ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neupro 1 mg/24 h transdermal patch
Neupro 3 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

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

Neupro 3 mg/24 h transdermal patch
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 (RLS) in adults.

4.2 Posology and method of administration

Posology

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 maximum dose of 3 mg/24 h. The need for treatment continuation should be reconsidered every 6 months.

Neupro is applied once a day. The patch should be applied at approximately the same time every day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different site of application.

If the patient forgets to apply the patch at the usual time of the day or if the patch becomes detached, another patch should be applied for the remainder of the day.

Treatment discontinuation

Neupro should be discontinued gradually. The daily dose should be reduced in steps of 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) has not been observed.

Special populations

Hepatic impairment

Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment. Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Rotigotine has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment.

Renal impairment

Adjustment of the dose is not necessary in patients with mild to severe renal impairment, including those requiring dialysis. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population

The safety and efficacy of rotigotine in children and adolescents have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

Neupro is for transdermal use.

The patch should be applied to clean, dry, intact healthy skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. Reapplication to the same site within 14 days should be avoided. Neupro should not be placed on skin that is red, irritated or damaged (see section 4.4).

Use and handling

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the release liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is fold back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch should be pressed down firmly with the palm of the hand for about 30 seconds, so that it sticks well.

The patch should not be cut into pieces.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Magnetic resonance imaging and cardioversion

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

Orthostatic hypotension

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

Syncope

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

Sudden onset of sleep and somnolence

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

Impulse control and other related disorders

Patients should be regularly monitored for the development of impulse control disorders and related disorders including dopamine dysregulation syndrome. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathologic gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including rotigotine. In some patients, dopamine dysregulation syndrome was observed under the treatment with rotigotine. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Neuroleptic malignant syndrome

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

Dopamine agonist withdrawal syndrome

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

Abnormal thinking and behaviour

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

Fibrotic complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when treatment is discontinued, complete resolution does not always occur.

Although these adverse reactions are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.

Neuroleptics

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

Ophthalmologic monitoring

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

Heat application

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

Application site reactions

Application site skin reactions may occur and are usually mild or moderate in intensity. It is recommended that the application site should be rotated on a daily basis (e.g. from the right side to the left side and from the upper body to the lower body). The same site should not be used within 14 days. If application site reactions occur which last for more than a few days or are persistent, if there is an increase in severity, or if the skin reaction spreads outside the application site, an assessment of the risk/benefit balance for the individual patient should be conducted.
If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals, as exposure could lead to changes in the skin color.
If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Neupro is observed, Neupro should be discontinued.

Peripheral oedema

Peripheral oedema has been observed in clinical trials conducted in patients with RLS.

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. In long-term clinical studies with rotigotine, the majority of augmentation episodes were seen in the first and second years of treatment. Doses higher than the approved dose range for RLS should be avoided as this may lead to higher rates of augmentation (see section 5.1).

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

Women of childbearing potential, contraception in females

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

Pregnancy

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

Breast-feeding

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

Fertility

For information on fertility studies, please see section 5.3.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 748 Neupro- and 214 placebo-treated patients, 65.5% 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 application site reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of Neupro in 7.2% of subjects.

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.

Tabulated list of adverse reactions

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

System/organ classes acc. to MedDRA	Very common	Common	Uncommon	Rare	Not known
Immune system disorders		Hypersensitivity, which may include angioedema, tongue oedema and lip oedema			
Psychiatric disorders		Sleep attacks/sudden onset of sleep, sexual desire disorders[a] (incl. hypersexuality, libido increased), insomnia, sleep disorder, abnormal dreams, impulse-control disorders[a,d] (incl. pathological gambling, stereotypy/ punding, binge eating/eating disorder[b], compulsive shopping[c])	Obsessive-compulsive disorder, agitation[d]	Aggressive behaviour/ aggression[b], disorientation[d]	Dopamine dysregulation syndrome[c], perception disturbances[e] (incl. hallucination, hallucination visual, hallucination auditory, illusion), nightmare[e], paranoia[e], confusional state[e], psychotic disorder[e], delusion[e], delirium[e]

System/organ classes acc. to MedDRA	Very common	Common	Uncommon	Rare	Not known
Nervous system disorders	Headache	Somnolence			Dizziness[e], disturbances in consciousness NEC[e] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia[e], dizziness postural[e], lethargy[e], convulsion[e]
Eye disorders					Vision blurred[e], visual impairment[e], photopsia[e]
Ear and labyrinth disorders					Vertigo[e]
Cardiac disorders					Palpitations[e], atrial fibrillation[e], supraventricular tachycardia[e]
Vascular disorders		Hypertension	Orthostatic hypotension		Hypotension[e]
Respiratory, thoracic and mediastinal disorders					Hiccups[e]
Gastrointestinal disorders	Nausea	Vomiting, dyspepsia			Constipation[e], dry mouth[e], abdominal pain[e], diarrhoea[c]
Skin and subcutaneous tissue disorders		Pruritus			Erythema[e], hyperhidrosis[e], pruritus generalised[e], skin irritation[e], dermatitis contact[e], rash generalised[e]
Reproductive system and breast disorder					Erectile dysfunction[e]

System/organ classes acc. to MedDRA	Very common	Common	Uncommon	Rare	Not known
General disorders and administration site conditions	Application and instillation site reactions[a] (incl. erythema, pruritus, irritation, rash, dermatitis, vesicles, pain, eczema, inflammation, swelling, discolouration, papules, exfoliation, urticaria, hypersensitivity), asthenic conditions[a] (incl. fatigue, asthenia, malaise)	Irritability, oedema peripheral			
Investigations					Weight decreased[e], hepatic enzyme increased[e] (incl. AST, ALT, GGT), weight increased[e], heart rate increased[e], CPK increased[d,e]
Injury, poisoning and procedural complications					Fall[e]
Musculoskeletal and connective tissue disorders					Rhabdomyolysis[c]

[a] High Level Term
[b] Observed in open-label studies
[c] Observed during post-marketing
[d] Observed in 2011 data pool of double-blind placebo-controlled studies
[e] Observed in studies performed in patients with Parkinson's disease

Description of selected adverse reactions

Sudden onset of sleep and somnolence

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

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including rotigotine (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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

Management

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Mechanism of action

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

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

Pharmacodynamic effects

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

Clinical efficacy

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 ($p<0.0001$).

Augmentation

In 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. In a 5-year open-label treatment study, augmentation occurred in 11.9% of patients treated with the approved dosages for RLS (1-3 mg/24 h), and 5.1% were considered clinically significant. In this study, the majority of augmentation episodes occurred in the first and second years of treatment. Furthermore, in this study a higher dose of 4 mg/24 h that is unapproved in RLS was also used and led to higher rates of augmentation.

5.2 Pharmacokinetic properties

Absorption

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

Approximately 45% of the active substance within the patch is released to the skin in 24 hours. The absolute bioavailability after transdermal application is approximately 37%.

