ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neupro 1 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 1 mg of rotigotine per 24 hours. Each patch of 5 cm^2 contains 2.25 mg of rotigotine.

For a 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. The outside of the backing layer is tan-coloured and imprinted with 'Neupro 1 mg/24 h'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults.

4.2 Posology and method of administration

Posology
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.

Dose
The dose recommendations made are in nominal dose.

A single daily dose should be initiated at 1 mg/24 h. Depending on the 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 (see section 4.4). Following this procedure, rebound (worsening of symptoms beyond initial intensity after discontinuation of treatment) was not observed.

Special populations
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. 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. Unexpected

accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population
The safety and efficacy of rotigotine in the paediatric population have not yet been established. No data are available.

Method of administration
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 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.

The patch should not be cut into pieces.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 were also observed during treatment with rotigotine, however the incidence was similar to that in placebo-treated patients.
Syncope was observed in association with rotigotine, but also at a similar rate in patients treated with placebo.
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.

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 disorders
Patients should be regularly monitored for the development of impulse control disorders. 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. 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).

Hallucinations
Hallucinations have been reported and patients should be informed that hallucinations can occur.

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.

Augmentation
Augmentation may occur. 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. Based on two open-label follow-up studies with one year duration, symptoms reflecting clinically relevant and not relevant augmentation may be as high as 9.4%. However, based on two 6-month, double-blind, placebo-controlled studies, clinically relevant augmentation was observed in 1.5% of rotigotine-treated patients versus 0.5% of placebo treated patients. In two open-label, follow-up studies over a subsequent 12 months, the rate of clinically relevant augmentation was 2.9%. None of these patients discontinued therapy because of augmentation. Analysis of a 5-year open-label treatment study showed that augmentation occurred in 11.9% of patients treated with the approved dosages for RLS (1-3 mg/24 h), and that 5.1% were considered clinically significant. The majority of augmentation episodes occurred in the first and second years of treatment. This study also allowed 4 mg/24 h dosing, which showed higher rates of augmentation. The 4 mg/24 h dosage is not approved for the treatment of RLS (see Section 4.2).

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.

Applications 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. 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.

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.

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

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) is 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

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 748 Neupro- and 214 placebo-treated patients, 65.2% of the patients on Neupro and 33.2% 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 are nausea, application site reactions, asthenic conditions and headache.

In trials where the application sites were rotated as reflected in the instructions provided in the SmPC and package leaflet, 34.2% of 748 patients using Neupro, experienced application site reactions. The majority of these reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of Neupro in 7.2% of subjects.

The following table covers adverse drug reactions from the pooled studies mentioned above in patients with Restless Legs Syndrome. 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
Immune system disorders		Hypersensitivity		
Psychiatric disorders		Sleep attacks/sudden onset of sleep, sexual desire disorders[a] (incl. hypersexuality, libido increased), insomnia, sleep disorder, abnormal dreams	Impulse control disorder[a] (incl. pathological gambling, punding), obsessive compulsive disorder	Aggressive behaviour/ aggression[b], binge eating and compulsive eating[b]
Nervous system disorders	Headache	Somnolence		
Vascular disorders		Hypertension	Orthostatic hypotension	
Gastrointestinal disorders	Nausea	Vomiting, dyspepsia		
Skin and subcutaneous tissue disorders		Pruritus		
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, excoriation, urticaria, hypersensitivity),	Irritability		

	asthenic conditions[a] (incl. fatigue, asthenia, malaise)			

[a] High Level Term
[b] Observed in open-label studies

Post-marketing experience: The post-marketing experience to date is consistent with the adverse effects profile observed in the clinical trials.

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 section 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 'Special warnings and precautions for use').

Discontinuation rate
The discontinuation rate was studied in 3 clinical trials ranging up to 3 years in duration. The percentage of subjects discontinuing was 25-38% over the first year, 10% in the second year, and 11% in the third year. Periodic assessment of efficacy should be performed, along with evaluation of safety, including augmentation.

4.9 Overdose

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.
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 drug 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-parkinsons 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.

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.

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.

Clinical studies:
The efficacy of rotigotine was evaluated in 5 placebo-controlled trials with more than 1,400 patients with idiopathic Restless Legs Syndrome (RLS). Efficacy was demonstrated in controlled trials in patients treated for up to 29 weeks. The effect was maintained over a 6 months period.

The changes from baseline in the International RLS Rating Scale (IRLS) and CGI-item 1 (severity of illness) were primary efficacy parameters. For both primary endpoints statistically significant differences have been observed for the doses 1 mg/24 h, 2 mg/24 h and 3 mg/24 h in comparison to placebo. After 6 months of maintenance treatment in patients with moderate to severe RLS, the baseline IRLS score improved from 30.7 to 20.7 for placebo and from 30.2 to 13.8 for rotigotine. The adjusted mean difference was -6.5 points ($CI_{95\%}$ -8.7; -4.4, $p < 0.0001$). CGI-I responder rates (much improved, very much improved) were 43.0% and 67.5% for placebo and rotigotine respectively (difference 24.5% $CI_{95\%}$: 14.2%; 34.8%, $p<0.0001$).
In a placebo-controlled, 7-week trial polysomnographic parameters were investigated. Rotigotine significantly reduced the periodic limb movement index (PLMI) from 50.9 to 7.7 *versus* 37.4 to 32.7 for placebo ($p<0.0001$).

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.

Metabolism
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 infomation 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.
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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer:
Polyester film, siliconized, aluminized,

colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, 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

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Peel off sachet in a cardboard 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, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) transdermal patches, individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 Special precaution 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 out of the reach of children. Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/038 - 046

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2006
Date of latest renewal: 17 February 2011

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Neupro 2 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 2 mg of rotigotine per 24 hours. Each patch of 10 cm^2 contains 4.5 mg of rotigotine.

For a 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. The outside of the backing layer is tan-coloured and imprinted with 'Neupro 2 mg/24 h'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Restless Legs Syndrome
Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults.

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).

4.2 Posology and method of administration

Posology
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.

Dose
The dose recommendations made are in nominal dose.

Restless Legs Syndrome
A single daily dose should be initiated at 1 mg/24 h. Depending on the 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.

Parkinson's disease
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 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.

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 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 combination of a 6 mg/24 h and a 4 mg/24 h patch.

Treatment discontinuation
Restless Legs Syndrome
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 (see section 4.4). Following this procedure, rebound (worsening of symptoms beyond initial intensity after discontinuation of treatment) was not observed.

Parkinson's disease
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 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. 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. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population
The safety and efficacy of rotigotine in the paediatric population have not yet been established. No data are available.

Method of administration
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 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.

The patch should not be cut into pieces.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
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 were also observed during treatment with rotigotine, however the incidence was similar to that in placebo-treated patients.
Syncope was observed in association with rotigotine, but also at a similar rate in patients treated with placebo.
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.

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 disorders
Patients should be regularly monitored for the development of impulse control disorders. 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. 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).

Hallucinations
Hallucinations have been reported and patients should be informed that hallucinations can occur.

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.

Augmentation
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. Based on two open-label follow-up studies with one year duration, symptoms reflecting clinically relevant and not relevant augmentation may be as high as 9.4%. However, based on two 6-month, double-blind, placebo-controlled studies, clinically relevant augmentation was observed in 1.5% of rotigotine-treated patients versus 0.5% of placebo treated patients. In two open-label, follow-up studies over a subsequent 12 months, the rate of clinically relevant augmentation was 2.9%. None of these patients discontinued therapy because of augmentation. Analysis of a 5-year open-label treatment study showed that augmentation occurred in 11.9% of patients treated with the approved dosages for RLS (1-3 mg/24 h), and that 5.1% were considered clinically significant. The majority of augmentation episodes occurred in the first and second years of treatment. This study also allowed 4 mg/24 h dosing, which showed higher rates of augmentation. The 4 mg/24 h dosage is not approved for the treatment of RLS (see Section 4.2).

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. 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.

Dopaminergic adverse events
The incidence of some dopaminergic adverse events, 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.

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

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

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) is 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

Restless Legs Syndrome
Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 748 Neupro- and 214 placebo-treated patients, 65.2% of the patients on Neupro and 33.2% 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 are nausea, application site reactions, asthenic conditions and headache.

In trials where the application sites were rotated as reflected in the instructions provided in the SmPC and package leaflet, 34.2% of 748 patients using Neupro, experienced application site reactions. The majority of these reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of Neupro in 7.2% of subjects.

The following table covers adverse drug reactions from the pooled studies mentioned above in patients with Restless Legs Syndrome. 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
Immune system disorders		Hypersensitivity		
Psychiatric disorders		Sleep attacks/sudden onset of sleep, sexual desire disorders[a] (incl. hypersexuality, libido increased), insomnia, sleep disorder, abnormal dreams	Impulse control disorder[a] (incl. pathological gambling, punding), obsessive compulsive disorder	Aggressive behaviour/ aggression[b], binge eating and compulsive eating[b]
Nervous system disorders	Headache	Somnolence		
Vascular disorders		Hypertension	Orthostatic hypotension	
Gastrointestinal disorders	Nausea	Vomiting, dyspepsia		
Skin and subcutaneous tissue disorders		Pruritus		
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, excoriation, urticaria, hypersensitivity), asthenic conditions[a] (incl. fatigue, asthenia, malaise)	Irritability		

[a] High Level Term
[b] Observed in open-label studies

Post-marketing experience: The post-marketing experience to date is consistent with the adverse effects profile observed in the clinical trials.

Discontinuation rate
The discontinuation rate was studied in 3 clinical trials ranging up to 3 years in duration. The percentage of subjects discontinuing was 25-38% over the first year, 10% in the second year, and 11% in the third year. Periodic assessment of efficacy should be performed, along with evaluation of safety, including augmentation.

Parkinson's disease
Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 1,307 Neupro- and 607 placebo-treated patients, 72.3% of the patients on Neupro and 57.8% 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 these 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.

The following table covers adverse drug reactions from the pooled studies mentioned above in patients with Parkinson's disease. 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
Immune system disorders			Hypersensitivity	
Psychiatric disorders		Perception disturbances[a] (incl. hallucination, hallucination visual, hallucination auditory, illusion), insomnia, sleep disorder, nightmare, abnormal dreams	Sleep attacks/sudden onset of sleep, paranoia, sexual desire disorders[a] (incl. hypersexuality, libido increased), impulse control disorder[a] (incl. pathological gambling, punding), confusional state	Psychotic disorder, obsessive-compulsive disorder, aggressive behaviour/ aggression[b], binge eating and compulsive eating[b]

Nervous system disorders	Somnolence, dizziness, headache	Disturbances in consciousness NEC[a] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia, dizziness postural, lethargy		Convulsion
Eye disorders			Vision blurred, visual disturbance, 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	
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, excoriation, 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	
Injury, poisoning and procedural complications		Fall		

[a] High Level Term

[b] Observed in open-label studies

Post-marketing experience: The post-marketing experience to date is consistent with the adverse effects profile observed in the clinical trials.

Both indications
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 section 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 'Special warnings and precautions for use').

4.9 Overdose

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.
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 drug 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.

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.

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.

Clinical studies:

Clinical studies in Restless Legs Syndrome
The efficacy of rotigotine was evaluated in 5 placebo-controlled trials with more than 1,400 patients with idiopathic Restless Legs Syndrome (RLS). Efficacy was demonstrated in controlled trials in patients treated for up to 29 weeks. The effect was maintained over a 6 months period.

The changes from baseline in the International RLS Rating Scale (IRLS) and CGI-item 1 (severity of illness) were primary efficacy parameters. For both primary endpoints statistically significant differences have been observed for the doses 1 mg/24 h, 2 mg/24 h and 3 mg/24 h in comparison to placebo. After 6 months of maintenance treatment in patients with moderate to severe RLS, the baseline IRLS score improved from 30.7 to 20.7 for placebo and from 30.2 to 13.8 for rotigotine. The adjusted mean difference was -6.5 points ($CI_{95\%}$ -8.7; -4.4, $p < 0.0001$). CGI-I responder rates (much improved, very much improved) were 43.0% and 67.5% for placebo and rotigotine respectively (difference 24.5% $CI_{95\%}$: 14.2%; 34.8%, $p<0.0001$).
In a placebo-controlled, 7-week trial polysomnographic parameters were investigated. Rotigotine significantly reduced the periodic limb movement index (PLMI) from 50.9 to 7.7 *versus* 37.4 to 32.7 for placebo ($p<0.0001$).

Clinical studies in Parkinson's disease
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. In further studies the effects of rotigotine on specific aspects of Parkinson's disease were evaluated.
Two pivotal trials 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 one double blind study, 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 a second double-blind study, 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, 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 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 these studies conducted since the initial comparative trial, rotigotine and ropinirole at equivalent doses were shown to have comparable efficacy.

Two additional pivotal trials 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 one double blind study, 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 a second double-blind study, 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 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.

Metabolism
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 infomation 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.

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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer:
Polyester film, siliconized, aluminized,
colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, 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

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Peel off sachet in a cardboard 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, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) transdermal patches, individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 Special precaution 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 out of the reach of children. Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/001 - 003
EU/1/05/331/014 - 019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2006
Date of latest renewal: 17 February 2011

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Neupro 3 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 3 mg of rotigotine per 24 hours. Each patch of 15 cm^2 contains 6.75 mg of rotigotine.

For a 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. The outside of the backing layer is tan-coloured and imprinted with 'Neupro 3 mg/24 h'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults.

4.2 Posology and method of administration

Posology
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.

Dose
The dose recommendations made are in nominal dose.

A single daily dose should be initiated at 1 mg/24 h. Depending on the 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 (see section 4.4). Following this procedure, rebound (worsening of symptoms beyond initial intensity after discontinuation of treatment) was not observed.

Special populations
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. 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. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population
The safety and efficacy of rotigotine in the paediatric population have not yet been established. No data are available.

Method of administration
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 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.

The patch should not be cut into pieces.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 were also observed during treatment with rotigotine, however the incidence was similar to that in placebo-treated patients.
Syncope was observed in association with rotigotine, but also at a similar rate in patients treated with placebo.
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.

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 disorders
Patients should be regularly monitored for the development of impulse control disorders. 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. 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).

Hallucinations
Hallucinations have been reported and patients should be informed that hallucinations can occur.

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.

Augmentation
Augmentation may occur. 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. Based on two open-label follow-up studies with one year duration, symptoms reflecting clinically relevant and not relevant augmentation may be as high as 9.4%. However, based on two 6-month, double-blind, placebo-controlled studies, clinically relevant augmentation was observed in 1.5% of rotigotine-treated patients versus 0.5% of placebo treated patients. In two open-label, follow-up studies over a subsequent 12 months, the rate of clinically relevant augmentation was 2.9%. None of these patients discontinued therapy because of augmentation. Analysis of a 5-year open-label treatment study showed that augmentation occurred in 11.9% of patients treated with the approved dosages for RLS (1-3 mg/24 h), and that 5.1% were considered clinically significant. The majority of augmentation episodes occurred in the first and second years of treatment. This study also allowed 4 mg/24 h dosing, which showed higher rates of augmentation. The 4 mg/24 h dosage is not approved for the treatment of RLS (see Section 4.2).

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. 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.

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.

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

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) is 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

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 748 Neupro- and 214 placebo-treated patients, 65.2% of the patients on Neupro and 33.2% 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 are nausea, application site reactions, asthenic conditions and headache.

In trials where the application sites were rotated as reflected in the instructions provided in the SmPC and package leaflet, 34.2% of 748 patients using Neupro, experienced application site reactions. The majority of these reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of Neupro in 7.2% of subjects.

The following table covers adverse drug reactions from the pooled studies mentioned above in patients with Restless Legs Syndrome. 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
Immune system disorders		Hypersensitivity		
Psychiatric disorders		Sleep attacks/sudden onset of sleep, sexual desire disorders[a] (incl. hypersexuality, libido increased), insomnia, sleep disorder, abnormal dreams	Impulse control disorder[a] (incl. pathological gambling, punding), obsessive compulsive disorder	Aggressive behaviour/ aggression[b], binge eating and compulsive eating[b]
Nervous system disorders	Headache	Somnolence		
Vascular disorders		Hypertension	Orthostatic hypotension	
Gastrointestinal disorders	Nausea	Vomiting, dyspepsia		
Skin and subcutaneous tissue disorders		Pruritus		
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, excoriation, urticaria, hypersensitivity),	Irritability		

	asthenic conditions[a] (incl. fatigue, asthenia, malaise)			

[a] High Level Term
[b] Observed in open-label studies

Post-marketing experience: The post-marketing experience to date is consistent with the adverse effects profile observed in the clinical trials.

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 section 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 'Special warnings and precautions for use').

Discontinuation rate
The discontinuation rate was studied in 3 clinical trials ranging up to 3 years in duration. The percentage of subjects discontinuing was 25-38% over the first year, 10% in the second year, and 11% in the third year. Periodic assessment of efficacy should be performed, along with evaluation of safety, including augmentation.

4.9 Overdose

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.
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 drug 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.

