylation of rotigotine. Main metabolites are sulfates and glucuronide conjugates of the parent compound as well as N-desalkyl-metabolites, which are biologically inactive.
The information on metabolites is incomplete.

Elimination

Approximately 71% of the rotigotine dose is excreted in urine and a smaller part of about 23% is excreted in faeces.
The clearance of rotigotine after transdermal administration is approximately 10 l/min and its overall elimination half-life is 5 to 7 hours. The pharmacokinetic profile shows a biphasic elimination with an initial half-life of about 2 to 3 hours.

Because the patch is administered transdermally, no effect of food and gastrointestinal conditions is expected.

Special patient groups

Because therapy with Neupro is initiated at a low dose and gradually titrated according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the dose based on gender, weight, or age is not necessary.

Hepatic and renal impairment

In subjects with moderate hepatic impairment or mild to severe renal impairment, no relevant increases of rotigotine plasma levels were observed. Neupro was not investigated in patients with severe hepatic impairment. Plasma levels of conjugates of rotigotine and its desalkyl metabolites increase with impaired renal function. However, a contribution of these metabolites to clinical effects is unlikely.

5.3 Preclinical safety data

In repeated dose and long-term toxicity studies, the major effects were associated with the dopamine agonist related pharmacodynamic effects and the consequent decrease of prolactin secretion.
After a single dose of rotigotine, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident, but was slowly cleared over the 14-day observation period.
Retinal degeneration was observed by transmission microscopy at a dose equivalent to 2.8 times the maximum recommended human dose on a mg/m² basis in a 3-month study in albino rats. The effects were more pronounced in female rats. Additional studies to further evaluate the specific pathology have not been performed. Retinal degeneration was not observed during the routine histopathological evaluation of the eyes in any of the toxicology studies in any species used. The relevance of these findings to humans is not known.
In a carcinogenicity study, male rats developed Leydig cell tumours and hyperplasia. Malignant tumours were noted predominantly in the uterus of mid- and high-dose females. These changes are well-known effects of dopamine agonists in rats after life-long therapy and assessed as not relevant to man.
The effects of rotigotine on reproduction have been investigated in rats, rabbits and mice. Rotigotine was not teratogenic in all three species, but was embryotoxic in rats and mice at materno-toxic doses. Rotigotine did not influence male fertility in rats, but clearly reduced female fertility in rats and mice, because of the effects on prolactin levels which are particularly significant in rodents.

Rotigotine did not induce gene mutations in the Ames test, but did show effects in the *in vitro* Mouse Lymphoma Assay with metabolic activation and weaker effects without metabolic activation. This mutagenic effect could be attributed to a clastogenic effect of rotigotine. This effect was not confirmed *in vivo* in the Mouse Micronucleus Test in the rat Unscheduled DNA Synthesis (UDS) test. Since it ran more or less parallel with a decreased relative total growth of the cells, it may be related to a cytotoxic effect of the compound. Therefore, the relevance of the one positive *in vitro* mutagenicity test is not known.

6.1 List of excipients

Backing layer

Polyester film, siliconized, aluminized,
colour coated with a pigment (titanium dioxide (E171), pigment yellow 13, pigment red 166, pigment yellow 12) layer and imprinted (pigment red 146, pigment yellow 180, pigment black 7).

Self adhesive matrix layer

Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate,
Povidone K90,
sodium metabisulphite (E223),
ascorbyl palmitate (E304) and
DL-α-tocopherol (E307).

Release liner

Transparent fluoropolymer coated polyester film.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Peel off sachet in a carton: One side is composed of an ethylene copolymer (innermost layer), an aluminium foil, low density polyethylene film and paper; the other side is composed of polyethylene (innermost layer), aluminium, ethylene copolymer and paper.

The carton contains 7, 14, 28, 30 or 84 (multipack containing 3 packs of 28) transdermal patches, individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

After use the patch still contains active substance. After removal, the used patch should be folded in half, adhesive side inwards so that the matrix layer is not exposed, placed in the original sachet and then discarded. Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7 MARKETING AUTHORISATION HOLDER

UCB Pharma Limited
208 Bath Road
Slough
Berkshire
SL1 3WE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00039/0782

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

21/01/2025