Rotating the site of patch application may result in day-to-day differences in plasma levels. Differences in bioavailability of rotigotine ranged from 2% (upper arm *versus* flank) to 46% (shoulder *versus* thigh). However, there is no indication of a relevant impact on the clinical outcome.

Distribution

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

Biotransformation

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

Elimination

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

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

Special patient groups

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

Hepatic and renal impairment

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

Paediatric population

Limited pharmacokinetic data obtained in adolescent patients with RLS (13-17 years, n=24) following treatment with multiple doses of 0.5 to 3mg/24h showed that systemic exposure to rotigotine was similar to that observed in adults. Efficacy/safety data is insufficient to establish a relation between exposure and response (see also paediatric information in section 4.2).

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

30 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Peel off sachet in a plastic box: 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 box contains 7, 14, 28, 30 or 84 (multipack containing 3 packs of 28) transdermal patches, individually sealed in sachets.

Not all pack sizes may be marketed.

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

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Neupro 1 mg/24 h transdermal patch
EU/1/05/331/038
EU/1/05/331/040
EU/1/05/331/041
EU/1/05/331/044
EU/1/05/331/056

Neupro 3 mg/24 h transdermal patch
EU/1/05/331/047
EU/1/05/331/049
EU/1/05/331/050
EU/1/05/331/053
EU/1/05/331/058

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2006
Date of latest renewal: 22 January 2016

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

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 maximum 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 maximum dose of 8 mg/24 h.
4 mg/24 h may be an effective dose in some patients. For most patients an effective dose is reached within 3 or 4 weeks at doses of 6 mg/24 h or 8 mg/24 h, respectively.
The maximum dose is 8 mg/24 h.

Dosing in patients with advanced stage Parkinson's disease with fluctuations:
A single daily dose should be initiated at 4 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximum dose of 16 mg/24 h.
4 mg/24 h or 6 mg/24 h may be effective doses in some patients. For most patients an effective dose is reached within 3 to 7 weeks at doses of 8 mg/24 h up to a maximum dose of 16 mg/24 h.

For doses higher than 8 mg/24 h multiple patches may be used to achieve the final dose e.g. 10 mg/24 h may be reached by combination of a 6 mg/24 h and a 4 mg/24 h patch.

Neupro is applied once a day. The patch should be applied at approximately the same time every day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different site of application.

If the patient forgets to apply the patch at the usual time of the day or if the patch becomes detached, another patch should be applied for the remainder of the day.

Treatment discontinuation

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) has not been 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 impairment

Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment. Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Rotigotine has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment.

Renal impairment

Adjustment of the dose is not necessary in patients with mild to severe renal impairment, including those requiring dialysis. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population

The safety and efficacy of rotigotine in children and adolescents have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology in children with RLS can be made.
There is no relevant use of Neupro in the paediatric population in Parkinson's disease.

Method of administration

Neupro is for transdermal use.

The patch should be applied to clean, dry, intact healthy skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. Reapplication to the same site within 14 days should be avoided. Neupro should not be placed on skin that is red, irritated or damaged (see section 4.4).

Use and handling

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the release liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is fold back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch should be pressed down firmly with the palm of the hand for about 30 seconds, so that it sticks well.

The patch should not be cut into pieces.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Both indications:

Magnetic resonance imaging and cardioversion

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

Orthostatic hypotension

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

Syncope

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

Sudden onset of sleep and somnolence

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

Impulse control and other related disorders
Patients should be regularly monitored for the development of impulse control disorders and related disorders including dopamine dysregulation syndrome. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathologic gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including rotigotine. In some patients, dopamine dysregulation syndrome was observed under the treatment with rotigotine. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Neuroleptic malignant syndrome

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

Dopamine agonist withdrawal syndrome

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

Abnormal thinking and behaviour

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

Fibrotic complications

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

Neuroleptics

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

Ophthalmologic monitoring

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

Heat application

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

Application site reactions

Application site skin reactions may occur and are usually mild or moderate in intensity. It is recommended that the application site should be rotated on a daily basis (e.g. from the right side to the left side and from the upper body to the lower body). The same site should not be used within 14 days. If application site reactions occur which last for more than a few days or are persistent, if there is an increase in severity, or if the skin reaction spreads outside the application site, an assessment of the risk/benefit balance for the individual patient should be conducted.

If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals, as exposure could lead to changes in the skin color.
If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Neupro is observed, Neupro should be discontinued.

Peripheral oedema

In clinical studies in Parkinson's patients, the 6 month-specific rates of peripheral oedema remained at about 4% through the entire observation period up to 36 months. Peripheral oedema has also been observed in clinical trials conducted in patients with RLS.

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.

Observed in patients with Parkinson's disease

Dopaminergic adverse reactions

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

Observed in patients with Restless Legs Syndrome

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. In long-term clinical studies with rotigotine, the majority of augmentation episodes were seen in the first and second years of treatment. Doses higher than the approved dose range for RLS should be avoided as this may lead to higher rates of augmentation (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential, contraception in females

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

Pregnancy

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

Breast-feeding

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

Fertility

For information on fertility studies, please see section 5.3.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Restless Legs Syndrome

Summary of the safety profile

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 748 Neupro- and 214 placebo-treated patients, 65.5% 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 application site reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of Neupro in 7.2% of subjects.

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.

Tabulated list of adverse reactions

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

System/organ classes acc. to MedDRA	Very common	Common	Uncommon	Rare	Not known
Immune system disorders		Hypersensitivity, which may include angioedema, tongue oedema and lip oedema			
Psychiatric disorders		Sleep attacks/sudden onset of sleep, sexual desire disorders[a] (incl. hypersexuality, libido increased), insomnia, sleep disorder, abnormal dreams, impulse-control disorders[a,d] (incl. pathological gambling, stereotypy/ punding, binge eating/eating disorder[b], compulsive shopping[c])	Obsessive-compulsive disorder, agitation[d]	Aggressive behaviour/ aggression[b], disorientation[d]	Dopamine dysregulation syndrome[c], perception disturbances[e] (incl. hallucination, hallucination visual, hallucination auditory, illusion), nightmare[e], paranoia[e], confusional state[e], psychotic disorder[e], delusion[e], delirium[e]

System/organ classes acc. to MedDRA	Very common	Common	Uncommon	Rare	Not known
Nervous system disorders	Headache	Somnolence			Dizziness[e], disturbances in consciousness NEC[e] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia[e], dizziness postural[e], lethargy[e], convulsion[e]
Eye disorders					Vision blurred[e], visual impairment[e], photopsia[e]
Ear and labyrinth disorders					Vertigo[e]
Cardiac disorders					Palpitations[e], atrial fibrillation[e], supraventricular tachycardia[e]
Vascular disorders		Hypertension	Orthostatic hypotension		Hypotension[e]
Respiratory, thoracic and mediastinal disorders					Hiccups[e]
Gastrointestinal disorders	Nausea	Vomiting, dyspepsia			Constipation[e], dry mouth[e], abdominal pain[e], diarrhoea[c]
Skin and subcutaneous tissue disorders		Pruritus			Erythema[e], hyperhidrosis[e], pruritus generalised[e], skin irritation[e], dermatitis contact[e], rash generalised[e]
Reproductive system and breast disorder					Erectile dysfunction[e]