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.

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.

Clinical studies:
The efficacy of rotigotine was evaluated in 5 placebo-controlled trials with more than 1,400 patients with idiopathic Restless Legs Syndrome (RLS). Efficacy was demonstrated in controlled trials in patients treated for up to 29 weeks. The effect was maintained over a 6 months period.

The changes from baseline in the International RLS Rating Scale (IRLS) and CGI-item 1 (severity of illness) were primary efficacy parameters. For both primary endpoints statistically significant differences have been observed for the doses 1 mg/24 h, 2 mg/24 h and 3 mg/24 h in comparison to placebo. After 6 months of maintenance treatment in patients with moderate to severe RLS, the baseline IRLS score improved from 30.7 to 20.7 for placebo and from 30.2 to 13.8 for rotigotine. The adjusted mean difference was -6.5 points ($CI_{95\%}$ -8.7; -4.4, $p < 0.0001$). CGI-I responder rates (much improved, very much improved) were 43.0% and 67.5% for placebo and rotigotine respectively (difference 24.5% $CI_{95\%}$: 14.2%; 34.8%, $p<0.0001$).
In a placebo-controlled, 7-week trial polysomnographic parameters were investigated. Rotigotine significantly reduced the periodic limb movement index (PLMI) from 50.9 to 7.7 *versus* 37.4 to 32.7 for placebo ($p<0.0001$).

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.

Metabolism
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 infomation 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.
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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer:
Polyester film, siliconized, aluminized,

colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, 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

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Peel off sachet in a cardboard 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, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) transdermal patches, individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 Special precaution 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 out of the reach of children. Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/047 - 055

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2006
Date of latest renewal: 17 February 2011

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Neupro 4 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 4 mg of rotigotine per 24 hours. Each patch of 20 cm^2 contains 9.0 mg of rotigotine.

For a 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. The outside of the backing layer is tan-coloured and imprinted with 'Neupro 4 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
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.

Dose
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 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.

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 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 combination of a 6 mg/24 h and a 4 mg/24 h patch.

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 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. 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. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population
The safety and efficacy of rotigotine in the paediatric population have not yet been established. No data are available.

Method of administration
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 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.

The patch should not be cut into pieces.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
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 were also observed during treatment with rotigotine, however the incidence was similar to that in placebo-treated patients.
Syncope was observed in association with rotigotine, but also at a similar rate in patients treated with placebo.

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.

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 disorders
Patients should be regularly monitored for the development of impulse control disorders. 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. 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).

Hallucinations
Hallucinations have been reported and patients should be informed that hallucinations can occur.

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. 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.

Dopaminergic adverse events
The incidence of some dopaminergic adverse events, 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.

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

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

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) is 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

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 1,307 Neupro- and 607 placebo-treated patients, 72.3% of the patients on Neupro and 57.8% 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 these 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.

The following table covers adverse drug reactions from the pooled studies mentioned above in patients with Parkinson's disease. 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
Immune system disorders			Hypersensitivity	

Psychiatric disorders		Perception disturbances[a] (incl. hallucination, hallucination visual, hallucination auditory, illusion), insomnia, sleep disorder, nightmare, abnormal dreams	Sleep attacks/sudden onset of sleep, paranoia, sexual desire disorders[a] (incl. hypersexuality , libido increased), impulse control disorder[a] (incl. pathological gambling, punding), confusional state	Psychotic disorder, obsessive-compulsive disorder, aggressive behaviour/ aggression[b], binge eating and compulsive eating[b]
Nervous system disorders	Somnolence, dizziness, headache	Disturbances in consciousness NEC[a] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia, dizziness postural, lethargy		Convulsion
Eye disorders			Vision blurred, visual disturbance, 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	
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, excoriation, 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	
Injury, poisoning and procedural complications		Fall		

[a] High Level Term
[b] Observed in open-label studies

Post-marketing experience: The post-marketing experience to date is consistent with the adverse effects profile observed in the clinical trials.

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 section 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 'Special warnings and precautions for use').

4.9 Overdose

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.
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 drug 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.

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.

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.

Clinical studies:
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. In further studies the effects of rotigotine on specific aspects of Parkinson's disease were evaluated.
Two pivotal trials 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 one double blind study, 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 a second double-blind study, 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, 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 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 these studies conducted since the initial comparative trial, rotigotine and ropinirole at equivalent doses were shown to have comparable efficacy.

Two additional pivotal trials 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 one double blind study, 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 a second double-blind study, 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 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.

Metabolism
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 infomation 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.
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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer:
Polyester film, siliconized, aluminized,
colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, 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

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Peel off sachet in a cardboard 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, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) transdermal patches, individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 Special precaution 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 out of the reach of children. Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/004 - 006
EU/1/05/331/020 - 025

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2006
Date of latest renewal: 17 February 2011

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Neupro 6 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a 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. 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
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.

Dose
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 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.

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 maximal dose of 16 mg/24 h.
4 mg/24 h or 6 mg/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.

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 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. 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. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population
The safety and efficacy of rotigotine in the paediatric population have not yet been established. No data are available.

Method of administration
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 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.

The patch should not be cut into pieces.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
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 were also observed during treatment with rotigotine, however the incidence was similar to that in placebo-treated patients.
Syncope was observed in association with rotigotine, but also at a similar rate in patients treated with placebo.
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.

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 disorders
Patients should be regularly monitored for the development of impulse control disorders. 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. 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).

Hallucinations
Hallucinations have been reported and patients should be informed that hallucinations can occur.

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. 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.

Dopaminergic adverse events
The incidence of some dopaminergic adverse events, 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.

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

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

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) is 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

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 1,307 Neupro- and 607 placebo-treated patients, 72.3% of the patients on Neupro and 57.8% 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 these 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.

The following table covers adverse drug reactions from the pooled studies mentioned above in patients with Parkinson's disease. 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
Immune system disorders			Hypersensitivity	

Psychiatric disorders		Perception disturbances[a] (incl. hallucination, hallucination visual, hallucination auditory, illusion), insomnia, sleep disorder, nightmare, abnormal dreams	Sleep attacks/sudden onset of sleep, paranoia, sexual desire disorders[a] (incl. hypersexuality, libido increased), impulse control disorder[a] (incl. pathological gambling, punding), confusional state	Psychotic disorder, obsessive-compulsive disorder, aggressive behaviour/ aggression[b], binge eating and compulsive eating[b]
Nervous system disorders	Somnolence, dizziness, headache	Disturbances in consciousness NEC[a] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia, dizziness postural, lethargy		Convulsion
Eye disorders			Vision blurred, visual disturbance, 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	
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, excoriation, 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	
Injury, poisoning and procedural complications		Fall		

[a] High Level Term
[b] Observed in open-label studies

Post-marketing experience: The post-marketing experience to date is consistent with the adverse effects profile observed in the clinical trials.

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 section 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 'Special warnings and precautions for use').

4.9 Overdose

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.
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 drug 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.

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.

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.

Clinical studies:
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. In further studies the effects of rotigotine on specific aspects of Parkinson's disease were evaluated.
Two pivotal trials 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 one double blind study, 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 a second double-blind study, 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, 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 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 these studies conducted since the initial comparative trial, rotigotine and ropinirole at equivalent doses were shown to have comparable efficacy.

Two additional pivotal trials 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 one double blind study, 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 a second double-blind study, 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 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.

Metabolism
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 infomation 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.
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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer:
Polyester film, siliconized, aluminized,
colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, 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

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Peel off sachet in a cardboard 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, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) transdermal patches, individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 Special precaution 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 out of the reach of children. Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/007 - 009
EU/1/05/331/026 - 031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2006
Date of latest renewal: 17 February 2011

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Neupro 8 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 8 mg of rotigotine per 24 hours. Each patch of 40 cm^2 contains 18.0 mg of rotigotine.

For a 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. The outside of the backing layer is tan-coloured and imprinted with 'Neupro 8 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
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.

Dose
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 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.

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 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 combination of a 6 mg/24 h and a 4 mg/24 h patch.

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 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. 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. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population
The safety and efficacy of rotigotine in the paediatric population have not yet been established. No data are available.

Method of administration
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 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.

The patch should not be cut into pieces.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
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 were also observed during treatment with rotigotine, however the incidence was similar to that in placebo-treated patients.
Syncope was observed in association with rotigotine, but also at a similar rate in patients treated with placebo.
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.

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 disorders
Patients should be regularly monitored for the development of impulse control disorders. 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. 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).

Hallucinations
Hallucinations have been reported and patients should be informed that hallucinations can occur.

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. 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.

Dopaminergic adverse events
The incidence of some dopaminergic adverse events, 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.

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

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 (0.03mg ethinylestradiol, 0.15mg levonorgestrel). Interactions with other forms of hormonal contraception have not been investigated.

4.6 Fertility, pregnancy and lactation

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) is 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

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 1,307 Neupro- and 607 placebo-treated patients, 72.3% of the patients on Neupro and 57.8% 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 these 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.

The following table covers adverse drug reactions from the pooled studies mentioned above in patients with Parkinson's disease. 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
Immune system disorders			Hypersensitivity	

Psychiatric disorders		Perception disturbances[a] (incl. hallucination, hallucination visual, hallucination auditory, illusion), insomnia, sleep disorder, nightmare, abnormal dreams	Sleep attacks/sudden onset of sleep, paranoia, sexual desire disorders[a] (incl. hypersexuality, libido increased), impulse control disorder[a] (incl. pathological gambling, punding), confusional state	Psychotic disorder, obsessive-compulsive disorder, aggressive behaviour/ aggression[b], binge eating and compulsive eating[b]
Nervous system disorders	Somnolence, dizziness, headache	Disturbances in consciousness NEC[a] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia, dizziness postural, lethargy		Convulsion
Eye disorders			Vision blurred, visual disturbance, 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	
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, excoriation, 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	
Injury, poisoning and procedural complications		Fall		

[a] High Level Term
[b] Observed in open-label studies

Post-marketing experience: The post-marketing experience to date is consistent with the adverse effects profile observed in the clinical trials.

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 section 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 'Special warnings and precautions for use').

4.9 Overdose

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.
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 drug 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.

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.

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.

Clinical studies:
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. In further studies the effects of rotigotine on specific aspects of Parkinson's disease were evaluated.
Two pivotal trials 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 one double blind study, 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 a second double-blind study, 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, 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 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 these studies conducted since the initial comparative trial, rotigotine and ropinirole at equivalent doses were shown to have comparable efficacy.

Two additional pivotal trials 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 one double blind study, 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 a second double-blind study, 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 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.

Metabolism
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 infomation 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.
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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer:
Polyester film, siliconized, aluminized,
colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, 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

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Peel off sachet in a cardboard 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, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) transdermal patches, individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 Special precaution 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 out of the reach of children. Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/010 - 012
EU/1/05/331/032 - 037

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2006
Date of latest renewal: 17 February 2011

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Neupro
2 mg/24 h
4 mg/24 h
6 mg/24 h
8 mg/24 h
Transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Neupro 2 mg/24 h transdermal patch
Each patch releases 2 mg of rotigotine per 24 hours. Each patch of 10 cm^2 contains 4.5 mg of rotigotine.

Neupro 4 mg/24 h transdermal patch
Each patch releases 4 mg of rotigotine per 24 hours. Each patch of 20 cm^2 contains 9.0 mg of rotigotine.

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.

Neupro 8 mg/24 h transdermal patch
Each patch releases 8 mg of rotigotine per 24 hours. Each patch of 40 cm^2 contains 18.0 mg of rotigotine.

For a 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. The outside of the backing layer is tan-coloured and imprinted with 'Neupro 2 mg/24 h, 4 mg/24 h, 6 mg/24 h or 8 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
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.

Dose
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 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.

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 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.

Neupro treatment initiation pack contains 4 different packages (one for each strength) with 7 patches each, for the first four weeks of therapy.
Depending on the patient's response, not all of the following dose steps may be required or additional higher doses may be needed after week 4, which are not covered by this package.
On the first day of treatment the patient starts with Neupro 2 mg/24 h. During the second week, the patient takes Neupro 4 mg/24 h. During the third week, he or she takes Neupro 6 mg/24 h and during the fourth week Neupro 8 mg/24 h. The packages are marked with "Week 1 (2, 3 or 4)".

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 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. 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. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population
The safety and efficacy of rotigotine in the paediatric population have not yet been established. No data are available.

Method of administration
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 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.

The patch should not be cut into pieces.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
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 were also observed during treatment with rotigotine, however the incidence was similar to that in placebo-treated patients.
Syncope was observed in association with rotigotine, but also at a similar rate in patients treated with placebo.
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.

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 disorders
Patients should be regularly monitored for the development of impulse control disorders. 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. 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).

Hallucinations
Hallucinations have been reported and patients should be informed that hallucinations can occur.

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. 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.

Dopaminergic adverse events
The incidence of some dopaminergic adverse events, 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.

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

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 (0.03mg ethinylestradiol, 0.15mg levonorgestrel). Interactions with other forms of hormonal contraception have not been investigated.

4.6 Fertility, pregnancy and lactation

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) is 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

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 1,307 Neupro- and 607 placebo-treated patients, 72.3% of the patients on Neupro and 57.8% 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 these 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.

The following table covers adverse drug reactions from the pooled studies mentioned above in patients with Parkinson's disease. 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
Immune system disorders			Hypersensitivity	
Psychiatric disorders		Perception disturbances[a] (hallucination, hallucination visual, hallucination auditory, illusion), insomnia sleep disorder, nightmare, abnormal dreams	Sleep attacks/sudden onset of sleep, paranoia, sexual desire disorders[a] (incl. hypersexuality, libido increased), impulse control disorder[a] (incl. pathological gambling, punding), confusional state	Psychotic disorder, obsessive-compulsive disorder, aggressive behaviour/ aggression[b], binge eating and compulsive eating[b]
Nervous system disorders	Somnolence, dizziness, headache	Disturbances in consciousness NEC[a] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia[a], dizziness postural, lethargy		Convulsion
Eye disorders			Vision blurred, visual disturbance, 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	
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, excoriation, 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	
Injury, poisoning and procedural complications		Fall		

[a] High Level Term
[b] Observed in open-label studies

Post-marketing experience: The post-marketing experience to date is consistent with the adverse effects profile observed in the clinical trials.

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 section 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 'Special warnings and precautions for use').

4.9 Overdose

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.
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 drug 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.

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.

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.

Clinical studies:
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. In further studies the effects of rotigotine on specific aspects of Parkinson's disease were evaluated.
Two pivotal trials 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 one double blind study, 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 a second double-blind study, 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, 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 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 these studies conducted since the initial comparative trial, rotigotine and ropinirole at equivalent doses were shown to have comparable efficacy.

Two additional pivotal trials 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 one double blind study, 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 a second double-blind study, 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 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.

Metabolism
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 infomation 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.
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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer:
Polyester film, siliconized, aluminized,
colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, 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

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Peel off sachet in a cardboard 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 treatment initiation pack contains 28 transdermal patches in 4 cartons with 7 patches of 2 mg, 4 mg, 6 mg, and 8 mg each, individually sealed in sachets.