System/organ classes acc. to MedDRA	Very common	Common	Uncommon	Rare	Not known
General disorders and administration site conditions	Application and instillation site reactions[a] (incl. erythema, pruritus, irritation, rash, dermatitis, vesicles, pain, eczema, inflammation, swelling, discolouration, papules, exfoliation, urticaria, hypersensitivity), asthenic conditions[a] (incl. fatigue, asthenia, malaise)	Irritability, oedema peripheral			
Investigations					Weight decreased[e], hepatic enzyme increased[e] (incl. AST, ALT, GGT), weight increased[e], heart rate increased[e], CPK increased[d,e]
Injury, poisoning and procedural complications					Fall[e]
Musculoskeletal and connective tissue disorders					Rhabdomyolysis[c]

[a] High Level Term
[b] Observed in open-label studies
[c] Observed during post-marketing
[d] Observed in 2011 data pool of double-blind placebo-controlled studies
[e] Observed in studies performed in patients with Parkinson's disease

Parkinson's disease

Summary of the safety profile

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

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

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

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

Tabulated list of adverse reactions

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

System/organ classes acc. to MedDRA	Very common	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity, which may include angioedema, tongue oedema and lip oedema		
Psychiatric disorders		Perception disturbances[a] (incl. hallucination, hallucination visual, hallucination auditory, illusion), insomnia, sleep disorder, nightmare, abnormal dreams, impulse-control disorders[a,d] (incl. pathological gambling, stereotypy/ punding, binge eating/eating disorder[b], compulsive shopping[c])	Sleep attacks/sudden onset of sleep, paranoia, sexual desire disorders[a] (incl. hypersexuality, libido increased), confusional state, disorientation[d], agitation[d]	Psychotic disorder, obsessive-compulsive disorder, aggressive behaviour/ aggression[b], delusion[d], delirium[d]	Dopamine dysregulation syndrome[c]

Nervous system disorders	Somnolence, dizziness, headache	Disturbances in consciousness NEC[a] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia, dizziness postural, lethargy		Convulsion	Dropped head syndrome[c,e]
Eye disorders			Vision blurred, visual impairment, photopsia		
Ear and labyrinth disorders		Vertigo			
Cardiac disorders		Palpitations	Atrial fibrillation	Supraventricular tachycardia	
Vascular disorders		Orthostatic hypotension, hypertension	Hypotension		
Respiratory, thoracic and mediastinal disorders		Hiccups			
Gastrointestinal disorders	Nausea, vomiting	Constipation, dry mouth, dyspepsia	Abdominal pain		Diarrhoea[c]
Skin and subcutaneous tissue disorders		Erythema, hyperhidrosis, pruritus	Pruritus generalised, skin irritation, dermatitis contact	Rash generalised	
Reproductive system and breast disorder			Erectile dysfunction		
General disorders and administration site conditions	Application and instillation site reactions[a] (incl. erythema, pruritus, irritation, rash, dermatitis, vesicles, pain, eczema, inflammation, swelling, discolouration, papules, exfoliation, urticaria, hypersensitivity)	Oedema peripheral, asthenic conditions[a] (incl. fatigue, asthenia, malaise)		Irritability	

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

[a] High Level Term
[b] Observed in open-label studies
[c] Observed during post-marketing
[d] Observed in 2011 data pool of double-blind placebo-controlled studies
[e] Only observed in Parkinson's disease patients

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 sections 4.4 and 4.7).

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including rotigotine (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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

Management

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Mechanism of action

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

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

Pharmacodynamic effects

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

Clinical efficacy and safety

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 ($p<0.0001$).

Augmentation

In 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. In a 5-year open-label treatment study, augmentation occurred in 11.9% of patients treated with the approved dosages for RLS (1-3 mg/24 h), and 5.1% were considered clinically significant. In this study, the majority of augmentation episodes occurred in the first and second years of treatment. Furthermore, in this study a higher dose of 4 mg/24 h that is unapproved in RLS was also used and led to higher rates of augmentation.

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 and three studies investigating specific aspects of Parkinson's disease.

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

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

In the double-blind study SP513 Part I, 213 patients received rotigotine, 227 received ropinirole and 117 patients received placebo. The patients were titrated to their optimal dose of rotigotine in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 8 mg/24 h over 4 weeks. In the ropinirole group, patients were titrated to their optimal dose up to a maximum of 24 mg/day over 13 weeks. Patients in each treatment group were maintained for 6 months.
At the end of the maintenance treatment in 92% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 8 mg/24 h. An improvement of 20% was seen in 52% of the subjects receiving rotigotine, 68% of the subjects receiving ropinirole and 30% of the subjects receiving placebo (Difference rotigotine *versus* placebo 21.7%, $CI_{95\%}$ 11.1%; 32.4%, difference ropinirole *versus* placebo 38.4%, $CI_{95\%}$ 28.1%; 48.6%, difference ropinirole *versus* rotigotine 16.6%, $CI_{95\%}$ 7.6%; 25.7%). The mean improvement in the UPDRS score (Parts II + III) was 6.83 points (baseline 33.2 points) in the rotigotine arm, 10.78 points in the ropinirole arm (baseline 32.2 points) and 2.33 points in the placebo arm (baseline 31.3 points). All differences between the active treatments and placebo were statistically significant. This study failed to demonstrate non-inferiority of rotigotine to ropinirole.

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

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

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

Two additional pivotal trials (SP650DB and SP515) were conducted in patients who were receiving concomitant levodopa therapy. The primary outcome assessment was the reduction in "off" time (hours). Efficacy was determined by the subject's response to therapy in terms of responder and absolute improvement in the time spent "off".

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

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

A further multinational double-blind study (SP889) was conducted in 287 patients with early or advanced stages of Parkinson's disease who had unsatisfactory early morning motor symptom control. 81.5% of these patients were on concomitant levodopa therapy. 190 patients received rotigotine, and 97 placebo. The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 16 mg/24 h over 8 weeks, followed by a maintenance period of 4 weeks. Early morning motor function, assessed by UPDRS part III, and nocturnal sleep disturbances, measured by the modified Parkinson's Disease Sleep Scale (PDSS-2), were co-primary outcome measures. At the end of maintenance, the mean UPDRS part III score had improved by 7.0 points in rotigotine-treated patients (baseline 29.6), and by 3.9 points in the placebo-group (baseline 32.0). Improvements in the mean PDSS-2 total score were 5.9 (rotigotine, baseline 19.3) and 1.9 points (placebo, baseline 20.5). Treatment differences for the coprimary variables were statistically significant ($p=0.0002$ and $p<0.0001$).

5.2 Pharmacokinetic properties

Absorption

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

Approximately 45% of the active substance within the patch is released to the skin in 24 hours. The absolute bioavailability after transdermal application is approximately 37%.

Rotating the site of patch application may result in day-to-day differences in plasma levels. Differences in bioavailability of rotigotine ranged from 2% (upper arm *versus* flank) to 46% (shoulder *versus* thigh). However, there is no indication of a relevant impact on the clinical outcome.

Distribution

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

Biotransformation

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

Elimination

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

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

Special patient groups

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

Hepatic and renal impairment

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

Paediatric population

Limited pharmacokinetic data obtained in adolescent patients with RLS (13-17 years, n=24) following treatment with multiple doses of 0.5 to 3mg/24h showed that systemic exposure to rotigotine was similar to that observed in adults. Efficacy/safety data is insufficient to establish a relation between exposure and response (see also paediatric information in section 4.2).

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

30 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Peel off sachet in a plastic box: 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 box contains 7, 14, 28, 30 or 84 (multipack containing 3 packs of 28) transdermal patches, individually sealed in sachets.

Not all pack sizes may be marketed.

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

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/001
EU/1/05/331/002
EU/1/05/331/015
EU/1/05/331/018
EU/1/05/331/057

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2006
Date of latest renewal: 22 January 2016

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal 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
Neupro 6 mg/24 h transdermal patch
Neupro 8 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

Neupro 4 mg/24 h transdermal patch
The outside of the backing layer is tan-coloured and imprinted with ‘Neupro 4 mg/24 h’.

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

Neupro 8 mg/24 h transdermal patch
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

The dose recommendations made are in nominal dose.

Dosing in patients with early-stage Parkinson's disease:
A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximum dose of 8 mg/24 h.
4 mg/24 h may be an effective dose in some patients. For most patients an effective dose is reached within 3 or 4 weeks at doses of 6 mg/24 h or 8 mg/24 h, respectively.
The maximum dose is 8 mg/24 h.

Dosing in patients with advanced stage Parkinson's disease with fluctuations:
A single daily dose should be initiated at 4 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximum dose of 16 mg/24 h.
4 mg/24 h or 6 mg/24 h may be effective doses in some patients. For most patients an effective dose is reached within 3 to 7 weeks at doses of 8 mg/24 h up to a maximum dose of 16 mg/24 h.

For doses higher than 8 mg/24 h multiple patches may be used to achieve the final dose e.g. 10 mg/24 h may be reached by combination of a 6 mg/24 h and a 4 mg/24 h patch.

Neupro is applied once a day. The patch should be applied at approximately the same time every day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different site of application.

If the patient forgets to apply the patch at the usual time of the day or if the patch becomes detached, another patch should be applied for the remainder of the day.

Treatment discontinuation

Neupro should be discontinued gradually. The daily dose should be reduced in steps of 2 mg/24 h with a dose reduction preferably every other day, until complete withdrawal of Neupro (see section 4.4).

Special populations

Hepatic impairment

Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment. Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Rotigotine has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment.

Renal impairment

Adjustment of the dose is not necessary in patients with mild to severe renal impairment, including those requiring dialysis. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population

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

Method of administration

Neupro is for transdermal use.

The patch should be applied to clean, dry, intact healthy skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. Reapplication to the same site within 14 days should be avoided. Neupro should not be placed on skin that is red, irritated or damaged (see section 4.4).

Use and handling

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the release liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is fold back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch should be pressed down firmly with the palm of the hand for about 30 seconds, so that it sticks well.

The patch should not be cut into pieces.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Magnetic resonance imaging and cardioversion

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

Orthostatic hypotension

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

Syncope

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

Sudden onset of sleep and somnolence

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

Impulse control and other related disorders

Patients should be regularly monitored for the development of impulse control disorders and related disorders including dopamine dysregulation syndrome. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathologic gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including rotigotine. In some patients, dopamine dysregulation syndrome was observed under the treatment with rotigotine. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Neuroleptic malignant syndrome

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

Dopamine agonist withdrawal syndrome

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

Abnormal thinking and behaviour

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

Fibrotic complications

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

Neuroleptics

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

Ophthalmologic monitoring

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

Heat application

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

Application site reactions

Application site skin reactions may occur and are usually mild or moderate in intensity. It is recommended that the application site should be rotated on a daily basis (e.g. from the right side to the left side and from the upper body to the lower body). The same site should not be used within 14 days. If application site reactions occur which last for more than a few days or are persistent, if there is an increase in severity, or if the skin reaction spreads outside the application site, an assessment of the risk/benefit balance for the individual patient should be conducted.
If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals, as exposure could lead to changes in the skin color.
If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Neupro is observed, Neupro should be discontinued.

Peripheral oedema

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

Dopaminergic adverse reactions

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

Sulphite sensitivity

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential, contraception in females

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

Pregnancy

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

Breast-feeding

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

Fertility

For information on fertility studies, please see section 5.3.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

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

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

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

Tabulated list of adverse reactions

The following table covers adverse drug reactions from the pooled studies mentioned above in patients with Parkinson's disease and from post-marketing experience. Within the system organ classes,

adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System/organ classes acc. to MedDRA	Very common	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity, which may include angioedema, tongue oedema and lip oedema		
Psychiatric disorders		Perception disturbances[a] (incl. hallucination, hallucination visual, hallucination auditory, illusion), insomnia, sleep disorder, nightmare, abnormal dreams, impulse-control disorders[a,d] (incl. pathological gambling, stereotypy/ punding, binge eating/eating disorder[b], compulsive shopping[c])	Sleep attacks/sudden onset of sleep, paranoia, sexual desire disorders[a] (incl. hypersexuality, libido increased), confusional state, disorientation[d], agitation[d]	Psychotic disorder, obsessive-compulsive disorder, aggressive behaviour/ aggression[b], delusion[d], delirium[d]	Dopamine dysregulation syndrome[c]
Nervous system disorders	Somnolence, dizziness, headache	Disturbances in consciousness NEC[a] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia, dizziness postural, lethargy		Convulsion	Dropped head syndrome[c]
Eye disorders			Vision blurred, visual impairment, photopsia		

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

Injury, poisoning and procedural complications		Fall			
Musculoskeletal and connective tissue disorders					Rhabdomyolysis[c]

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

Description of selected adverse reactions

Sudden onset of sleep and somnolence

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

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including rotigotine (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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

Management

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Mechanism of action

Rotigotine is believed to elicit its beneficial effect on Parkinson's disease by activation of the D_3, D_2 and D_1 receptors of the caudate-putamen in the brain.
The precise mechanism of action of rotigotine as a treatment of RLS is unknown. It is thought that rotigotine may exert its activity mainly via dopamine receptors.