6.6 Special precaution 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 out of the reach of children. Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2006
Date of latest renewal: 17 February 2011

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

UCB Manufacturing Ireland Ltd.
Shannon Industrial Estate
Shannon, Co. Clare
Ireland

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not aplicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

Further to the first renewal, the PSUR cycle was restarted with four 6-month reports and two 1-year reports to be submitted, followed by the second 5-year renewal.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON (WITH BLUE BOX)
(EXCLUDING MULTIPACKS)
BOX OF 7 [20] [28] [30] [56] [60] [90] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 1 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 1 mg of rotigotine per 24 hours.
Each patch of 5 cm^2 contains 2.25 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
20 transdermal patches
28 transdermal patches
30 transdermal patches
56 transdermal patches
60 transdermal patches
90 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/038 [7 transdermal patches]
EU/1/05/331/040 [28 transdermal patches]
EU/1/05/331/039 [20 transdermal patches]
EU/1/05/331/041 [30 transdermal patches]
EU/1/05/331/042 [56 transdermal patches]
EU/1/05/331/043 [60 transdermal patches]
EU/1/05/331/045 [90 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 1 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 [100] PATCHES CONTAINING 2 BOXES OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 1 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 1 mg of rotigotine per 24 hours.
Each patch of 5 cm^2 contains 2.25 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 transdermal patches, multipack, containing 2 boxes with 42 patches each
100 transdermal patches, multipack, containing 2 boxes with 50 patches each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/044 [84 transdermal patches]
EU/1/05/331/046 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 1 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
INTERMEDIATE CARTON (WITHOUT BLUE BOX)
BOX OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 1 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 1 mg of rotigotine per 24 hours.
Each patch of 5 cm^2 contains 2.25 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

42 transdermal patches, component of a multipack comprising 2 boxes, each containing 42 patches
50 transdermal patches, component of a multipack comprising 2 boxes, each containing 50 patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/044 [84 transdermal patches]
EU/1/05/331/046 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 1 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neupro 1 mg/24 h transdermal patch
Rotigotine
Transdermal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON (WITH BLUE BOX)
(EXCLUDING MULTIPACKS)
BOX OF 7 [20] [28] [30] [56] [60] [90] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 2 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 2 mg of rotigotine per 24 hours.
Each patch of 10 cm^2 contains 4.5 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
20 transdermal patches
28 transdermal patches
30 transdermal patches
56 transdermal patches
60 transdermal patches
90 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/001 [7 transdermal patches]
EU/1/05/331/002 [28 transdermal patches]
EU/1/05/331/014 [20 transdermal patches]
EU/1/05/331/015 [30 transdermal patches]
EU/1/05/331/016 [56 transdermal patches]
EU/1/05/331/017 [60 transdermal patches]
EU/1/05/331/019 [90 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 2 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 [100] PATCHES CONTAINING 2 BOXES OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 2 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 2 mg of rotigotine per 24 hours.
Each patch of 10 cm^2 contains 4.5 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 transdermal patches, multipack, containing 2 boxes with 42 patches each
100 transdermal patches, multipack, containing 2 boxes with 50 patches each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/018 [84 transdermal patches]
EU/1/05/331/003 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 2 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
INTERMEDIATE CARTON (WITHOUT BLUE BOX)
BOX OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 2 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 2 mg of rotigotine per 24 hours.
Each patch of 10 cm^2 contains 4.5 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

42 transdermal patches, component of a multipack comprising 2 boxes, each containing 42 patches
50 transdermal patches, component of a multipack comprising 2 boxes, each containing 50 patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/018 [84 transdermal patches]
EU/1/05/331/003 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 2 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neupro 2 mg/24 h transdermal patch
Rotigotine
Transdermal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON (WITH BLUE BOX)
(EXCLUDING MULTIPACKS)
BOX OF 7 [20] [28] [30] [56] [60] [90] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 3 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 3 mg of rotigotine per 24 hours.
Each patch of 15 cm^2 contains 6.75 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
20 transdermal patches
28 transdermal patches
30 transdermal patches
56 transdermal patches
60 transdermal patches
90 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/047 [7 transdermal patches]
EU/1/05/331/049 [28 transdermal patches]
EU/1/05/331/048 [20 transdermal patches]
EU/1/05/331/050 [30 transdermal patches]
EU/1/05/331/051 [56 transdermal patches]
EU/1/05/331/052 [60 transdermal patches]
EU/1/05/331/054 [90 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 3 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 [100] PATCHES CONTAINING 2 BOXES OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 3 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 3 mg of rotigotine per 24 hours.
Each patch of 15 cm^2 contains 6.75 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 transdermal patches, multipack, containing 2 boxes with 42 patches each
100 transdermal patches, multipack, containing 2 boxes with 50 patches each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/053 [84 transdermal patches]
EU/1/05/331/055 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 3 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
INTERMEDIATE CARTON (WITHOUT BLUE BOX)
BOX OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 3 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 3 mg of rotigotine per 24 hours.
Each patch of 15 cm^2 contains 6.75 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

42 transdermal patches, component of a multipack comprising 2 boxes, each containing 42 patches
50 transdermal patches, component of a multipack comprising 2 boxes, each containing 50 patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/053 [84 transdermal patches]
EU/1/05/331/055 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 3 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neupro 3 mg/24 h transdermal patch
Rotigotine
Transdermal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON (WITH BLUE BOX)
(EXCLUDING MULTIPACKS)
BOX OF 7 [20] [28] [30] [56] [60] [90] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 4 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 4 mg of rotigotine per 24 hours.
Each patch of 20 cm^2 contains 9.0 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
20 transdermal patches
28 transdermal patches
30 transdermal patches
56 transdermal patches
60 transdermal patches
90 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/004 [7 transdermal patches]
EU/1/05/331/005 [28 transdermal patches]
EU/1/05/331/020 [20 transdermal patches]
EU/1/05/331/021 [30 transdermal patches]
EU/1/05/331/022 [56 transdermal patches]
EU/1/05/331/023 [60 transdermal patches]
EU/1/05/331/025 [90 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 4 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 [100] PATCHES CONTAINING 2 BOXES OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 4 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 4 mg of rotigotine per 24 hours.
Each patch of 20 cm^2 contains 9.0 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 transdermal patches; multipack, containing 2 boxes with 42 patches each
100 transdermal patches, multipack, containing 2 boxes with 50 patches each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/024 [84 transdermal patches]
EU/1/05/331/006 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 4 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
INTERMEDIATE CARTON (WITHOUT BLUE BOX)
BOX OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 4 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 4 mg of rotigotine per 24 hours.
Each patch of 20 cm^2 contains 9.0 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

42 transdermal patches, component of a multipack comprising 2 boxes, each containing 42 patches
50 transdermal patches, component of a multipack comprising 2 boxes, each containing 50 patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/024 [84 transdermal patches]
EU/1/05/331/006 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 4 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neupro 4 mg/24 h transdermal patch
Rotigotine
Transdermal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON (WITH BLUE BOX)
(EXCLUDING MULTIPACKS)
BOX OF 7 [20] [28] [30] [56] [60] [90] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 6 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
20 transdermal patches
28 transdermal patches
30 transdermal patches
56 transdermal patches
60 transdermal patches
90 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/007 [7 transdermal patches]
EU/1/05/331/008 [28 transdermal patches]
EU/1/05/331/026 [20 transdermal patches]
EU/1/05/331/027 [30 transdermal patches]
EU/1/05/331/028 [56 transdermal patches]
EU/1/05/331/029 [60 transdermal patches]
EU/1/05/331/031 [90 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 6 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 [100] PATCHES CONTAINING 2 BOXES OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 6 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 transdermal patches; multipack, containing 2 boxes with 42 patches each
100 transdermal patches, multipack, containing 2 boxes with 50 patches each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/030 [84 transdermal patches]
EU/1/05/331/009 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 6 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
INTERMEDIATE CARTON (WITHOUT BLUE BOX)
BOX OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 6 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

42 transdermal patches, component of a multipack comprising 2 boxes, each containing 42 patches
50 transdermal patches, component of a multipack comprising 2 boxes, each containing 50 patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/030 [84 transdermal patches]
EU/1/05/331/009 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 6 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neupro 6 mg/24 h transdermal patch
Rotigotine
Transdermal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON (WITH BLUE BOX)
(EXCLUDING MULTIPACKS)
BOX OF 7 [20] [28] [30] [56] [60] [90] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 8 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 8 mg of rotigotine per 24 hours.
Each patch of 40 cm^2 contains 18.0 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
20 transdermal patches
28 transdermal patches
30 transdermal patches
56 transdermal patches
60 transdermal patches
90 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/010 [7 transdermal patches]
EU/1/05/331/011 [28 transdermal patches]
EU/1/05/331/032 [20 transdermal patches]
EU/1/05/331/033 [30 transdermal patches]
EU/1/05/331/034 [56 transdermal patches]
EU/1/05/331/035 [60 transdermal patches]
EU/1/05/331/037 [90 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 8 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 [100] PATCHES CONTAINING 2 BOXES OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 8 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 8 mg of rotigotine per 24 hours.
Each patch of 40 cm^2 contains 18.0 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 transdermal patches, multipack, containing 2 boxes with 42 patches each
100 transdermal patches, multipack, containing 2 boxes with 50 patches each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/036 [84 transdermal patches]
EU/1/05/331/012 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 8 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACKS ONLY
INTERMEDIATE CARTON (WITHOUT BLUE BOX)
BOX OF 42 [50] PATCHES

1. NAME OF THE MEDICINAL PRODUCT

Neupro 8 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 8 mg of rotigotine per 24 hours.
Each patch of 40 cm^2 contains 18.0 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

42 transdermal patches, component of a multipack comprising 2 boxes, each containing 42 patches
50 transdermal patches, component of a multipack comprising 2 boxes, each containing 50 patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/036 [84 transdermal patches]
EU/1/05/331/012 [100 transdermal patches]

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 8 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neupro 8 mg/24 h transdermal patch
Rotigotine
Transdermal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 28 PATCHES –TREATMENT INITIATION PACK – 4 WEEK TREATMENT SCHEDULE

1. NAME OF THE MEDICINAL PRODUCT

Neupro
2 mg/24 h
4 mg/24 h
6 mg/24 h
8 mg/24 h

Transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Neupro 2 mg/24 h
Each patch releases 2 mg of rotigotine per 24 hours.
Each patch of 10 cm^2 contains 4.5 mg of rotigotine.

Neupro 4 mg/24 h
Each patch releases 4 mg of rotigotine per 24 hours.
Each patch of 20 cm^2 contains 9.0 mg of rotigotine.

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

Neupro 8 mg/24 h
Each patch releases 8 mg of rotigotine per 24 hours.
Each patch of 40 cm^2 contains 18.0 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Treatment initiation pack with 28 transdermal patches for a 4 week treatment schedule contains:
7 transdermal patches of Neupro 2 mg/24 h
7 transdermal patches of Neupro 4 mg/24 h
7 transdermal patches of Neupro 6 mg/24 h
7 transdermal patches of Neupro 8 mg/24 h

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/013

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 2 mg/24 h, 4 mg/24 h, 6 mg/24 h, 8 mg/24 h

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 7 PATCHES – WEEK 1

1. NAME OF THE MEDICINAL PRODUCT

Neupro 2 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 2 mg of rotigotine per 24 hours.
Each patch of 10 cm^2 contains 4.5 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches.
Week 1.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/013

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 2 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL – WEEK 1

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neupro 2 mg/24 h transdermal patch
Rotigotine
Transdermal use

Week 1

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 7 PATCHES – WEEK 2

1. NAME OF THE MEDICINAL PRODUCT

Neupro 4 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 4 mg of rotigotine per 24 hours.
Each patch of 20 cm^2 contains 9.0 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches.
Week 2.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/013

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 4 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL – WEEK 2

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neupro 4 mg/24 h transdermal patch
Rotigotine
Transdermal use

Week 2

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 7 PATCHES – WEEK 3

1. NAME OF THE MEDICINAL PRODUCT

Neupro 6 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches.
Week 3.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/013

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 6 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL - WEEK 3

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neupro 6 mg/24 h transdermal patch
Rotigotine
Transdermal use

Week 3

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 7 PATCHES – WEEK 4

1. NAME OF THE MEDICINAL PRODUCT

Neupro 8 mg/24 h transdermal patch
Rotigotine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 8 mg of rotigotine per 24 hours.
Each patch of 40 cm^2 contains 18.0 mg of rotigotine.

3. LIST OF EXCIPIENTS

Other ingredients: Poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, E171, E223, E304, E307, fluoropolymer, polyester, silicone, aluminium, pigments (yellow95, red166, red144, black7)
Contains E223. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches.
Week 4.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/013

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

neupro 8 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL – WEEK 4

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Neupro 8 mg/24 h transdermal patch
Rotigotine
Transdermal use

Week 4

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 1 mg/24 h transdermal patch
Rotigotine

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT NEUPRO IS AND WHAT IT IS USED FOR

Neupro belongs to a group of medicines called dopamine agonists which stimulate a certain type of cells that bind with dopamine receptors in the brain.

Neupro is used to treat:
- the signs and symptoms of **Restless Legs Syndrome (RLS)**, a condition that is characterized by an irresistible urge to move the legs.

2. BEFORE YOU USE NEUPRO

Do not use Neupro

- if you are **allergic** (hypersensitive) to **rotigotine** or any of the **other ingredients** of Neupro (see Section 6, **'Further information'**).
- if you need to have **magnetic resonance imaging** (method to visualise internal organs and tissues of the body) or **cardioversion** (treatment of abnormal heart rhythm). You must take your Neupro patch off before such procedures. You can put a new patch on after the procedure.

Take special care with Neupro

- This medicine may affect your **blood pressure**, so it should be measured regularly, especially at the beginning of your treatment.

- **Eye examinations** are recommended at regular intervals while using Neupro. However, if you notice any problems with your sight in-between examinations, you should contact your doctor immediately.

- If you have serious **liver problems**, your doctor may need to adjust the dose. If during treatment your liver problems get worse, you should contact your doctor as soon as possible.

- If you **feel very drowsy** or find that you **fall asleep suddenly**, please contact your doctor (see also below in this section, under **'Driving and using machines'**).

- Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormal high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

- Neupro may cause **hallucinations** (seeing or hearing things that are not real). If you notice such effects, please contact your doctor.

- You may experience that symptoms of **Restless Legs Syndrome** start earlier than usual, be more intense and involve other limbs.

- As with every patch or bandage, Neupro can cause **skin reactions**, such as reddening and itching. They are usually mild or moderate, and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch. If you have a skin reaction which lasts for more than a few days, is severe, or spreads outside the area of skin that was covered by the patch, please contact your doctor.
  Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro. To help avoid the skin reactions, you should put the patch on a different area of skin every day, and only use the same area again after 14 days.

- Neupro should **not be used by children.**

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not take the following medicines while using Neupro, because they may decrease its effect: anti-psychotics (used to treat certain mental conditions) or metoclopramide (used to treat nausea and vomiting).

If you are treated with Neupro and levodopa at the same time, some side effects may get more serious, such as seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), and swelling of legs and feet.

Please ask your doctor whether it is safe for you to:
- drink alcohol or
- take sedating medicines (for example benzodiazepines, medicines used to treat mental conditions or depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect the way this medicine works. You should discuss with your doctor if it is safe for you to drink alcohol while using Neupro.

Pregnancy and breast-feeding

You should not use Neupro if you are pregnant, as the effects of rotigotine on pregnancy and the unborn baby are not known. Tell your doctor if you are pregnant or planning to become pregnant.

Breast-feeding is not recommended during treatment with Neupro. Rotigotine may pass into your breast milk and affect your baby and is also likely to reduce the amount of milk you produce.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.
In isolated cases people have fallen asleep while driving and this has caused accidents.

Important information about some of the ingredients of Neupro

Neupro contains sodium metabisulphite (E223), a substance that may rarely cause severe hypersensitivity reactions and bronchospasm.

3. HOW TO USE NEUPRO

Dose

Always use Neupro exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Neupro is generally used as a long term treatment. Normally, you will start your treatment with a low dose and, if necessary, increase it week by week, as told by your doctor, until reaching the right dose for you. You will then continue treatment with this dose, also called the maintenance dose.

You should change your Neupro patch once a day. For reaching the needed doses, different patches of Neupro are available, each releasing a different amount of the active substance per day: 1 mg/24 h, 2 mg/24 h and 3 mg/24 h.

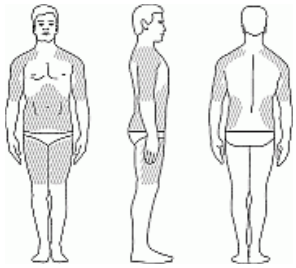
Treatment of Restless Legs Syndrome
You will start by using one Neupro 1 mg/24 h patch daily. If necessary, this daily dose may be increased by 1 mg, on a weekly basis, until reaching the right (maintenance) dose for you.
The maximum dose is 3 mg per day.

If you have to stop taking this medicine, see Section 3, **'If you stop using Neupro'**.

FOLLOW THESE INSTRUCTIONS WHEN USING NEUPRO:

You should stick a new Neupro patch onto the skin **once a day**. Leave the patch on your skin for 24 hours, then remove it and apply a new one. Make sure that you take the old patch off before applying a new one; place the new patch on a different area of skin.
You should **change your patch** at around the **same time every day**.
Do not cut the Neupro patches into pieces.

Where to stick the patch



Put the sticky side of the patch onto clean, dry, healthy skin on the following areas, as indicated by the grey areas in the picture:

- shoulder
- upper arm
- belly
- thigh
- hip
- flank (your side, between your ribs and your hip).

To **help avoid skin irritation:**

- Stick the patch onto a different area of skin each day, for example on the right side of your body one day, then on the left side the next day; on your upper body one day, then on your lower body.
- Do not stick Neupro on the same area of skin twice within 14 days.
- Do not stick the patch on broken or damaged skin or on skin that is red or irritated.

If you still get problems with your skin because of the patch, please see in Section 4 **'Possible side effects'** the details about what you should do.

To **prevent the patch becoming loose or falling off**

- Do not put the patch in an area where it can be rubbed by tight clothing.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least 3 days before sticking the patch there.

If the patch falls off, a new patch should be applied for the rest of the day, then replace the patch at the same time as usual.

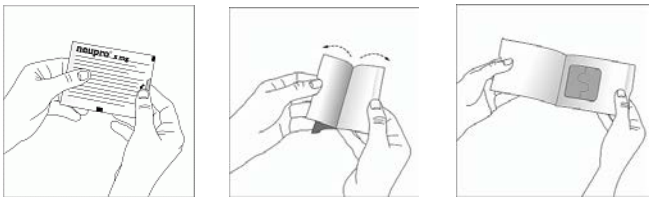
NOTE

- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off afterwards.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area protected from direct sunlight, as it may cause changes in the colour of the skin.