Pharmacodynamic effects

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

Clinical efficacy and safety

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

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

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

In the double-blind study SP513 Part I, 213 patients received rotigotine, 227 received ropinirole and 117 patients received placebo. The patients were titrated to their optimal dose of rotigotine in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 8 mg/24 h over 4 weeks. In the ropinirole group, patients were titrated to their optimal dose up to a maximum of 24 mg/day over 13 weeks. Patients in each treatment group were maintained for 6 months.

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

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

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

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

Two additional pivotal trials (SP650DB and SP515) were conducted in patients who were receiving concomitant levodopa therapy. The primary outcome assessment was the reduction in "off" time (hours). Efficacy was determined by the subject's response to therapy in terms of responder and absolute improvement in the time spent "off".

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

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

A further multinational double-blind study (SP889) was conducted in 287 patients with early or advanced stages of Parkinson's disease who had unsatisfactory early morning motor symptom control. 81.5% of these patients were on concomitant levodopa therapy. 190 patients received rotigotine, and 97 placebo. The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 16 mg/24 h over 8 weeks, followed by a maintenance period of 4 weeks. Early morning motor function, assessed by UPDRS part III, and nocturnal sleep disturbances, measured by the modified Parkinson's Disease Sleep Scale (PDSS-2), were co-primary outcome measures. At the end of maintenance, the mean UPDRS part III score had improved by 7.0 points in rotigotine-treated patients (baseline 29.6), and by 3.9 points in the placebo-group (baseline 32.0). Improvements in the mean PDSS-2 total score were 5.9 (rotigotine, baseline 19.3) and 1.9 points (placebo, baseline 20.5). Treatment differences for the coprimary variables were statistically significant ($p=0.0002$ and $p<0.0001$).

5.2 Pharmacokinetic properties

Absorption

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

Approximately 45% of the active substance within the patch is released to the skin in 24 hours. The absolute bioavailability after transdermal application is approximately 37%.

Rotating the site of patch application may result in day-to-day differences in plasma levels. Differences in bioavailability of rotigotine ranged from 2% (upper arm *versus* flank) to 46% (shoulder *versus* thigh). However, there is no indication of a relevant impact on the clinical outcome.

Distribution

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

Biotransformation

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

Elimination

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

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

Special patient groups

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

Hepatic and renal impairment

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

5.3 Preclinical safety data

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

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

6. 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

30 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Peel off sachet in a plastic box: 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 box contains 7, 14, 28, 30 or 84 (multipack containing 3 packs of 28) transdermal patches, individually sealed in sachets.

Not all pack sizes may be marketed.

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

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Neupro 4 mg/24 h transdermal patch
EU/1/05/331/004
EU/1/05/331/005
EU/1/05/331/021
EU/1/05/331/024
EU/1/05/331/059

Neupro 6 mg/24 h transdermal patch
EU/1/05/331/007
EU/1/05/331/008
EU/1/05/331/027
EU/1/05/331/030
EU/1/05/331/060

Neupro 8 mg/24 h transdermal patch
EU/1/05/331/010
EU/1/05/331/011
EU/1/05/331/033
EU/1/05/331/036
EU/1/05/331/061

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2006
Date of latest renewal: 22 January 2016

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

The dose recommendations made are in nominal dose.

Dosing in patients with early-stage Parkinson's disease:
A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximum dose of 8 mg/24 h.
4 mg/24 h may be an effective dose in some patients. For most patients an effective dose is reached within 3 or 4 weeks at doses of 6 mg/24 h or 8 mg/24 h, respectively.
The maximum dose is 8 mg/24 h.

Dosing in patients with advanced stage Parkinson's disease with fluctuations:
A single daily dose should be initiated at 4 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximum dose of 16 mg/24 h.
4 mg/24 h or 6 mg/24 h may be effective doses in some patients. For most patients an effective dose is reached within 3 to 7 weeks at doses of 8 mg/24 h up to a maximum dose of 16 mg/24 h.

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)".

Neupro is applied once a day. The patch should be applied at approximately the same time every day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different site of application.

If the patient forgets to apply the patch at the usual time of the day or if the patch becomes detached, another patch should be applied for the remainder of the day.

Treatment discontinuation

Neupro should be discontinued gradually. The daily dose should be reduced in steps of 2 mg/24 h with a dose reduction preferably every other day, until complete withdrawal of Neupro (see section 4.4).

Special populations

Hepatic impairment

Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment. Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Rotigotine has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment.

Renal impairment

Adjustment of the dose is not necessary in patients with mild to severe renal impairment, including those requiring dialysis. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see section 5.2).

Paediatric population

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

Method of administration

Neupro is for transdermal use.

The patch should be applied to clean, dry, intact healthy skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. Reapplication to the same site within 14 days should be avoided. Neupro should not be placed on skin that is red, irritated or damaged (see section 4.4).

Use and handling

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the release liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is fold back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch should be pressed down firmly with the palm of the hand for about 30 seconds, so that it sticks well.

The patch should not be cut into pieces.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Magnetic resonance imaging and cardioversion

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

Orthostatic hypotension

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

Syncope

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

Sudden onset of sleep and somnolence

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

Impulse control and other related disorders

Patients should be regularly monitored for the development of impulse control disorders and related disorders including dopamine dysregulation syndrome. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathologic gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including rotigotine. In some patients, dopamine dysregulation syndrome was observed under the treatment with rotigotine. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Neuroleptic malignant syndrome

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

Dopamine agonist withdrawal syndrome

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

Abnormal thinking and behaviour

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

Fibrotic complications

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

Neuroleptics

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

Ophthalmologic monitoring

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

Heat application

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

Application site reactions

Application site skin reactions may occur and are usually mild or moderate in intensity. It is recommended that the application site should be rotated on a daily basis (e.g. from the right side to the left side and from the upper body to the lower body). The same site should not be used within 14 days. If application site reactions occur which last for more than a few days or are persistent, if there is an increase in severity, or if the skin reaction spreads outside the application site, an assessment of the risk/benefit balance for the individual patient should be conducted.
If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals, as exposure could lead to changes in the skin color.
If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Neupro is observed, Neupro should be discontinued.
Peripheral oedema

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

Dopaminergic adverse reactions

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

Sulphite sensitivity

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

Co-administration of rotigotine (3 mg/24 h) did not affect the pharmacodynamics and pharmacokinetics of oral contraceptives (0.03 mg ethinylestradiol, 0.15 mg levonorgestrel).

Interactions with other forms of hormonal contraception have not been investigated.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential, contraception in females

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

Pregnancy

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

Breast-feeding

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

Fertility

For information on fertility studies, please see section 5.3.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

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

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

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

Tabulated list of adverse reactions

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

System/organ classes acc. to MedDRA	Very common	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity, which may include angioedema, tongue oedema and lip oedema		
Psychiatric disorders		Perception disturbances[a] (incl. hallucination, hallucination visual, hallucination auditory, illusion), insomnia, sleep disorder, nightmare, abnormal dreams, impulse-control disorders[a,d] (incl. pathological gambling, stereotypy/ punding, binge eating/eating disorder[b], compulsive shopping[c])	Sleep attacks/sudden onset of sleep, paranoia, sexual desire disorders[a] (incl. hypersexuality, libido increased), confusional state, disorientation[d], agitation[d]	Psychotic disorder, obsessive-compulsive disorder, aggressive behaviour/ aggression[b], delusion[d], delirium[d]	Dopamine dysregulation syndrome[c]
Nervous system disorders	Somnolence, dizziness, headache	Disturbances in consciousness NEC[a] (incl. syncope, syncope vasovagal, loss of consciousness), dyskinesia, dizziness postural, lethargy		Convulsion	Dropped head syndrome[c]

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

Injury, poisoning and procedural complications		Fall			
Musculoskeletal and connective tissue disorders					Rhabdomyolysis[c]

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

Description of selected adverse reactions

Sudden onset of sleep and somnolence

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

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including rotigotine (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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

Management

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Mechanism of action

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

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

Pharmacodynamic effects

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

Clinical efficacy and safety

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

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

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

In the double-blind study SP513 Part I, 213 patients received rotigotine, 227 received ropinirole and 117 patients received placebo. The patients were titrated to their optimal dose of rotigotine in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 8 mg/24 h over 4 weeks. In the ropinirole group, patients were titrated to their optimal dose up to a maximum of 24 mg/day over 13 weeks. Patients in each treatment group were maintained for 6 months.

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

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

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

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

Two additional pivotal trials (SP650DB and SP515) were conducted in patients who were receiving concomitant levodopa therapy. The primary outcome assessment was the reduction in "off" time (hours). Efficacy was determined by the subject's response to therapy in terms of responder and absolute improvement in the time spent "off".

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

In the double-blind study SP515, 201 patients received rotigotine, 200 received pramipexole and 100 patients received placebo. The patients were titrated to their optimal dose of rotigotine in weekly increments of 2 mg/24 h starting at 4 mg/24 h to a maximum dose of 16 mg/24 h. In the pramipexole group, patients received 0,375 mg in the first week, 0.75 mg in the second week and were titrated further in weekly increments of 0.75 mg to their optimal dose up to a maximum of 4.5 mg/day. Patients in each treatment group were maintained for 4 months.

At the end of the maintenance treatment an improvement of at least 30% was seen in 60% of the subjects receiving rotigotine, 67% of the subjects receiving pramipexole and 35% of the subjects receiving placebo (Difference rotigotine *versus* placebo 25%, $CI_{95\%}$ 13%; 36%, difference pramipexole *versus* placebo 32%, $CI_{95\%}$ 21%; 43%, difference pramipexole *versus* rotigotine 7%, $CI_{95\%}$ -2%; 17%). The mean reduction in the "off" time was 2.5 hours in the rotigotine arm, 2.8 hours in the pramipexole arm and 0.9 hours in the placebo arm. All differences between the active treatments and placebo were statistically significant.

A further multinational double-blind study (SP889) was conducted in 287 patients with early or advanced stages of Parkinson's disease who had unsatisfactory early morning motor symptom control. 81.5% of these patients were on concomitant levodopa therapy. 190 patients received rotigotine, and 97 placebo. The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 16 mg/24 h over 8 weeks, followed by a maintenance period of 4 weeks. Early morning motor function, assessed by UPDRS part III, and nocturnal sleep disturbances, measured by the modified Parkinson's Disease Sleep Scale (PDSS-2), were co-primary outcome measures. At the end of maintenance, the mean UPDRS part III score had improved by 7.0 points in rotigotine-treated patients (baseline 29.6), and by 3.9 points in the placebo-group (baseline 32.0). Improvements in the mean PDSS-2 total score were 5.9 (rotigotine, baseline 19.3) and 1.9 points (placebo, baseline 20.5). Treatment differences for the coprimary variables were statistically significant ($p=0.0002$ and $p<0.0001$).

5.2 Pharmacokinetic properties

Absorption

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

Approximately 45% of the active substance within the patch is released to the skin in 24 hours. The absolute bioavailability after transdermal application is approximately 37%.

Rotating the site of patch application may result in day-to-day differences in plasma levels. Differences in bioavailability of rotigotine ranged from 2% (upper arm *versus* flank) to 46% (shoulder *versus* thigh). However, there is no indication of a relevant impact on the clinical outcome.

Distribution

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

Biotransformation

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

Elimination

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

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

Special patient groups

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

Hepatic and renal impairment

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

5.3 Preclinical safety data

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

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

6. 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

30 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Peel off sachet in a 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. Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

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: 22 January 2016

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

UCB Pharma S.A.
Chemin du Foriest
B-1420 Braine l'Alleud
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 7 [14] [28] [30] 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
14 transdermal patches
28 transdermal patches
30 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/038 [7 transdermal patches]
EU/1/05/331/040 [28 transdermal patches]
EU/1/05/331/041 [30 transdermal patches]
EU/1/05/331/056 [14 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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 PATCHES CONTAINING 3 BOXES OF 28 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

Multipack: 84 (3 packs of 28) transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/044 [84 transdermal patches (3 packs of 28)]

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
INTERMEDIATE BOX (WITHOUT BLUE BOX)
BOX OF 28 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

28 transdermal patches. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/044 [84 transdermal patches (3 packs of 28)]

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

BOX OF 7 [14] [28] [30] 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
14 transdermal patches
28 transdermal patches
30 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/001 [7 transdermal patches]
EU/1/05/331/002 [28 transdermal patches]
EU/1/05/331/015 [30 transdermal patches]
EU/1/05/331/057 [14 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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 PATCHES CONTAINING 3 BOXES OF 28 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

Multipack: 84 (3 packs of 28) transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/018 [84 transdermal patches (3 packs of 28)]

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
INTERMEDIATE BOX (WITHOUT BLUE BOX)
BOX OF 28 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

28 transdermal patches. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/018 [84 transdermal patches (3 packs of 28)]

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

BOX OF 7 [14] [28] [30] 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
14 transdermal patches
28 transdermal patches
30 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/047 [7 transdermal patches]
EU/1/05/331/049 [28 transdermal patches]
EU/1/05/331/050 [30 transdermal patches]
EU/1/05/331/058 [14 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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 PATCHES CONTAINING 3 BOXES OF 28 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

Multipack: 84 (3 packs of 28) transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/053 [84 transdermal patches (3 packs of 28)]

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
INTERMEDIATE BOX (WITHOUT BLUE BOX)
BOX OF 28 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

28 transdermal patches. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/053 [84 transdermal patches (3 packs of 28)]

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

BOX OF 7 [14] [28] [30] 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
14 transdermal patches
28 transdermal patches
30 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/004 [7 transdermal patches]
EU/1/05/331/005 [28 transdermal patches]
EU/1/05/331/021 [30 transdermal patches]
EU/1/05/331/059 [14 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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 PATCHES CONTAINING 3 BOXES OF 28 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