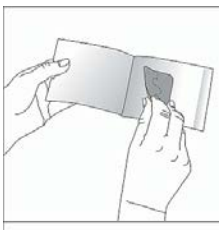
How to use the patch

Each patch is packed in a separate sachet. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the release liner.

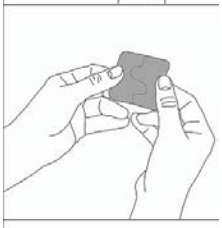
1.
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.



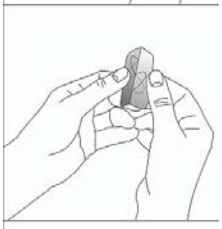
2.
Take the patch out of the sachet.



3.
The sticky side of the patch is covered by a transparent release liner. Hold the patch in both hands with the release liner facing you.

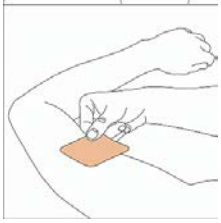


4.
Bend the patch in half so that the S-shaped break in the liner opens.

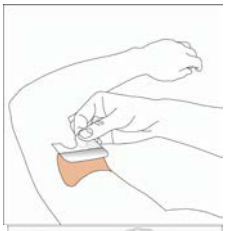


5.
Peel off one side of the release liner. Don't touch the sticky side of the patch with your fingers.

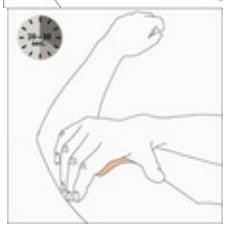
6.
Hold the other half of the rigid release liner and put the sticky surface of the patch onto your skin. Press the sticky side of the patch firmly into place.



7.
Fold back the other half of the patch and remove the other side of the release liner.



8.
Press the patch down firmly with the palm of your hand for about 20 to 30 seconds to make sure the patch is touching the skin and the edges stick well.



Wash your hands with soap and water immediately after handling the patch.

How to remove a used patch

Slowly and carefully peel off the used patch.

Gently washing the area with warm water and mild soap should remove any adhesive that stays on your skin after you remove the patch. You can also use a small amount of baby oil to remove any adhesive that won't wash off.

Do not use alcohol or other dissolving liquids such as nail polish remover as these may irritate your skin.
Choose a new area of skin where you will apply a new patch, then follow the instructions above.

If you use more Neupro than you should

Using higher doses of Neupro than your doctor has prescribed may cause side effects such as nausea (feeling sick), vomiting, low blood pressure, hallucinations (seeing or hearing things that are not real), confusion, extreme sleepiness, involuntary movements and convulsions.
If you have used more patches than your doctor told you to, contact your doctor or hospital for advice immediately, and follow their advice on removal of patches.

If you have forgotten to change the patch at the usual time

If you have forgotten to change the patch at your usual time, change it as soon as you remember: remove the old patch and use a new one. If you have forgotten to stick on a new patch after removing the old one, use a new patch as soon as you remember.
In both cases, on the following day you should use a new patch at the usual time. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro

Do not stop using Neupro suddenly without talking to your doctor. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include: akinesia (loss of muscle movement), rigid muscles, fever, unstable blood pressure, tachycardia (increased heart rate), confusion, depressed level of consciousness (e.g. coma).
Your daily dose of Neupro should be reduced gradually

- by 1 mg every other day - if you use Neupro **for Restless Legs Syndrome**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Neupro can cause side effects, although not everybody gets them.

You may experience **nausea** (feeling sick) and **vomiting at the beginning of treatment**. These effects are usually mild or moderate and only last for a short time. You should contact your doctor if they last for a long time or if you worry about them.

Skin problems caused by the patch
You may get skin reactions from the patch such as redness, itching. They are usually mild or moderate and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch.
If you have a skin reaction that lasts longer than a few days, is severe, or spreads outside the area of skin that was covered by the patch, you should contact your doctor.

You may experience the following side effects:
Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:

- strong impulse to gamble excessively despite serious personal or family consequences
- altered or increased sexual interest and behaviour of significant concern to you or others, for example, an increased sex drive
- uncontrolled excessive shopping or spending

- binge eating (eating large amounts of food in a short period of time) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)

Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing symptoms.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

If you are using Neupro for Restless Legs Syndrome the following side effects may occur:

Very common side effects
- feeling sick (nausea)
- skin irritations under the patch such as redness and itching
- weakness (fatigue)
- headache

Common side effects
- vomiting, heartburn
- irritability
- allergic reaction
- sleepiness, falling asleep suddenly without warning, difficulty in sleeping, sleep problems, having unusual dreams
- increased sex drive
- itching
- high blood pressure

Uncommon side effects
- inability to resist the impulse to perform an action that is harmful involving excessive gambling and repetitive meaningless actions
- feeling dizzy when standing up because of a fall in blood pressure
- unwanted and uncontrolled thoughts and behaviours

Rare side effects
- aggressive behaviour/aggression
- binge eating and compulsive eating

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEUPRO

Keep out of the reach and sight of children.
Do not use Neupro after the expiry date which is stated on the label and carton.
Do not store above 25°C.

What to do with the used and unused patches

Used patches still contain active substance, which may be harmful to others. Fold the used patch with the sticky side inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines not longer required. These measures will help to protect the environment..

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.
  Each patch releases 1 mg of rotigotine per 24 hours. Each patch of 5 cm^2 contains 2.25 mg of rotigotine.

- The other ingredients are poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, sodium metabisulphite (E223), ascorbyl palmitate (E304) and DL-α-tocopherol (E307).
  Backing layer: Polyester film, siliconized, aluminized, colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7).
  Release liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

Neupro is a transdermal patch. It is thin and has three layers. It is square-shaped with rounded edges. The outside is tan-coloured and is imprinted with Neupro 1 mg/24 h.

Neupro is available in the following pack-sizes:
Cartons containing 7, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) patches, which are individually sealed in sachets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
UCB Pharma SA/NV
Tel/Tél: +32 / (0)2 559 92 00

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Ю СИ БИ България ЕООД
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Luxembourg/Luxemburg
UCB Pharma SA/NV
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Magyarország
UCB Magyarország Kft.
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Danmark
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Tlf: + 45 / 32 46 24 00

Deutschland
UCB Pharma GmbH
Tel: + 49 / (0) 2173 48 48 48

Eesti
UCB Pharma Oy Finland
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Puh/Tel: + 358 10 234 6800

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United Kingdom
UCB Pharma Ltd.
Tel : +44 / (0)1753 534 655

This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 2 mg/24 h transdermal patch
Rotigotine

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT NEUPRO IS AND WHAT IT IS USED FOR

Neupro belongs to a group of medicines called dopamine agonists which stimulate a certain type of cells that bind with dopamine receptors in the brain.

Neupro is used to treat:
- the signs and symptoms of **Restless Legs Syndrome (RLS)**, a condition that is characterized by an irresistible urge to move the legs.
- the signs and symptoms of **Parkinson's disease** either alone or in combination with the medicine called levodopa.

2. BEFORE YOU USE NEUPRO

Do not use Neupro

- if you are **allergic** (hypersensitive) to **rotigotine** or any of the **other ingredients** of Neupro (see Section 6, **'Further information'**).
- if you need to have **magnetic resonance imaging** (method to visualise internal organs and tissues of the body) or **cardioversion** (treatment of abnormal heart rhythm). You must take your Neupro patch off before such procedures. You can put a new patch on after the procedure.

Take special care with Neupro

- This medicine may affect your **blood pressure**, so it should be measured regularly, especially at the beginning of your treatment.

- **Eye examinations** are recommended at regular intervals while using Neupro. However, if you notice any problems with your sight in-between examinations, you should contact your doctor immediately.

- If you have serious **liver problems**, your doctor may need to adjust the dose. If during treatment your liver problems get worse, you should contact your doctor as soon as possible.

- If you **feel very drowsy** or find that you **fall asleep suddenly**, please contact your doctor (see also below in this section, under **'Driving and using machines'**).

- Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormal high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

- Neupro may cause **hallucinations** (seeing or hearing things that are not real). If you notice such effects, please contact your doctor.

- You may experience that symptoms of **Restless Legs Syndrome** start earlier than usual, be more intense and involve other limbs.

- As with every patch or bandage, Neupro can cause **skin reactions**, such as reddening and itching. They are usually mild or moderate, and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch. If you have a skin reaction which lasts for more than a few days, is severe, or spreads outside the area of skin that was covered by the patch, please contact your doctor.
  Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro. To help avoid the skin reactions, you should put the patch on a different area of skin every day, and only use the same area again after 14 days.

- Neupro should **not be used by children.**

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not take the following medicines while using Neupro, because they may decrease its effect: anti-psychotics (used to treat certain mental conditions) or metoclopramide (used to treat nausea and vomiting).

If you are treated with Neupro and levodopa at the same time, some side effects may get more serious, such as seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), and swelling of legs and feet.

Please ask your doctor whether it is safe for you to:
- drink alcohol or
- take sedating medicines (for example benzodiazepines, medicines used to treat mental conditions or depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect the way this medicine works. You should discuss with your doctor if it is safe for you to drink alcohol while using Neupro.

Pregnancy and breast-feeding

You should not use Neupro if you are pregnant, as the effects of rotigotine on pregnancy and the unborn baby are not known. Tell your doctor if you are pregnant or planning to become pregnant.

Breast-feeding is not recommended during treatment with Neupro. Rotigotine may pass into your breast milk and affect your baby and is also likely to reduce the amount of milk you produce.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.
In isolated cases people have fallen asleep while driving and this has caused accidents.

Important information about some of the ingredients of Neupro

Neupro contains sodium metabisulphite (E223), a substance that may rarely cause severe hypersensitivity reactions and bronchospasm.

3. HOW TO USE NEUPRO

Dose

Always use Neupro exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Neupro is generally used as a long term treatment. Normally, you will start your treatment with a low dose and, if necessary, increase it week by week, as told by your doctor, until reaching the right dose for you. You will then continue treatment with this dose, also called the maintenance dose.

You should change your Neupro patch once a day. For reaching the needed doses, different patches of Neupro are available, each releasing a different amount of the active substance per day: 1 mg/24 h, 2 mg/24 h, 3 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h. For higher doses, multiple patches must be applied. For example a daily dose of 10 mg may be reached by applying one patch of 6 mg/24 h and one patch of 4 mg/24 h.

Treatment of Restless Legs Syndrome
You will start by using one Neupro 1 mg/24 h patch daily. If necessary, this daily dose may be increased by 1 mg, on a weekly basis, until reaching the right (maintenance) dose for you.
The maximum dose is 3 mg per day.

Treatment of Parkinson's disease
Patients not taking levodopa (early stage of Parkinson's disease)
You will start by using one Neupro 2 mg/24 h patch daily. From the second week, the daily dose will be increased by 2 mg, on a weekly basis, until reaching the right (maintenance) dose for you. For most patients, the right dose is between 6 mg and 8 mg per day (reached within 3 to 4 weeks).
The maximum dose is 8 mg per day.

Patients taking levodopa (advanced stage of Parkinson's disease)
You will start by using one Neupro 4 mg/24 h patch daily. From the second week, the daily dose will be increased by 2 mg, on a weekly basis, until reaching the right (maintenance) dose for you. For most patients, the right dose is between 8 mg and 16 mg per day (reached within 3 to 7 weeks).
The maximum dose is 16 mg per day.

If you have to stop taking this medicine, see Section 3, **'If you stop using Neupro**'.

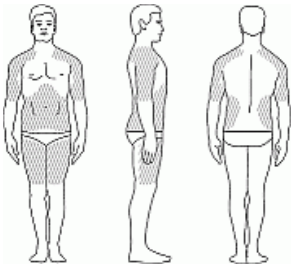
FOLLOW THESE INSTRUCTIONS WHEN USING NEUPRO:

You should stick a new Neupro patch onto the skin **once a day**. Leave the patch on your skin for 24 hours, then remove it and apply a new one. Make sure that you take the old patch off before applying a new one; place the new patch on a different area of skin.
You should **change your patch** at around the **same time every day**.
Do not cut the Neupro patches into pieces.

Where to stick the patch

Put the sticky side of the patch onto clean, dry, healthy skin on the following areas, as indicated by the grey areas in the picture:

- shoulder
- upper arm
- belly
- thigh
- hip
- flank (your side, between your ribs and your hip).



To **help avoid skin irritation:**

- Stick the patch onto a different area of skin each day, for example on the right side of your body one day, then on the left side the next day; on your upper body one day, then on your lower body.
- Do not stick Neupro on the same area of skin twice within 14 days.
- Do not stick the patch on broken or damaged skin or on skin that is red or irritated.

If you still get problems with your skin because of the patch, please see in Section 4 **'Possible side effects'** the details about what you should do.

To **prevent the patch becoming loose or falling off**

- Do not put the patch in an area where it can be rubbed by tight clothing.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least 3 days before sticking the patch there.

If the patch falls off, a new patch should be applied for the rest of the day, then replace the patch at the same time as usual.

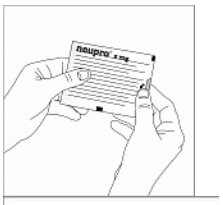
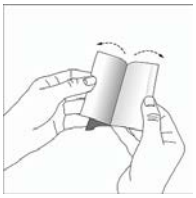
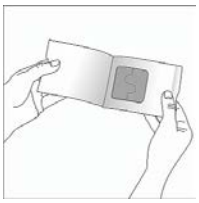
NOTE

- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off afterwards.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area protected from direct sunlight, as it may cause changes in the colour of the skin.

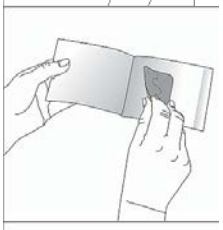
How to use the patch

Each patch is packed in a separate sachet. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the release liner.

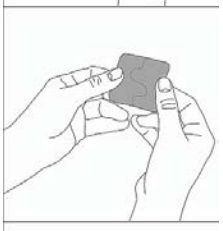
1.
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.

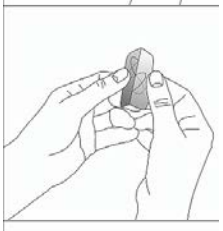
2.
Take the patch out of the sachet.



3.
The sticky side of the patch is covered by a transparent release liner. Hold the patch in both hands with the release liner facing you.

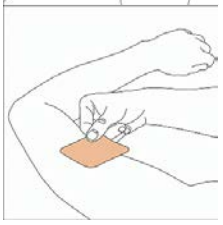


4.
Bend the patch in half so that the S-shaped break in the liner opens.

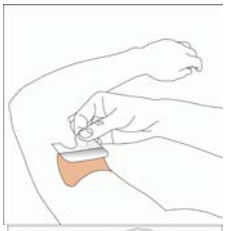


5.
Peel off one side of the release liner. Don’t touch the sticky side of the patch with your fingers.

6.
Hold the other half of the rigid release liner and put the sticky surface of the patch onto your skin. Press the sticky side of the patch firmly into place.



7.
Fold back the other half of the patch and remove the other side of the release liner.



8.
Press the patch down firmly with the palm of your hand for about 20 to 30 seconds to make sure the patch is touching the skin and the edges stick well.

Wash your hands with soap and water immediately after handling the patch.

How to remove a used patch

Slowly and carefully peel off the used patch.

Gently washing the area with warm water and mild soap should remove any adhesive that stays on your skin after you remove the patch. You can also use a small amount of baby oil to remove any adhesive that won't wash off.
Do not use alcohol or other dissolving liquids such as nail polish remover as these may irritate your skin.
Choose a new area of skin where you will apply a new patch, then follow the instructions above.

If you use more Neupro than you should

Using higher doses of Neupro than your doctor has prescribed may cause side effects such as nausea (feeling sick), vomiting, low blood pressure, hallucinations (seeing or hearing things that are not real), confusion, extreme sleepiness, involuntary movements and convulsions.
If you have used more patches than your doctor told you to, contact your doctor or hospital for advice immediately, and follow their advice on removal of patches.

If you have forgotten to change the patch at the usual time

If you have forgotten to change the patch at your usual time, change it as soon as you remember: remove the old patch and use a new one. If you have forgotten to stick on a new patch after removing the old one, use a new patch as soon as you remember.
In both cases, on the following day you should use a new patch at the usual time. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro

Do not stop using Neupro suddenly without talking to your doctor. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include: akinesia (loss of muscle movement), rigid muscles, fever, unstable blood pressure, tachycardia (increased heart rate), confusion, depressed level of consciousness (e.g. coma).
Your daily dose of Neupro should be reduced gradually

- by 1 mg every other day - if you use Neupro **for Restless Legs Syndrome** or
- by 2 mg every other day - if you use Neupro **for Parkinson's disease**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Neupro can cause side effects, although not everybody gets them.

You may experience **nausea** (feeling sick) and **vomiting at the beginning of treatment**. These effects are usually mild or moderate and only last for a short time. You should contact your doctor if they last for a long time or if you worry about them.