Multipack: 84 (3 packs of 28) transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/024 [84 transdermal patches (3 packs of 28)]

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
INTERMEDIATE BOX (WITHOUT BLUE BOX)
BOX OF 28 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

28 transdermal patches. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/024 [84 transdermal patches (3 packs of 28)]

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

BOX OF 7 [14] [28] [30] 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
14 transdermal patches
28 transdermal patches
30 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/007 [7 transdermal patches]
EU/1/05/331/008 [28 transdermal patches]
EU/1/05/331/027 [30 transdermal patches]
EU/1/05/331/060 [14 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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 PATCHES CONTAINING 3 BOXES OF 28 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

Multipack: 84 (3 packs of 28) transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/030 [84 transdermal patches (3 packs of 28)]

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
INTERMEDIATE BOX (WITHOUT BLUE BOX)
BOX OF 28 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

28 transdermal patches. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/030 [84 transdermal patches (3 packs of 28)]

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

BOX OF 7 [14] [28] [30] 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
14 transdermal patches
28 transdermal patches
30 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/010 [7 transdermal patches]
EU/1/05/331/011 [28 transdermal patches]
EU/1/05/331/033 [30 transdermal patches]
EU/1/05/331/061 [14 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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
OUTER LABEL (WITH BLUE BOX)
BOX OF 84 PATCHES CONTAINING 3 BOXES OF 28 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

Multipack: 84 (3 packs of 28) transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/036 [84 transdermal patches (3 packs of 28)]

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
INTERMEDIATE BOX (WITHOUT BLUE BOX)
BOX OF 28 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

28 transdermal patches. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/331/036 [84 transdermal patches (3 packs of 28)]

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
Each pack of 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

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

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

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

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

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

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

Read the package leaflet before use.
Transdermal use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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 Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

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
Neupro 3 mg/24 h transdermal patch
Rotigotine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Neupro is and what it is used for

What Neupro is
Neupro contains the active substance rotigotine.

It belongs to a group of medicines called 'dopamine agonists'. Dopamine is a messenger in the brain which is important for movement.

What Neupro is used for
Neupro is used in adults to treat the signs and symptoms of:
- **Restless Legs Syndrome (RLS) –** this can be associated with discomfort in your legs or arms, urges to move around, sleep disturbance and feeling tired or sleepy during the day. These symptoms are either reduced or their duration is shortened with Neupro treatment.

2. What you need to know before you use Neupro

Do not use Neupro if:
- you are **allergic** to **rotigotine** or any of the **other ingredients** of this medicine (listed in section 6)
- you need to have a **magnetic resonance imaging** (MRI) scan (diagnostic pictures of the inside of the body, created using magnetic rather than x-ray energy)
- you need '**cardioversion**' (specific treatment for abnormal heart beat).

You must take your Neupro patch off just before undergoing magnetic resonance imaging (MRI) or cardioversion to avoid skin burns because the patch contains aluminium. You can put a new patch on afterwards.

If any of the above apply to you, do not use Neupro. If you are not sure about this, talk to your doctor or pharmacist or nurse first.

Warnings and precautions
Talk to your doctor or pharmacist or nurse before using Neupro. This is because:
- your **blood pressure** needs checking regularly while using Neupro, especially at the start of the treatment. Neupro may affect your blood pressure.
- your **eyes** need checking regularly while using Neupro. If you notice any problems with your eyesight between checks, talk to your doctor straight away.
- if you have serious **liver problems**, your doctor may need to change the dose. If your liver problems get worse during treatment, talk to your doctor straight away.
- you may get **skin problems** caused by the patch – see '**Skin problems caused by the patch**' in section 4.
- you may **feel very sleepy** or **fall asleep suddenly** – see '**Driving and using machines**' in section 2.
- your symptoms of **Restless Legs Syndrome** may start earlier than usual, be more intense and involve other limbs. If you experience such symptoms either before or after beginning treatment with Neupro, contact your doctor as your treatment may need to be adjusted.

Medicines used to treat Restless Legs Syndrome should be reduced or stopped gradually. Tell your doctor if after stopping or reducing your Neupro treatment you experience symptoms such as depression, anxiety, fatigue, sweating or pain.

Loss of consciousness can occur
Neupro can cause loss of consciousness. This can happen especially when you start using Neupro or when your dose is increased. Tell your doctor if you lose consciousness or feel dizzy.

Changes in behaviour and abnormal thinking
Neupro can cause side effects that change your behaviour (how you act). You may find it helpful to tell a member of your family or carer that you are using this medicine and ask them to read this leaflet. This is so that your family or carer can tell you, or your doctor, if they are worried about any changes in your behaviour. Tell your doctor if you or your family/carer notices you are using the drug excessively or developing craving for large doses of Neupro or other medicines used to treat Restless Legs Syndrome.

See '**Changes to your behaviour and abnormal thinking**' in section 4 for more information.

Children and adolescents
Do **not** give this medicine to **children** below 18 years of age because it is not known if it is safe or effective in this age group**.**

Other medicines and Neupro
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Do not take the following medicines while using Neupro – because they may decrease its effect:
- 'anti-psychotic' medicines – used to treat certain mental illnesses
- metoclopramide – used to treat nausea (feeling sick) and vomiting.

Talk to your doctor before using Neupro if you are taking:
- sedating medicines such as benzodiazepines or medicines used to treat mental illness or depression.
- medicines that lower blood pressure. Neupro may decrease blood pressure when you stand up – this effect may be worsened by the medicines used to lower blood pressure.

Your doctor will let you know if it is safe to keep taking these medicines while using Neupro.

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

Pregnancy and breast-feeding
Do not use Neupro if you are pregnant. This is because the effects of rotigotine on pregnancy and the unborn baby are not known.

Do not breast-feed during treatment with Neupro. This is because rotigotine may pass into your breast milk and affect your baby. It is also likely to lower the amount of milk you produce.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines
Neupro may make you feel very sleepy and you may fall asleep very suddenly. If this happens, do not drive. In isolated cases, people have fallen asleep while driving and this has caused accidents.

Also do not use tools or machines if you feel very sleepy – or do anything else which may put others or yourself at risk of serious injury.

Neupro contains sodium metabisulphite (E223)
Sodium metabisulphite (E223) may rarely cause severe hypersensitivity (allergic) reactions and bronchospasm (breathing distress caused by narrowing of the airways).

3. How to use Neupro

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Which strength patches to use
Neupro is available in different strength patches which release the medicine over 24 hours. The strengths are 1 mg/24 h, 2 mg/24 h and 3 mg/24 h for the treatment of Restless Leg Syndrome.

- Your starting dose will be one, 1 mg/24 h patch each day.
- From the second week, your daily dose may be increased by 1 mg each week until you get to the right maintenance dose for you. This is when you and your doctor agree that the symptoms are being controlled well enough and the side effects of the medicines are acceptable.
- Please follow the instructions of the prescriber carefully.
- The maximum dose is 3 mg per day.