Skin problems caused by the patch
You may get skin reactions from the patch such as redness, itching. They are usually mild or moderate and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch.
If you have a skin reaction that lasts longer than a few days, is severe, or spreads outside the area of skin that was covered by the patch, you should contact your doctor.

You may experience the following side effects:
Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:

- strong impulse to gamble excessively despite serious personal or family consequences
- altered or increased sexual interest and behaviour of significant concern to you or others, for example, an increased sex drive
- uncontrolled excessive shopping or spending
- binge eating (eating large amounts of food in a short period of time) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)

Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing symptoms.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

If you are using Neupro for Restless Legs Syndrome the following side effects may occur:

Very common side effects

- feeling sick (nausea)
- skin irritations under the patch such as redness and itching
- weakness (fatigue)
- headache

Common side effects

- vomiting, heartburn
- irritability
- allergic reaction
- sleepiness, falling asleep suddenly without warning, difficulty in sleeping, sleep problems, having unusual dreams
- increased sex drive
- itching
- high blood pressure

Uncommon side effects

- inability to resist the impulse to perform an action that is harmful involving excessive gambling and repetitive meaningless actions
- feeling dizzy when standing up because of a fall in blood pressure
- unwanted and uncontrolled thoughts and behaviours

Rare side effects

- aggressive behaviour/aggression
- binge eating and compulsive eating

If you are using Neupro for Parkinson's disease the following side effects may occur:

Very common side effects

- sleepiness, dizziness, headache
- feeling sick (nausea) , vomiting

- skin irritations under the patch such as redness and itching

Common side effects
- seeing or hearing things that are not real (hallucinations)
- difficulty falling asleep, sleep disorder, difficulty sleeping, nightmare, unusual dreams
- loss of consciousness, involuntary movements related to Parkinson's disease (dyskinesia), feeling dizzy when standing up because of fall in blood pressure
- vertigo (sensation of whirling motion)
- feeling of heartbeat (palpitation)
- low blood pressure when standing up, high blood pressure
- hiccups
- constipation, dry mouth, heartburn
- redness, increased sweating, itching
- swelling of legs and feet
- feeling weak, feeling tired
- falling
- weight loss

Uncommon side effects
- allergic reaction
- falling asleep suddenly without warning
- abnormal thinking about reality and behaviour
- increased sex drive, inability to resist the impulse to perform an action that is harmful involving excessive gambling and repetitive meaningless actions
- confusion
- blurred vision
- visual disturbances such as seeing colours or lights
- abnormal heart rhythm
- low blood pressure
- stomach discomfort and pain
- generalised itching, skin irritation
- unable to achieve or maintain an erection
- increased or abnormal liver function test results
- weight increase
- increased heart rate

Rare side effects
- psychotic disorders
- unwanted and uncontrolled thoughts and behaviours
- aggressive behaviour/aggression
- binge eating and compulsive eating
- involuntary muscle spasms (convulsion)
- generalised rash
- irritability

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEUPRO

Keep out of the reach and sight of children.
Do not use Neupro after the expiry date which is stated on the label and carton.
Do not store above 25°C.

What to do with the used and unused patches

Used patches still contain active substance, which may be harmful to others. Fold the used patch with the sticky side inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines not longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.
  Each patch releases 2 mg of rotigotine per 24 hours. Each patch of 10 cm^2 contains 4.5 mg of rotigotine.

- The other ingredients are poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, sodium metabisulphite (E223), ascorbyl palmitate (E304) and DL-α-tocopherol (E307).
  Backing layer: Polyester film, siliconized, aluminized, colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7).
  Release liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

Neupro is a transdermal patch. It is thin and has three layers. It is square-shaped with rounded edges. The outside is tan-coloured and is imprinted with Neupro 2 mg/24 h.

Neupro is available in the following pack-sizes:
Cartons containing 7, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) patches, which are individually sealed in sachets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
UCB Pharma SA/NV
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Tel: + 46 / (0) 40 29 49 00

United Kingdom
UCB Pharma Ltd.
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This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 3 mg/24 h transdermal patch
Rotigotine

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT NEUPRO IS AND WHAT IT IS USED FOR

Neupro belongs to a group of medicines called dopamine agonists which stimulate a certain type of cells that bind with dopamine receptors in the brain.

Neupro is used to treat:
- the signs and symptoms of **Restless Legs Syndrome (RLS)**, a condition that is characterized by an irresistible urge to move the legs..

2. BEFORE YOU USE NEUPRO

Do not use Neupro

- if you are **allergic** (hypersensitive) to **rotigotine** or any of the **other ingredients** of Neupro (see Section 6, **'Further information'**).
- if you need to have **magnetic resonance** imaging (method to visualise internal organs and tissues of the body) or **cardioversion** (treatment of abnormal heart rhythm). You must take your Neupro patch off before such procedures. You can put a new patch on after the procedure.

Take special care with Neupro

- This medicine may affect your **blood pressure**, so it should be measured regularly, especially at the beginning of your treatment.

- **Eye examinations** are recommended at regular intervals while using Neupro. However, if you notice any problems with your sight in-between examinations, you should contact your doctor immediately.

- If you have serious **liver problems**, your doctor may need to adjust the dose. If during treatment your liver problems get worse, you should contact your doctor as soon as possible.

- If you **feel very drowsy** or find that you **fall asleep suddenly**, please contact your doctor (see also below in this section, under **'Driving and using machines'**).

- Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormal high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

- Neupro may cause **hallucinations** (seeing or hearing things that are not real). If you notice such effects, please contact your doctor.

- You may experience that symptoms of **Restless Legs Syndrome** start earlier than usual, be more intense and involve other limbs.

- As with every patch or bandage, Neupro can cause **skin reactions**, such as reddening and itching. They are usually mild or moderate, and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch. If you have a skin reaction which lasts for more than a few days, is severe, or spreads outside the area of skin that was covered by the patch, please contact your doctor.
  Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro. To help avoid the skin reactions, you should put the patch on a different area of skin every day, and only use the same area again after 14 days.

- Neupro should **not be used by children.**

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not take the following medicines while using Neupro, because they may decrease its effect: anti-psychotics (used to treat certain mental conditions) or metoclopramide (used to treat nausea and vomiting).

If you are treated with Neupro and levodopa at the same time, some side effects may get more serious, such as seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), and swelling of legs and feet.

Please ask your doctor whether it is safe for you to:
- drink alcohol or
- take sedating medicines (for example benzodiazepines, medicines used to treat mental conditions or depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect the way this medicine works. You should discuss with your doctor if it is safe for you to drink alcohol while using Neupro.

Pregnancy and breast-feeding

You should not use Neupro if you are pregnant, as the effects of rotigotine on pregnancy and the unborn baby are not known. Tell your doctor if you are pregnant or planning to become pregnant.

Breast-feeding is not recommended during treatment with Neupro. Rotigotine may pass into your breast milk and affect your baby and is also likely to reduce the amount of milk you produce.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.
In isolated cases people have fallen asleep while driving and this has caused accidents.

Important information about some of the ingredients of Neupro

Neupro contains sodium metabisulphite (E223), a substance that may rarely cause severe hypersensitivity reactions and bronchospasm.

3. HOW TO USE NEUPRO

Dose

Always use Neupro exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Neupro is generally used as a long term treatment. Normally, you will start your treatment with a low dose and, if necessary, increase it week by week, as told by your doctor, until reaching the right dose for you. You will then continue treatment with this dose, also called the maintenance dose.

You should change your Neupro patch once a day. For reaching the needed doses, different patches of Neupro are available, each releasing a different amount of the active substance per day: 1 mg/24 h, 2 mg/24 h and 3 mg/24 h.

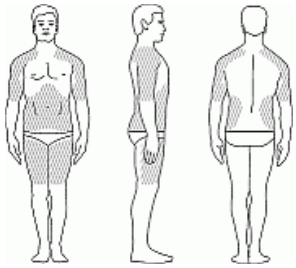
Treatment of Restless Legs Syndrome
You will start by using one Neupro 1 mg/24 h patch daily. If necessary, this daily dose may be increased by 1 mg, on a weekly basis, until reaching the right (maintenance) dose for you.
The maximum dose is 3 mg per day.

If you have to stop taking this medicine, see Section 3, **'If you stop using Neupro'**.

FOLLOW THESE INSTRUCTIONS WHEN USING NEUPRO:

You should stick a new Neupro patch onto the skin **once a day**. Leave the patch on your skin for 24 hours, then remove it and apply a new one. Make sure that you take the old patch off before applying a new one; place the new patch on a different area of skin.
You should **change your patch** at around the **same time every day**.
Do not cut the Neupro patches into pieces.

Where to stick the patch



Put the sticky side of the patch onto clean, dry, healthy skin on the following areas, as indicated by the grey areas in the picture:

- shoulder
- upper arm
- belly
- thigh
- hip
- flank (your side, between your ribs and your hip).

To **help avoid skin irritation:**

- Stick the patch onto a different area of skin each day, for example on the right side of your body one day, then on the left side the next day; on your upper body one day, then on your lower body.
- Do not stick Neupro on the same area of skin twice within 14 days.
- Do not stick the patch on broken or damaged skin or on skin that is red or irritated.

If you still get problems with your skin because of the patch, please see in Section 4 **'Possible side effects'** the details about what you should do.

To **prevent the patch becoming loose or falling off**

- Do not put the patch in an area where it can be rubbed by tight clothing.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least 3 days before sticking the patch there.

If the patch falls off, a new patch should be applied for the rest of the day, then replace the patch at the same time as usual.

NOTE

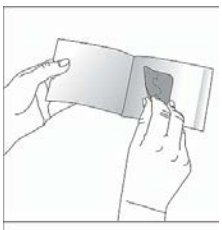
- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off afterwards.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area protected from direct sunlight, as it may cause changes in the colour of the skin.

How to use the patch

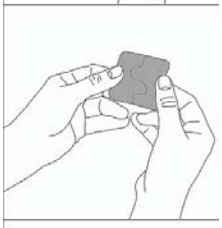
Each patch is packed in a separate sachet. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the release liner.

1.
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.

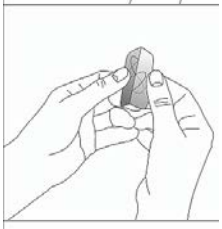
2.
Take the patch out of the sachet.



3.
The sticky side of the patch is covered by a transparent release liner. Hold the patch in both hands with the release liner facing you.

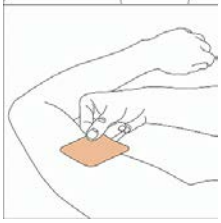


4.
Bend the patch in half so that the S-shaped break in the liner opens.

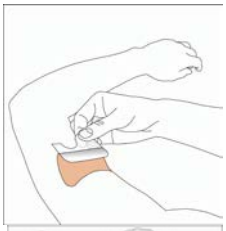


5.
Peel off one side of the release liner. Don't touch the sticky side of the patch with your fingers.

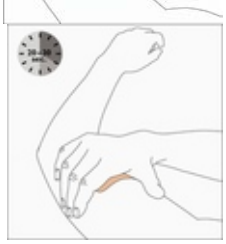
6.
Hold the other half of the rigid release liner and put the sticky surface of the patch onto your skin. Press the sticky side of the patch firmly into place.



7.
Fold back the other half of the patch and remove the other side of the release liner.



8.
Press the patch down firmly with the palm of your hand for about 20 to 30 seconds to make sure the patch is touching the skin and the edges stick well.



Wash your hands with soap and water immediately after handling the patch.

How to remove a used patch

Slowly and carefully peel off the used patch.

Gently washing the area with warm water and mild soap should remove any adhesive that stays on your skin after you remove the patch. You can also use a small amount of baby oil to remove any adhesive that won't wash off.

Do not use alcohol or other dissolving liquids such as nail polish remover as these may irritate your skin.
Choose a new area of skin where you will apply a new patch, then follow the instructions above.

If you use more Neupro than you should

Using higher doses of Neupro than your doctor has prescribed may cause side effects such as nausea (feeling sick), vomiting, low blood pressure, hallucinations (seeing or hearing things that are not real), confusion, extreme sleepiness, involuntary movements and convulsions.
If you have used more patches than your doctor told you to, contact your doctor or hospital for advice immediately, and follow their advice on removal of patches.

If you have forgotten to change the patch at the usual time

If you have forgotten to change the patch at your usual time, change it as soon as you remember: remove the old patch and use a new one. If you have forgotten to stick on a new patch after removing the old one, use a new patch as soon as you remember.
In both cases, on the following day you should use a new patch at the usual time. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro

Do not stop using Neupro suddenly without talking to your doctor. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include: akinesia (loss of muscle movement), rigid muscles, fever, unstable blood pressure, tachycardia (increased heart rate), confusion, depressed level of consciousness (e.g. coma).
Your daily dose of Neupro should be reduced gradually

- by 1 mg every other day - if you use Neupro **for Restless Legs Syndrome**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Neupro can cause side effects, although not everybody gets them.

You may experience **nausea** (feeling sick) and **vomiting at the beginning of treatment**. These effects are usually mild or moderate and only last for a short time. You should contact your doctor if they last for a long time or if you worry about them.

Skin problems caused by the patch
You may get skin reactions from the patch such as redness, itching. They are usually mild or moderate and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch.
If you have a skin reaction that lasts longer than a few days, is severe, or spreads outside the area of skin that was covered by the patch, you should contact your doctor.

You may experience the following side effects:
Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:

- strong impulse to gamble excessively despite serious personal or family consequences
- altered or increased sexual interest and behaviour of significant concern to you or others, for example, an increased sex drive
- uncontrolled excessive shopping or spending

- binge eating (eating large amounts of food in a short period of time) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)

Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing symptoms.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

If you are using Neupro for Restless Legs Syndrome the following side effects may occur:

Very common side effects
- feeling sick (nausea)
- skin irritations under the patch such as redness and itching
- weakness (fatigue)
- headache

Common side effects
- vomiting, heartburn
- irritability
- allergic reaction
- sleepiness, falling asleep suddenly without warning, difficulty in sleeping, sleep problems, having unusual dreams
- increased sex drive
- itching
- high blood pressure

Uncommon side effects
- inability to resist the impulse to perform an action that is harmful involving excessive gambling and repetitive meaningless actions
- feeling dizzy when standing up because of a fall in blood pressure
- unwanted and uncontrolled thoughts and behaviours

Rare side effects
- aggressive behaviour/aggression
- binge eating and compulsive eating

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEUPRO

Keep out of the reach and sight of children.
Do not use Neupro after the expiry date which is stated on the label and carton.
Do not store above 25°C.

What to do with the used and unused patches

Used patches still contain active substance, which may be harmful to others. Fold the used patch with the sticky side inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines not longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.
  Each patch releases 3 mg of rotigotine per 24 hours. Each patch of 15 cm^2 contains 6.75 mg of rotigotine.

- The other ingredients are poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, sodium metabisulphite (E223), ascorbyl palmitate (E304) and DL-α-tocopherol (E307).
  Backing layer: Polyester film, siliconized, aluminized, colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7).
  Release liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

Neupro is a transdermal patch. It is thin and has three layers. It is square-shaped with rounded edges. The outside is tan-coloured and is imprinted with Neupro 3 mg/24 h.

Neupro is available in the following pack-sizes:
Cartons containing 7, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) patches, which are individually sealed in sachets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 4 mg/24 h transdermal patch
Rotigotine

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT NEUPRO IS AND WHAT IT IS USED FOR

Neupro belongs to a group of medicines called dopamine agonists which stimulate a certain type of cells that bind with dopamine receptors in the brain.

Neupro is used to treat:
- the signs and symptoms of **Parkinson's disease** either alone or in combination with the medicine called levodopa.

2. BEFORE YOU USE NEUPRO

Do not use Neupro

- if you are **allergic** (hypersensitive) to **rotigotine** or any of the **other ingredients** of Neupro (see Section 6, **'Further information'**).
- if you need to have **magnetic resonance imaging** (method to visualise internal organs and tissues of the body) or **cardioversion** (treatment of abnormal heart rhythm). You must take your Neupro patch off before such procedures. You can put a new patch on after the procedure.

Take special care with Neupro

- This medicine may affect your **blood pressure**, so it should be measured regularly, especially at the beginning of your treatment.

- **Eye examinations** are recommended at regular intervals while using Neupro. However, if you notice any problems with your sight in-between examinations, you should contact your doctor immediately.

- If you have serious **liver problems**, your doctor may need to adjust the dose. If during treatment your liver problems get worse, you should contact your doctor as soon as possible.

- If you **feel very drowsy** or find that you **fall asleep suddenly**, please contact your doctor (see also below in this section, under **'Driving and using machines'**).

- Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormal high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

- Neupro may cause **hallucinations** (seeing or hearing things that are not real). If you notice such effects, please contact your doctor.

- As with every patch or bandage, Neupro can cause **skin reactions**, such as reddening and itching. They are usually mild or moderate, and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch. If you have a skin reaction which lasts for more than a few days, is severe, or spreads outside the area of skin that was covered by the patch, please contact your doctor.
  Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro. To help avoid the skin reactions, you should put the patch on a different area of skin every day, and only use the same area again after 14 days.

- Neupro should **not be used by children.**

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not take the following medicines while using Neupro, because they may decrease its effect: anti-psychotics (used to treat certain mental conditions) or metoclopramide (used to treat nausea and vomiting).

If you are treated with Neupro and levodopa at the same time, some side effects may get more serious, such as seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), and swelling of legs and feet.

Please ask your doctor whether it is safe for you to:
- drink alcohol or
- take sedating medicines (for example benzodiazepines, medicines used to treat mental conditions or depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect the way this medicine works. You should discuss with your doctor if it is safe for you to drink alcohol while using Neupro.

Pregnancy and breast-feeding

You should not use Neupro if you are pregnant, as the effects of rotigotine on pregnancy and the unborn baby are not known. Tell your doctor if you are pregnant or planning to become pregnant.

Breast-feeding is not recommended during treatment with Neupro. Rotigotine may pass into your breast milk and affect your baby and is also likely to reduce the amount of milk you produce.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.
In isolated cases people have fallen asleep while driving and this has caused accidents.

Important information about some of the ingredients of Neupro

Neupro contains sodium metabisulphite (E223), a substance that may rarely cause severe hypersensitivity reactions and bronchospasm.

3. HOW TO USE NEUPRO

Dose

Always use Neupro exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Neupro is generally used as a long term treatment. Normally, you will start your treatment with a low dose and, if necessary, increase it week by week, as told by your doctor, until reaching the right dose for you. You will then continue treatment with this dose, also called the maintenance dose.

You should change your Neupro patch once a day. For reaching the needed doses, different patches of Neupro are available, each releasing a different amount of the active substance per day: 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h. For higher doses, multiple patches must be applied. For example a daily dose of 10 mg may be reached by applying one patch of 6 mg/24 h and one patch of 4 mg/24 h.

Treatment of Parkinson's disease
Patients not taking levodopa (early stage of Parkinson's disease)
You will start by using one Neupro 2 mg/24 h patch daily. From the second week, the daily dose will be increased by 2 mg, on a weekly basis, until reaching the right (maintenance) dose for you. For most patients, the right dose is between 6 mg and 8 mg per day (reached within 3 to 4 weeks).
The maximum dose is 8 mg per day.

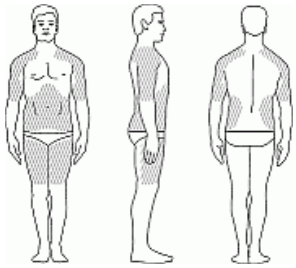
Patients taking levodopa (advanced stage of Parkinson's disease)
You will start by using one Neupro 4 mg/24 h patch daily. From the second week, the daily dose will be increased by 2 mg, on a weekly basis, until reaching the right (maintenance) dose for you. For most patients, the right dose is between 8 mg and 16 mg per day (reached within 3 to 7 weeks).
The maximum dose is 16 mg per day.

If you have to stop taking this medicine, see Section 3, **'If you stop using Neupro**'.

FOLLOW THESE INSTRUCTIONS WHEN USING NEUPRO:

You should stick a new Neupro patch onto the skin **once a day**. Leave the patch on your skin for 24 hours, then remove it and apply a new one. Make sure that you take the old patch off before applying a new one; place the new patch on a different area of skin.
You should **change your patch** at around the **same time every day**.
Do not cut the Neupro patches into pieces.

Where to stick the patch



Put the sticky side of the patch onto clean, dry, healthy skin on the following areas, as indicated by the grey areas in the picture:

- shoulder
- upper arm
- belly
- thigh
- hip
- flank (your side, between your ribs and your hip).

To **help avoid skin irritation:**

- Stick the patch onto a different area of skin each day, for example on the right side of your body one day, then on the left side the next day; on your upper body one day, then on your lower body.
- Do not stick Neupro on the same area of skin twice within 14 days.
- Do not stick the patch on broken or damaged skin or on skin that is red or irritated.

If you still get problems with your skin because of the patch, please see in Section 4 **'Possible side effects'** the details about what you should do.

To **prevent the patch becoming loose or falling off**

- Do not put the patch in an area where it can be rubbed by tight clothing.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least 3 days before sticking the patch there.

If the patch falls off, a new patch should be applied for the rest of the day, then replace the patch at the same time as usual.

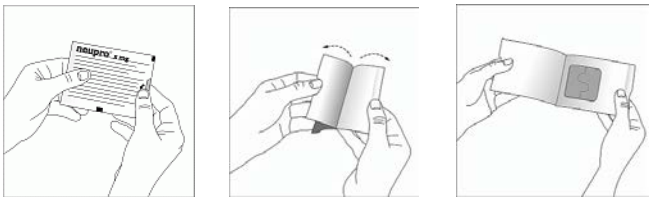
NOTE

- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off afterwards.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area protected from direct sunlight, as it may cause changes in the colour of the skin.

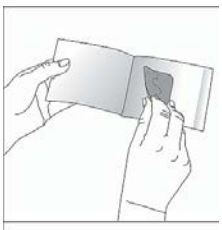
How to use the patch

Each patch is packed in a separate sachet. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the release liner.

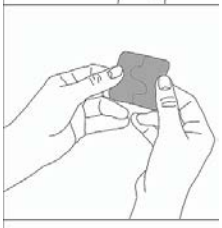
1.
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.



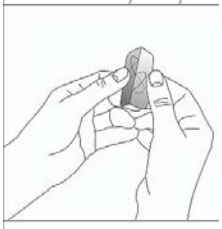
2.
Take the patch out of the sachet.



3.
The sticky side of the patch is covered by a transparent release liner. Hold the patch in both hands with the release liner facing you.

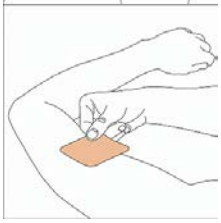


4.
Bend the patch in half so that the S-shaped break in the liner opens.

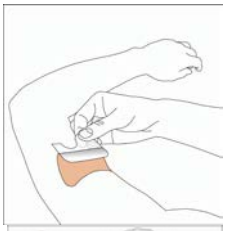


5.
Peel off one side of the release liner. Don't touch the sticky side of the patch with your fingers.

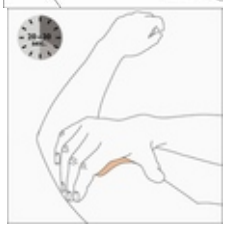
6.
Hold the other half of the rigid release liner and put the sticky surface of the patch onto your skin. Press the sticky side of the patch firmly into place.



7.
Fold back the other half of the patch and remove the other side of the release liner.



8.
Press the patch down firmly with the palm of your hand for about 20 to 30 seconds to make sure the patch is touching the skin and the edges stick well.



Wash your hands with soap and water immediately after handling the patch.

How to remove a used patch

Slowly and carefully peel off the used patch.

Gently washing the area with warm water and mild soap should remove any adhesive that stays on your skin after you remove the patch. You can also use a small amount of baby oil to remove any adhesive that won't wash off.

Do not use alcohol or other dissolving liquids such as nail polish remover as these may irritate your skin.
Choose a new area of skin where you will apply a new patch, then follow the instructions above.

If you use more Neupro than you should

Using higher doses of Neupro than your doctor has prescribed may cause side effects such as nausea (feeling sick), vomiting, low blood pressure, hallucinations (seeing or hearing things that are not real), confusion, extreme sleepiness, involuntary movements and convulsions.
If you have used more patches than your doctor told you to, contact your doctor or hospital for advice immediately, and follow their advice on removal of patches.

If you have forgotten to change the patch at the usual time

If you have forgotten to change the patch at your usual time, change it as soon as you remember: remove the old patch and use a new one. If you have forgotten to stick on a new patch after removing the old one, use a new patch as soon as you remember.
In both cases, on the following day you should use a new patch at the usual time. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro

Do not stop using Neupro suddenly without talking to your doctor. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include: akinesia (loss of muscle movement), rigid muscles, fever, unstable blood pressure, tachycardia (increased heart rate), confusion, depressed level of consciousness (e.g. coma).
Your daily dose of Neupro should be reduced gradually

- by 2 mg every other day - if you use Neupro **for Parkinson's disease**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Neupro can cause side effects, although not everybody gets them.

You may experience **nausea** (feeling sick) and **vomiting at the beginning of treatment**. These effects are usually mild or moderate and only last for a short time. You should contact your doctor if they last for a long time or if you worry about them.

Skin problems caused by the patch
You may get skin reactions from the patch such as redness, itching. They are usually mild or moderate and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch.
If you have a skin reaction that lasts longer than a few days, is severe, or spreads outside the area of skin that was covered by the patch, you should contact your doctor.

You may experience the following side effects:
Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:

- strong impulse to gamble excessively despite serious personal or family consequences
- altered or increased sexual interest and behaviour of significant concern to you or others, for example, an increased sex drive
- uncontrolled excessive shopping or spending

- binge eating (eating large amounts of food in a short period of time) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)

Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing symptoms.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

If you are using Neupro for Parkinson's disease the following side effects may occur:

Very common side effects
- sleepiness, dizziness, headache
- feeling sick (nausea), vomiting
- skin irritations under the patch such as redness and itching

Common side effects
- seeing or hearing things that are not real (hallucinations)
- difficulty falling asleep, sleep disorder, difficulty sleeping, nightmare, unusual dreams
- loss of consciousness, involuntary movements related to Parkinson's disease (dyskinesia), feeling dizzy when standing up because of fall in blood pressure
- vertigo (sensation of whirling motion)
- feeling of heartbeat (palpitation)
- low blood pressure when standing up, high blood pressure
- hiccups
- constipation, dry mouth, heartburn
- redness, increased sweating, itching
- swelling of legs and feet
- feeling weak, feeling tired
- falling
- weight loss

Uncommon side effects
- allergic reaction
- falling asleep suddenly without warning
- abnormal thinking about reality and behaviour
- increased sex drive, inability to resist the impulse to perform an action that is harmful involving excessive gambling and repetitive meaningless actions
- confusion
- blurred vision
- visual disturbances such as seeing colours or lights
- abnormal heart rhythm
- low blood pressure
- stomach discomfort and pain
- generalised itching, skin irritation
- unable to achieve or maintain an erection
- increased or abnormal liver function test results
- weight increase
- increased heart rate

Rare side effects
- psychotic disorders
- unwanted and uncontrolled thoughts and behaviours
- aggressive behaviour/aggression
- binge eating and compulsive eating
- involuntary muscle spasms (convulsion)
- generalised rash
- irritability

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEUPRO

Keep out of the reach and sight of children.
Do not use Neupro after the expiry date which is stated on the label and carton.
Do not store above 25°C.

What to do with the used and unused patches

Used patches still contain active substance, which may be harmful to others. Fold the used patch with the sticky side inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines not longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.
  Each patch releases 4 mg of rotigotine per 24 hours. Each patch of 20 cm^2 contains 9.0 mg of rotigotine.

- The other ingredients are poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, sodium metabisulphite (E223), ascorbyl palmitate (E304) and DL-α-tocopherol (E307).
  Backing layer: Polyester film, siliconized, aluminized, colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7).
  Release liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

Neupro is a transdermal patch. It is thin and has three layers. It is square-shaped with rounded edges. The outside is tan-coloured and is imprinted with Neupro 4 mg/24 h.

Neupro is available in the following pack-sizes:
Cartons containing 7, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) patches, which are individually sealed in sachets.

Not all pack sizes may be marketed.

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 6 mg/24 h transdermal patch
Rotigotine

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT NEUPRO IS AND WHAT IT IS USED FOR

Neupro belongs to a group of medicines called dopamine agonists which stimulate a certain type of cells that bind with dopamine receptors in the brain.

Neupro is used to treat:
- the signs and symptoms of **Parkinson's disease** either alone or in combination with the medicine called levodopa.

2. BEFORE YOU USE NEUPRO

Do not use Neupro

- if you are **allergic** (hypersensitive) to **rotigotine** or any of the **other ingredients** of Neupro (see Section 6, **'Further information'**).
- if you need to have **magnetic resonance imaging** (method to visualise internal organs and tissues of the body) or **cardioversion** (treatment of abnormal heart rhythm). You must take your Neupro patch off before such procedures. You can put a new patch on after the procedure.

Take special care with Neupro

- This medicine may affect your **blood pressure**, so it should be measured regularly, especially at the beginning of your treatment.

- **Eye examinations** are recommended at regular intervals while using Neupro. However, if you notice any problems with your sight in-between examinations, you should contact your doctor immediately.

- If you have serious **liver problems**, your doctor may need to adjust the dose. If during treatment your liver problems get worse, you should contact your doctor as soon as possible.

- If you **feel very drowsy** or find that you **fall asleep suddenly**, please contact your doctor (see also below in this section, under **'Driving and using machines'**).

- Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormal high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

- Neupro may cause **hallucinations** (seeing or hearing things that are not real). If you notice such effects, please contact your doctor.

- As with every patch or bandage, Neupro can cause **skin reactions**, such as reddening and itching. They are usually mild or moderate, and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch. If you have a skin reaction which lasts for more than a few days, is severe, or spreads outside the area of skin that was covered by the patch, please contact your doctor.
  Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro. To help avoid the skin reactions, you should put the patch on a different area of skin every day, and only use the same area again after 14 days.

- Neupro should **not be used by children.**

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not take the following medicines while using Neupro, because they may decrease its effect: anti-psychotics (used to treat certain mental conditions) or metoclopramide (used to treat nausea and vomiting).

If you are treated with Neupro and levodopa at the same time, some side effects may get more serious, such as seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), and swelling of legs and feet.

Please ask your doctor whether it is safe for you to:
- drink alcohol or
- take sedating medicines (for example benzodiazepines, medicines used to treat mental conditions or depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect the way this medicine works. You should discuss with your doctor if it is safe for you to drink alcohol while using Neupro.

Pregnancy and breast-feeding

You should not use Neupro if you are pregnant, as the effects of rotigotine on pregnancy and the unborn baby are not known. Tell your doctor if you are pregnant or planning to become pregnant.

Breast-feeding is not recommended during treatment with Neupro. Rotigotine may pass into your breast milk and affect your baby and is also likely to reduce the amount of milk you produce.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.
In isolated cases people have fallen asleep while driving and this has caused accidents.

Important information about some of the ingredients of Neupro

Neupro contains sodium metabisulphite (E223), a substance that may rarely cause severe hypersensitivity reactions and bronchospasm.

3. HOW TO USE NEUPRO

Dose

Always use Neupro exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Neupro is generally used as a long term treatment. Normally, you will start your treatment with a low dose and, if necessary, increase it week by week, as told by your doctor, until reaching the right dose for you. You will then continue treatment with this dose, also called the maintenance dose.

You should change your Neupro patch once a day. For reaching the needed doses, different patches of Neupro are available, each releasing a different amount of the active substance per day: 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h. For higher doses, multiple patches must be applied. For example a daily dose of 10 mg may be reached by applying one patch of 6 mg/24 h and one patch of 4 mg/24 h.

Treatment of Parkinson's disease
Patients not taking levodopa (early stage of Parkinson's disease)
You will start by using one Neupro 2 mg/24 h patch daily. From the second week, the daily dose will be increased by 2 mg, on a weekly basis, until reaching the right (maintenance) dose for you. For most patients, the right dose is between 6 mg and 8 mg per day (reached within 3 to 4 weeks).
The maximum dose is 8 mg per day.

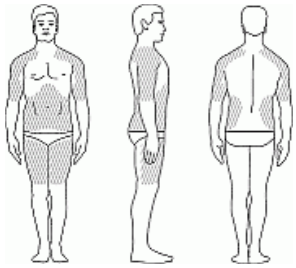
Patients taking levodopa (advanced stage of Parkinson's disease)
You will start by using one Neupro 4 mg/24 h patch daily. From the second week, the daily dose will be increased by 2 mg, on a weekly basis, until reaching the right (maintenance) dose for you. For most patients, the right dose is between 8 mg and 16 mg per day (reached within 3 to 7 weeks).
The maximum dose is 16 mg per day.

If you have to stop taking this medicine, see Section 3, **'If you stop using Neupro**'.

FOLLOW THESE INSTRUCTIONS WHEN USING NEUPRO:

You should stick a new Neupro patch onto the skin **once a day**. Leave the patch on your skin for 24 hours, then remove it and apply a new one. Make sure that you take the old patch off before applying a new one; place the new patch on a different area of skin.
You should **change your patch** at around the **same time every day**.
Do not cut the Neupro patches into pieces.

Where to stick the patch



Put the sticky side of the patch onto clean, dry, healthy skin on the following areas, as indicated by the grey areas in the picture:

- shoulder
- upper arm
- belly
- thigh
- hip
- flank (your side, between your ribs and your hip).

To **help avoid skin irritation:**

- Stick the patch onto a different area of skin each day, for example on the right side of your body one day, then on the left side the next day; on your upper body one day, then on your lower body.
- Do not stick Neupro on the same area of skin twice within 14 days.
- Do not stick the patch on broken or damaged skin or on skin that is red or irritated.

If you still get problems with your skin because of the patch, please see in Section 4 **'Possible side effects'** the details about what you should do.

To **prevent the patch becoming loose or falling off**

- Do not put the patch in an area where it can be rubbed by tight clothing.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least 3 days before sticking the patch there.

If the patch falls off, a new patch should be applied for the rest of the day, then replace the patch at the same time as usual.

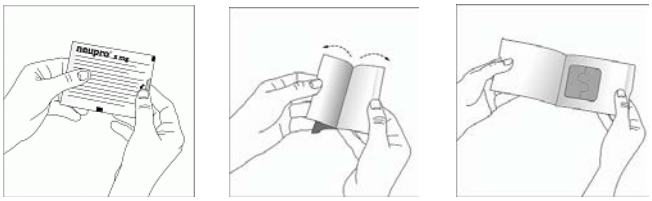
NOTE

- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off afterwards.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area protected from direct sunlight, as it may cause changes in the colour of the skin.

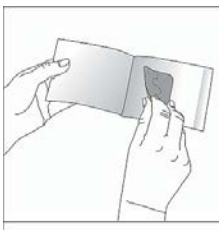
How to use the patch

Each patch is packed in a separate sachet. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the release liner.

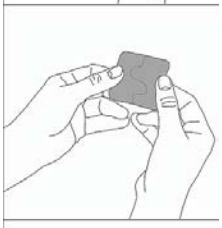
1.
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.



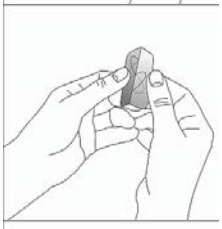
2.
Take the patch out of the sachet.



3.
The sticky side of the patch is covered by a transparent release liner. Hold the patch in both hands with the release liner facing you.

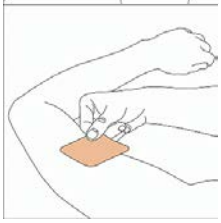


4.
Bend the patch in half so that the S-shaped break in the liner opens.

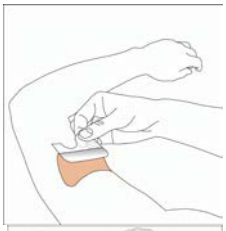


5.
Peel off one side of the release liner. Don't touch the sticky side of the patch with your fingers.

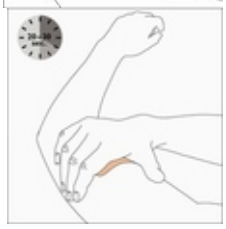
6.
Hold the other half of the rigid release liner and put the sticky surface of the patch onto your skin. Press the sticky side of the patch firmly into place.



7.
Fold back the other half of the patch and remove the other side of the release liner.



8.
Press the patch down firmly with the palm of your hand for about 20 to 30 seconds to make sure the patch is touching the skin and the edges stick well.



Wash your hands with soap and water immediately after handling the patch.

How to remove a used patch

Slowly and carefully peel off the used patch.

Gently washing the area with warm water and mild soap should remove any adhesive that stays on your skin after you remove the patch. You can also use a small amount of baby oil to remove any adhesive that won't wash off.

Do not use alcohol or other dissolving liquids such as nail polish remover as these may irritate your skin.
Choose a new area of skin where you will apply a new patch, then follow the instructions above.

If you use more Neupro than you should

Using higher doses of Neupro than your doctor has prescribed may cause side effects such as nausea (feeling sick), vomiting, low blood pressure, hallucinations (seeing or hearing things that are not real), confusion, extreme sleepiness, involuntary movements and convulsions.
If you have used more patches than your doctor told you to, contact your doctor or hospital for advice immediately, and follow their advice on removal of patches.

If you have forgotten to change the patch at the usual time

If you have forgotten to change the patch at your usual time, change it as soon as you remember: remove the old patch and use a new one. If you have forgotten to stick on a new patch after removing the old one, use a new patch as soon as you remember.
In both cases, on the following day you should use a new patch at the usual time. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro

Do not stop using Neupro suddenly without talking to your doctor. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include: akinesia (loss of muscle movement), rigid muscles, fever, unstable blood pressure, tachycardia (increased heart rate), confusion, depressed level of consciousness (e.g. coma).
Your daily dose of Neupro should be reduced gradually

- by 2 mg every other day - if you use Neupro **for Parkinson's disease**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Neupro can cause side effects, although not everybody gets them.

You may experience **nausea** (feeling sick) and **vomiting at the beginning of treatment**. These effects are usually mild or moderate and only last for a short time. You should contact your doctor if they last for a long time or if you worry about them.

Skin problems caused by the patch
You may get skin reactions from the patch such as redness, itching. They are usually mild or moderate and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch.
If you have a skin reaction that lasts longer than a few days, is severe, or spreads outside the area of skin that was covered by the patch, you should contact your doctor.

You may experience the following side effects:
Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:

- strong impulse to gamble excessively despite serious personal or family consequences
- altered or increased sexual interest and behaviour of significant concern to you or others, for example, an increased sex drive
- uncontrolled excessive shopping or spending

- binge eating (eating large amounts of food in a short period of time) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)

Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing symptoms.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

If you are using Neupro for Parkinson's disease the following side effects may occur:

Very common side effects
- sleepiness, dizziness, headache
- feeling sick (nausea), vomiting
- skin irritations under the patch such as redness and itching

Common side effects
- seeing or hearing things that are not real (hallucinations)
- difficulty falling asleep, sleep disorder, difficulty sleeping, nightmare, unusual dreams
- loss of consciousness, involuntary movements related to Parkinson's disease (dyskinesia), feeling dizzy when standing up because of fall in blood pressure
- vertigo (sensation of whirling motion)
- feeling of heartbeat (palpitation)
- low blood pressure when standing up, high blood pressure
- hiccups
- constipation, dry mouth, heartburn
- redness, increased sweating, itching
- swelling of legs and feet
- feeling weak, feeling tired
- falling
- weight loss

Uncommon side effects
- allergic reaction
- falling asleep suddenly without warning
- abnormal thinking about reality and behaviour
- increased sex drive, inability to resist the impulse to perform an action that is harmful involving excessive gambling and repetitive meaningless actions
- confusion
- blurred vision
- visual disturbances such as seeing colours or lights
- abnormal heart rhythm
- low blood pressure
- stomach discomfort and pain
- generalised itching, skin irritation
- unable to achieve or maintain an erection
- increased or abnormal liver function test results
- weight increase
- increased heart rate

Rare side effects
- psychotic disorders
- unwanted and uncontrolled thoughts and behaviours
- aggressive behaviour/aggression
- binge eating and compulsive eating
- involuntary muscle spasms (convulsion)
- generalised rash
- irritability

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEUPRO

Keep out of the reach and sight of children.
Do not use Neupro after the expiry date which is stated on the label and carton.
Do not store above 25°C.

What to do with the used and unused patches

Used patches still contain active substance, which may be harmful to others. Fold the used patch with the sticky side inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines not longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.
  Each patch releases 6 mg of rotigotine per 24 hours. Each patch of 30 cm^2 contains 13.5 mg of rotigotine.

- The other ingredients are poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, sodium metabisulphite (E223), ascorbyl palmitate (E304) and DL-α-tocopherol (E307).
  Backing layer: Polyester film, siliconized, aluminized, colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7).
  Release liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

Neupro is a transdermal patch. It is thin and has three layers. It is square-shaped with rounded edges. The outside is tan-coloured and is imprinted with Neupro 6 mg/24 h.

Neupro is available in the following pack-sizes:
Cartons containing 7, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) patches, which are individually sealed in sachets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
UCB Pharma SA/NV
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This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 8 mg/24 h transdermal patch
Rotigotine

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- Keep this leaflet. You may need to read it again.
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- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
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- if you need to have **magnetic resonance imaging** (method to visualise internal organs and tissues of the body) or **cardioversion** (treatment of abnormal heart rhythm). You must take your Neupro patch off before such procedures. You can put a new patch on after the procedure.

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- This medicine may affect your **blood pressure**, so it should be measured regularly, especially at the beginning of your treatment.

- **Eye examinations** are recommended at regular intervals while using Neupro. However, if you notice any problems with your sight in-between examinations, you should contact your doctor immediately.

- If you have serious **liver problems**, your doctor may need to adjust the dose. If during treatment your liver problems get worse, you should contact your doctor as soon as possible.

- If you **feel very drowsy** or find that you **fall asleep suddenly**, please contact your doctor (see also below in this section, under **'Driving and using machines'**).

- Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormal high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

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Please ask your doctor whether it is safe for you to:
- drink alcohol or
- take sedating medicines (for example benzodiazepines, medicines used to treat mental conditions or depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect the way this medicine works. You should discuss with your doctor if it is safe for you to drink alcohol while using Neupro.

Pregnancy and breast-feeding

You should not use Neupro if you are pregnant, as the effects of rotigotine on pregnancy and the unborn baby are not known. Tell your doctor if you are pregnant or planning to become pregnant.

Breast-feeding is not recommended during treatment with Neupro. Rotigotine may pass into your breast milk and affect your baby and is also likely to reduce the amount of milk you produce.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.
In isolated cases people have fallen asleep while driving and this has caused accidents.

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Neupro contains sodium metabisulphite (E223), a substance that may rarely cause severe hypersensitivity reactions and bronchospasm.

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Neupro is generally used as a long term treatment. Normally, you will start your treatment with a low dose and, if necessary, increase it week by week, as told by your doctor, until reaching the right dose for you. You will then continue treatment with this dose, also called the maintenance dose.

You should change your Neupro patch once a day. For reaching the needed doses, different patches of Neupro are available, each releasing a different amount of the active substance per day: 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h. For higher doses, multiple patches must be applied. For example a daily dose of 10 mg may be reached by applying one patch of 6 mg/24 h and one patch of 4 mg/24 h.

Treatment of Parkinson's disease
Patients not taking levodopa (early stage of Parkinson's disease)
You will start by using one Neupro 2 mg/24 h patch daily. From the second week, the daily dose will be increased by 2 mg, on a weekly basis, until reaching the right (maintenance) dose for you. For most patients, the right dose is between 6 mg and 8 mg per day (reached within 3 to 4 weeks).
The maximum dose is 8 mg per day.

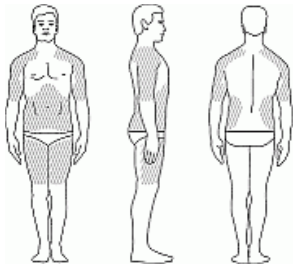
Patients taking levodopa (advanced stage of Parkinson's disease)
You will start by using one Neupro 4 mg/24 h patch daily. From the second week, the daily dose will be increased by 2 mg, on a weekly basis, until reaching the right (maintenance) dose for you. For most patients, the right dose is between 8 mg and 16 mg per day (reached within 3 to 7 weeks).
The maximum dose is 16 mg per day.

If you have to stop taking this medicine, see Section 3, **'If you stop using Neupro**'.

FOLLOW THESE INSTRUCTIONS WHEN USING NEUPRO:

You should stick a new Neupro patch onto the skin **once a day**. Leave the patch on your skin for 24 hours, then remove it and apply a new one. Make sure that you take the old patch off before applying a new one; place the new patch on a different area of skin.
You should **change your patch** at around the **same time every day**.
Do not cut the Neupro patches into pieces.

Where to stick the patch



Put the sticky side of the patch onto clean, dry, healthy skin on the following areas, as indicated by the grey areas in the picture:

- shoulder
- upper arm
- belly
- thigh
- hip
- flank (your side, between your ribs and your hip).

To **help avoid skin irritation:**

- Stick the patch onto a different area of skin each day, for example on the right side of your body one day, then on the left side the next day; on your upper body one day, then on your lower body.
- Do not stick Neupro on the same area of skin twice within 14 days.
- Do not stick the patch on broken or damaged skin or on skin that is red or irritated.

If you still get problems with your skin because of the patch, please see in Section 4 **'Possible side effects'** the details about what you should do.

To **prevent the patch becoming loose or falling off**

- Do not put the patch in an area where it can be rubbed by tight clothing.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least 3 days before sticking the patch there.

If the patch falls off, a new patch should be applied for the rest of the day, then replace the patch at the same time as usual.

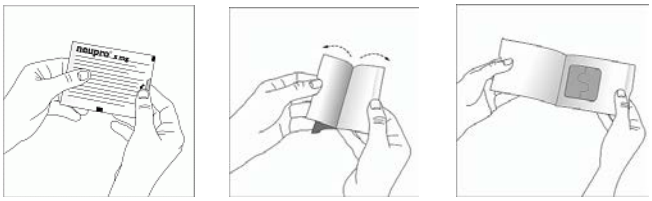
NOTE

- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off afterwards.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area protected from direct sunlight, as it may cause changes in the colour of the skin.

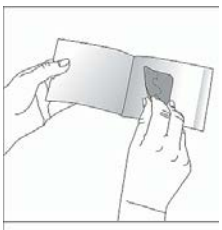
How to use the patch

Each patch is packed in a separate sachet. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the release liner.

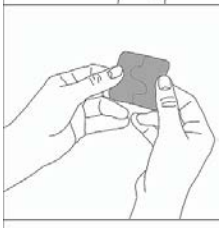
1.
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.



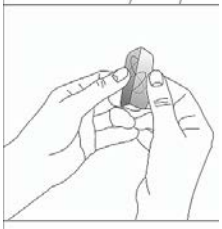
2.
Take the patch out of the sachet.



3.
The sticky side of the patch is covered by a transparent release liner. Hold the patch in both hands with the release liner facing you.

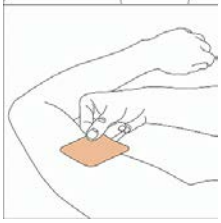


4.
Bend the patch in half so that the S-shaped break in the liner opens.

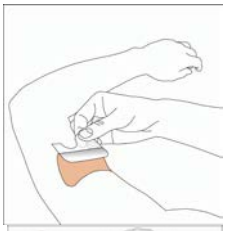


5.
Peel off one side of the release liner. Don't touch the sticky side of the patch with your fingers.

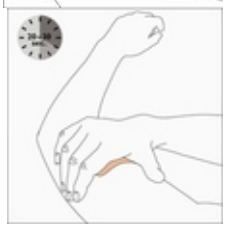
6.
Hold the other half of the rigid release liner and put the sticky surface of the patch onto your skin. Press the sticky side of the patch firmly into place.



7.
Fold back the other half of the patch and remove the other side of the release liner.



8.
Press the patch down firmly with the palm of your hand for about 20 to 30 seconds to make sure the patch is touching the skin and the edges stick well.



Wash your hands with soap and water immediately after handling the patch.

How to remove a used patch

Slowly and carefully peel off the used patch.

Gently washing the area with warm water and mild soap should remove any adhesive that stays on your skin after you remove the patch. You can also use a small amount of baby oil to remove any adhesive that won't wash off.

Do not use alcohol or other dissolving liquids such as nail polish remover as these may irritate your skin.
Choose a new area of skin where you will apply a new patch, then follow the instructions above.

If you use more Neupro than you should

Using higher doses of Neupro than your doctor has prescribed may cause side effects such as nausea (feeling sick), vomiting, low blood pressure, hallucinations (seeing or hearing things that are not real), confusion, extreme sleepiness, involuntary movements and convulsions.
If you have used more patches than your doctor told you to, contact your doctor or hospital for advice immediately, and follow their advice on removal of patches.

If you have forgotten to change the patch at the usual time

If you have forgotten to change the patch at your usual time, change it as soon as you remember: remove the old patch and use a new one. If you have forgotten to stick on a new patch after removing the old one, use a new patch as soon as you remember.
In both cases, on the following day you should use a new patch at the usual time. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro

Do not stop using Neupro suddenly without talking to your doctor. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include: akinesia (loss of muscle movement), rigid muscles, fever, unstable blood pressure, tachycardia (increased heart rate), confusion, depressed level of consciousness (e.g. coma).
Your daily dose of Neupro should be reduced gradually

- by 2 mg every other day - if you use Neupro **for Parkinson's disease**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Neupro can cause side effects, although not everybody gets them.

You may experience **nausea** (feeling sick) and **vomiting at the beginning of treatment**. These effects are usually mild or moderate and only last for a short time. You should contact your doctor if they last for a long time or if you worry about them.

Skin problems caused by the patch
You may get skin reactions from the patch such as redness, itching. They are usually mild or moderate and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch.
If you have a skin reaction that lasts longer than a few days, is severe, or spreads outside the area of skin that was covered by the patch, you should contact your doctor.

You may experience the following side effects:
Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:

- strong impulse to gamble excessively despite serious personal or family consequences
- altered or increased sexual interest and behaviour of significant concern to you or others, for example, an increased sex drive
- uncontrolled excessive shopping or spending

- binge eating (eating large amounts of food in a short period of time) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)

Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing symptoms.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

If you are using Neupro for Parkinson's disease the following side effects may occur:

Very common side effects
- sleepiness, dizziness, headache
- feeling sick (nausea), vomiting
- skin irritations under the patch such as redness and itching

Common side effects
- seeing or hearing things that are not real (hallucinations)
- difficulty falling asleep, sleep disorder, difficulty sleeping, nightmare, unusual dreams
- loss of consciousness, involuntary movements related to Parkinson's disease (dyskinesia), feeling dizzy when standing up because of fall in blood pressure
- vertigo (sensation of whirling motion)
- feeling of heartbeat (palpitation)
- low blood pressure when standing up, high blood pressure
- hiccups
- constipation, dry mouth, heartburn
- redness, increased sweating, itching
- swelling of legs and feet
- feeling weak, feeling tired
- falling
- weight loss

Uncommon side effects
- allergic reaction
- falling asleep suddenly without warning
- abnormal thinking about reality and behaviour
- increased sex drive, inability to resist the impulse to perform an action that is harmful involving excessive gambling and repetitive meaningless actions
- confusion
- blurred vision
- visual disturbances such as seeing colours or lights
- abnormal heart rhythm
- low blood pressure
- stomach discomfort and pain
- generalised itching, skin irritation
- unable to achieve or maintain an erection
- increased or abnormal liver function test results
- weight increase
- increased heart rate

Rare side effects
- psychotic disorders
- unwanted and uncontrolled thoughts and behaviours
- aggressive behaviour/aggression
- binge eating and compulsive eating
- involuntary muscle spasms (convulsion)
- generalised rash
- irritability

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEUPRO

Keep out of the reach and sight of children.
Do not use Neupro after the expiry date which is stated on the label and carton.
Do not store above 25°C.

What to do with the used and unused patches

Used patches still contain active substance, which may be harmful to others. Fold the used patch with the sticky side inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines not longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.
  Each patch releases 8 mg of rotigotine per 24 hours. Each patch of 40 cm^2 contains 18.0 mg of rotigotine.

- The other ingredients are poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, sodium metabisulphite (E223), ascorbyl palmitate (E304) and DL-α-tocopherol (E307).
  Backing layer: Polyester film, siliconized, aluminized, colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7).
  Release liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

Neupro is a transdermal patch. It is thin and has three layers. It is square-shaped with rounded edges. The outside is tan-coloured and is imprinted with Neupro 8 mg/24 h.

Neupro is available in the following pack-sizes:
Cartons containing 7, 20, 28, 30, 56, 60, 84 (2x42), 90 or 100 (2x50) patches, which are individually sealed in sachets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
UCB Pharma SA/NV
Tel/Tél: +32 / (0)2 559 92 00

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This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 2 mg/24 h
Neupro 4 mg/24 h
Neupro 6 mg/24 h
Neupro 8 mg/24 h
Transdermal patch
Rotigotine

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT NEUPRO IS AND WHAT IT IS USED FOR

Neupro belongs to a group of medicines called dopamine agonists which stimulate a certain type of cells that bind with dopamine receptors in the brain.

Neupro is used to treat:
- the signs and symptoms of **Parkinson's disease** either alone or in combination with the medicine called levodopa.

2. BEFORE YOU USE NEUPRO

Do not use Neupro

- if you are **allergic** (hypersensitive) to **rotigotine** or any of the **other ingredients** of Neupro (see Section 6, **'Further information'**).
- if you need to have **magnetic resonance imaging** (method to visualise internal organs and tissues of the body) or **cardioversion** (treatment of abnormal heart rhythm). You must take your Neupro patch off before such procedures. You can put a new patch on after the procedure.

Take special care with Neupro

- This medicine may affect your **blood pressure**, so it should be measured regularly, especially at the beginning of your treatment.

- **Eye examinations** are recommended at regular intervals while using Neupro. However, if you notice any problems with your sight in-between examinations, you should contact your doctor immediately.

- If you have serious **liver problems**, your doctor may need to adjust the dose. If during treatment your liver problems get worse, you should contact your doctor as soon as possible.

- If you **feel very drowsy** or find that you **fall asleep suddenly**, please contact your doctor (see also below in this section, under **'Driving and using machines'**).

- Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormal high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

- Neupro may cause **hallucinations** (seeing or hearing things that are not real). If you notice such effects, please contact your doctor.

- As with every patch or bandage, Neupro can cause **skin reactions**, such as reddening and itching. They are usually mild or moderate, and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch. If you have a skin reaction which lasts for more than a few days, is severe, or spreads outside the area of skin that was covered by the patch, please contact your doctor.
  Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro. To help avoid the skin reactions, you should put the patch on a different area of skin every day, and only use the same area again after 14 days.

- Neupro should **not be used by children.**

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not take the following medicines while using Neupro, because they may decrease its effect: anti-psychotics (used to treat certain mental conditions) or metoclopramide (used to treat nausea and vomiting).

If you are treated with Neupro and levodopa at the same time, some side effects may get more serious, such as seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), and swelling of legs and feet.

Please ask your doctor whether it is safe for you to:
- drink alcohol or
- take sedating medicines (for example benzodiazepines, medicines used to treat mental conditions or depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect the way this medicine works. You should discuss with your doctor if it is safe for you to drink alcohol while using Neupro.

Pregnancy and breast-feeding

You should not use Neupro if you are pregnant, as the effects of rotigotine on pregnancy and the unborn baby are not known. Tell your doctor if you are pregnant or planning to become pregnant.

Breast-feeding is not recommended during treatment with Neupro. Rotigotine may pass into your breast milk and affect your baby and is also likely to reduce the amount of milk you produce.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.
In isolated cases people have fallen asleep while driving and this has caused accidents.

Important information about some of the ingredients of Neupro

Neupro contains sodium metabisulphite (E223), a substance that may rarely cause severe hypersensitivity reactions and bronchospasm.

3. HOW TO USE NEUPRO

Dose

Always use Neupro exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Neupro is generally used as a long term treatment. Normally, you will start your treatment with a low dose and, if necessary, increase it week by week, as told by your doctor, until reaching the right dose for you. You will then continue treatment with this dose, also called the maintenance dose.

The Neupro treatment initiation pack contains 4 different packages (one for each strength) with 7 patches in each package. These packages are usually needed for the first four weeks of therapy, but depending on your response to Neupro, you may not need to use all of the dose packages included or you may need additional higher doses after week 4, which are not covered by this package.

On the first day of treatment, start with Neupro 2 mg (package marked "**Week 1**)", and use one Neupro 2 mg transdermal patch daily. You should take Neupro 2 mg for 7 days
(e.g. if you start on a Sunday, switch to the next dose on the following Sunday.).
At the beginning of the second week, you should take Neupro 4 mg (package marked with "**Week 2**").
At the beginning of the third week, you should take Neupro 6 mg (package marked with "**Week 3**").
At the beginning of the fourth week, you should take Neupro 8 mg (package marked with "**Week 4**").

The right dose for you will depend on your needs.

4 mg of Neupro every day may be an effective dose for some patients. For most patients with early stage Parkinson's disease, the right dose is reached within 3 or 4 weeks, at doses of 6 mg per day or 8 mg per day respectively. The maximum dose is 8 mg per day. For most patients with advanced-stage Parkinson's disease the right dose is reached within 3 to 7 weeks, at doses of 8 mg per day up to a maximum dose of 16 mg per day.

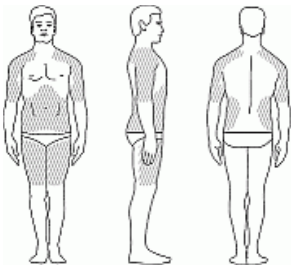
If you have to stop taking this medicine, see Section 3, **'If you stop using Neupro**'.

FOLLOW THESE INSTRUCTIONS WHEN USING NEUPRO:

You should stick a new Neupro patch onto the skin **once a day**. Leave the patch on your skin for 24 hours, then remove it and apply a new one. Make sure that you take the old patch off before applying a new one; place the new patch on a different area of skin.
You should **change your patch** at around the **same time every day**.
Do not cut the Neupro patches into pieces.

Where to stick the patch

Put the sticky side of the patch onto clean, dry, healthy skin on the following areas, as indicated by the grey areas in the picture:



- shoulder
- upper arm
- belly
- thigh
- hip
- flank (your side, between your ribs and your hip).

To **help avoid skin irritation:**

- Stick the patch onto a different area of skin each day, for example on the right side of your body one day, then on the left side the next day; on your upper body one day, then on your lower body.
- Do not stick Neupro on the same area of skin twice within 14 days.
- Do not stick the patch on broken or damaged skin or on skin that is red or irritated.

If you still get problems with your skin because of the patch, please see in Section 4 **'Possible side effects'** the details about what you should do.

To **prevent the patch becoming loose or falling off**

- Do not put the patch in an area where it can be rubbed by tight clothing.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least 3 days before sticking the patch there.

If the patch falls off, a new patch should be applied for the rest of the day, then replace the patch at the same time as usual.

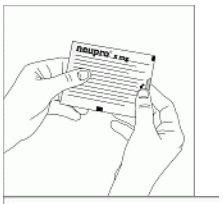
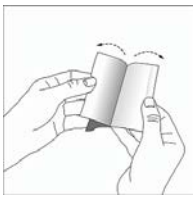
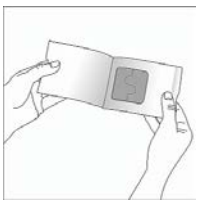
NOTE

- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off afterwards.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area protected from direct sunlight, as it may cause changes in the colour of the skin.

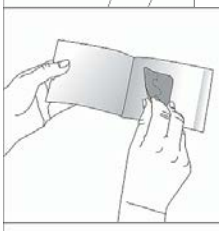
How to use the patch

Each patch is packed in a separate sachet. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the release liner.

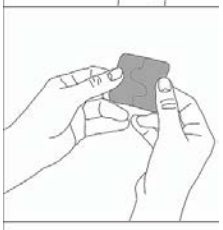
1.
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.

2.
Take the patch out of the sachet.



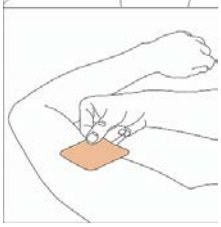
3.
The sticky side of the patch is covered by a transparent release liner. Hold the patch in both hands with the release liner facing you.



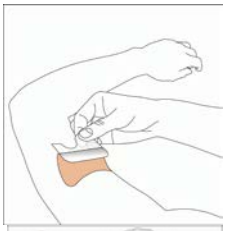
4.
Bend the patch in half so that the S-shaped break in the liner opens.

5.
Peel off one side of the release liner. Don't touch the sticky side of the patch with your fingers.

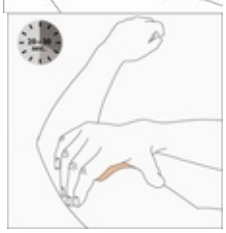
6.
Hold the other half of the rigid release liner and put the sticky surface of the patch onto your skin. Press the sticky side of the patch firmly into place.



7.
Fold back the other half of the patch and remove the other side of the release liner.



8.
Press the patch down firmly with the palm of your hand for about 20 to 30 seconds to make sure the patch is touching the skin and the edges stick well.



Wash your hands with soap and water immediately after handling the patch.

How to remove a used patch

Slowly and carefully peel off the used patch.

Gently washing the area with warm water and mild soap should remove any adhesive that stays on your skin after you remove the patch. You can also use a small amount of baby oil to remove any adhesive that won't wash off.
Do not use alcohol or other dissolving liquids such as nail polish remover as these may irritate your skin.
Choose a new area of skin where you will apply a new patch, then follow the instructions above.

If you use more Neupro than you should

Using higher doses of Neupro than your doctor has prescribed may cause side effects such as nausea (feeling sick), vomiting, low blood pressure, hallucinations (seeing or hearing things that are not real), confusion, extreme sleepiness, involuntary movements and convulsions.
If you have used more patches than your doctor told you to, contact your doctor or hospital for advice immediately, and follow their advice on removal of patches.

If you have used a different patch (e.g. Neupro 4 mg/24 h instead of Neupro 2 mg/24 h) than your doctor told you to, contact your doctor or hospital for advice immediately, and follow their advice on changes of patches.
If you have any unpleasant reactions, contact your doctor.

If you have forgotten to change the patch at the usual time

If you have forgotten to change the patch at your usual time, change it as soon as you remember: remove the old patch and use a new one. If you have forgotten to stick on a new patch after removing the old one, use a new patch as soon as you remember.
In both cases, on the following day you should use a new patch at the usual time. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro

Do not stop using Neupro suddenly without talking to your doctor. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include: akinesia (loss of muscle movement), rigid muscles, fever, unstable blood pressure, tachycardia (increased heart rate), confusion, depressed level of consciousness (e.g. coma).
Your daily dose of Neupro should be reduced gradually

- by 2 mg every other day - if you use Neupro **for Parkinson's disease**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Neupro can cause side effects, although not everybody gets them.

You may experience **nausea** (feeling sick) and **vomiting at the beginning of treatment**. These effects are usually mild or moderate and only last for a short time. You should contact your doctor if they last for a long time or if you worry about them.

Skin problems caused by the patch
You may get skin reactions from the patch such as redness, itching. They are usually mild or moderate and only affect the area of skin the patch has been on. The reactions normally disappear after a few hours when you remove the patch.
If you have a skin reaction that lasts longer than a few days, is severe, or spreads outside the area of skin that was covered by the patch, you should contact your doctor.

You may experience the following side effects:
Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
- strong impulse to gamble excessively despite serious personal or family consequences
- altered or increased sexual interest and behaviour of significant concern to you or others, for example, an increased sex drive
- uncontrolled excessive shopping or spending
- binge eating (eating large amounts of food in a short period of time) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)

Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing symptoms.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

If you are using Neupro for Parkinson's disease the following side effects may occur:

Very common side effects
- sleepiness, dizziness, headache
- feeling sick (nausea), vomiting
- skin irritations under the patch such as redness and itching

Common side effects
- seeing or hearing things that are not real (hallucinations)
- difficulty falling asleep, sleep disorder, difficulty sleeping, nightmare, unusual dreams
- loss of consciousness, involuntary movements related to Parkinson's disease (dyskinesia), feeling dizzy when standing up because of fall in blood pressure
- vertigo (sensation of whirling motion)
- feeling of heartbeat (palpitation)
- low blood pressure when standing up, high blood pressure
- hiccups
- constipation, dry mouth, heartburn
- redness, increased sweating, itching
- swelling of legs and feet
- feeling weak, feeling tired
- falling
- weight loss

Uncommon side effects
- allergic reaction
- falling asleep suddenly without warning
- abnormal thinking about reality and behaviour

- increased sex drive, inability to resist the impulse to perform an action that is harmful involving excessive gambling and repetitive meaningless actions
- confusion
- blurred vision
- visual disturbances such as seeing colours or lights
- abnormal heart rhythm
- low blood pressure
- stomach discomfort and pain
- generalised itching, skin irritation
- unable to achieve or maintain an erection
- increased or abnormal liver function test results
- weight increase
- increased heart rate

Rare side effects
- psychotic disorders
- unwanted and uncontrolled thoughts and behaviours
- aggressive behaviour/aggression
- binge eating and compulsive eating
- involuntary muscle spasms (convulsion)
- generalised rash
- irritability

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEUPRO

Keep out of the reach and sight of children.
Do not use Neupro after the expiry date which is stated on the label and carton.
Do not store above 25°C.

What to do with the used and unused patches

Used patches still contain active substance, which may be harmful to others. Fold the used patch with the sticky side inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines not longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.

  Neupro 2 mg/24 h
  Each patch releases 2 mg of rotigotine per 24 hours. Each patch of 10 cm^2 contains 4.5 mg of rotigotine.

  Neupro 4 mg/24 h

Each patch releases 4 mg of rotigotine per 24 hours. Each patch of 20 cm^2 contains 9.0 mg of rotigotine.

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

Neupro 8 mg/24 h
Each patch releases 8 mg of rotigotine per 24 hours. Each patch of 40 cm^2 contains 18.0 mg of rotigotine.

- The other ingredients are poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, sodium metabisulphite (E223), ascorbyl palmitate (E304) and DL-α-tocopherol (E307).
  Backing layer: Polyester film, siliconized, aluminized, colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7).
  Release liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

Neupro is a transdermal patch. It is thin and has three layers. It is square-shaped with rounded edges. The outside is tan-coloured and is imprinted with Neupro 2 mg/24 h, 4 mg/24 h, 6 mg/24 h or 8 mg/24 h.

Neupro is available in the following pack-sizes:
One treatment initiation pack contains 28 transdermal patches in 4 cartons with 7 patches of 2 mg, 4 mg, 6 mg, and 8 mg each, which are individually sealed in sachets.

Marketing Authorisation Holder and Manufacturer

UCB Manufacturing Ireland Ltd.
Shannon, Industrial Estate,
Co. Clare, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.