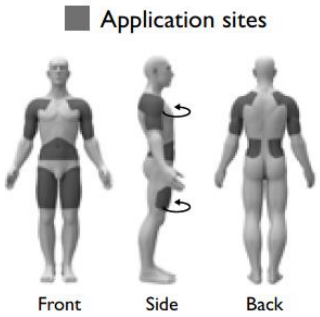
If you have to stop taking this medicine, see **'If you stop using Neupro'** in section 3.

How to use the Neupro patches
Neupro is a patch that is put on the skin.
- Make sure that you take the old patch off before putting on a new one.
- Stick the new patch on **a different area of the skin each day**.
- Leave the patch on your skin for 24 hours, then take it off and put on a new one.
- **Change the patches** at about 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 shown in grey on the pictures opposite:

- Shoulder or upper arm.
- Belly.
- Flank (your side, between the ribs and hips).
- Thigh or hip.



To avoid skin irritation

- Stick the patch onto a **different area of skin each day**. For example, put it on the right side of your body one day, then on the left side of your body the next day. Or on your upper body one day, then on your lower body the day after that.
- 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 **'Skin problems caused by the patch'** in section 4 for more information.

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** where you will put the patch. Also do not use them 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 edges of the patch lift, the patch may be taped down with adhesive medical tape.

If the patch falls off, put on a new patch for the rest of the day – then replace the patch at the usual time.

- Do **not** let the area of the patch **get hot** – for example too much sunlight, saunas, hot baths, heating pads or hot-water bottles. This is because the medicine may be released faster. If you think that too much heat has been applied, contact your doctor or pharmacist.
- Always check that the patch has not fallen off after activities such as **bathing, showering or exercising.**
- If the patch has **irritated your skin**, **keep** that area **protected from direct sunlight**. This is because it may change the colour of the skin.

How to use the patch

- Each patch is packed in a separate sachet.
- Before opening the sachet decide where you are going to stick this new patch and check you have removed any old patch.
- Stick the Neupro patch onto your skin as soon as you have opened the sachet and removed the release liner.

1.
To open the sachet, hold the sachet in both hands.

2.
Peel apart the foil.

3.
Open the sachet.

4.
Take the patch out of the sachet.

5.
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.

6.

- Bend the patch in half.

This makes the S-shaped break in the liner open up.

7.

- Peel off one side of the release liner.
- Do not touch the sticky side of the patch with your fingers.

8.

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

9.

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

10.

- Press the patch down firmly with the palm of your hand.
- Keep it pressed for about 30 seconds.

This makes sure the patch is touching the skin and the edges stick down well.

11.
Wash your hands with soap and water straight after handling the patch.

How to take off a used patch

- Slowly and carefully peel off the used patch.
- Gently wash the area with warm water and mild soap. This will remove any stickiness that stays on your skin. You can also use a little baby oil to remove any stickiness that will not wash off.
- Do not use alcohol or other dissolving liquids – such as nail polish remover. These may irritate your skin.

If you use more Neupro than you should
Using higher doses of Neupro than your doctor has prescribed may cause side effects such as feeling sick (nausea) or vomiting, low blood pressure, seeing or hearing things that are not real (hallucinations), feeling confused, very sleepy, having involuntary movements and convulsions.
In such cases, contact your doctor or hospital straight away. They will tell you what to do.

If you forget to change the patch at your usual time

- If you have forgotten to change the patch at your usual time, change it as soon as you remember. Take off 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, use a new patch at the usual time on the following day. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro
Do not stop using Neupro without talking to your doctor. A sudden stop could lead to a medical condition called ‘neuroleptic malignant syndrome’ which could be life-threatening. The signs include: loss of muscle movement (akinesia), rigid muscles, fever, unstable blood pressure, increased heart rate (tachycardia), confusion, low level of consciousness (such as a coma).

If your doctor says you should stop Neupro, the **daily dose** should be **lowered gradually**:

- **Restless Legs** Syndrome – lowered by 1 mg every other day.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor or pharmacist or nurse if you notice any side effects.

Side effects more likely at the start of treatment
You may **feel sick** (nausea) and **vomit at the start of treatment**. These effects are usually mild or moderate and only last for a short time. **Talk to your doctor** if they last for a long time or if you are worried about them.

Skin problems caused by the patch

- You may get redness and itching on the skin where the patch has been – these reactions are usually mild or moderate.
- The reactions normally go away after a few hours – once you remove the patch.
- **Talk to your doctor** if you have a skin reaction that lasts longer than a few days or is severe. Also do this if it spreads outside the area of skin that was covered by the patch.
- Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by the patch.
- 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.

Loss of consciousness can occur
Neupro can cause loss of consciousness. This can happen especially when you start using Neupro or when your dose is increased. Tell your doctor if you lose consciousness or feel dizzy.

Changes in behaviour and abnormal thinking
Tell your doctor if you notice any changes in behaviour, thinking or both, that are listed below. They will discuss ways of managing or reducing symptoms.

You may find it helpful to also tell a member of your family or carer that you are using this medicine and ask them to read this leaflet. This is so that your family or carer can tell you, or your doctor, if they are worried about any changes in your behaviour. Neupro can cause unusual urges or cravings which you cannot resist such as the impulse, drive or temptation to do things that could harm yourself or others.

These may include:

- strong impulse to gamble too much – even if this seriously affects you or your family
- altered or increased sexual interest and behaviour which causes significant concern to you or others – for example, an increased sex drive
- uncontrolled shopping or spending too much
- 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).

Neupro may cause other behaviours and abnormal thinking. These may include:

- abnormal thoughts about reality
- delusions and hallucinations (seeing or hearing things that are not real)
- confusion
- disorientation
- aggressive behaviour
- agitation
- delirium.

Tell your doctor if you notice any changes in behaviour, thinking or both that are listed above. They will discuss ways of managing or reducing symptoms.

Allergic reactions
Contact your doctor if you notice signs of an allergic reaction – these can include swelling of the face, tongue or lips.

Side effects when using Neupro for Restless Legs Syndrome
Tell your doctor or pharmacist if you get any of the following side effects:

Very common: may affect more than 1 in 10 people
- headache
- feeling sick (nausea)
- feeling weak (fatigue)
- skin irritations under the patch such as redness and itching

Common: may affect up to 1 in 10 people
- itching
- feeling irritable
- allergic reaction
- increased sex drive
- high blood pressure
- vomiting, heartburn
- swelling of legs and feet
- feeling sleepy, falling asleep suddenly without warning, difficulty in sleeping, sleep problems, having unusual dreams
- unable to resist the impulse to perform an action that is harmful involving excessive gambling, repetitive meaningless actions, uncontrolled shopping or spending too much
- binge eating (eating large amount of food in a short period of time) or compulsive eating (eating more food than normal and more than needed to satisfy hunger)

Uncommon: may affect up to 1 in 100 people
- feeling agitated
- feeling dizzy when standing up because of a fall in blood pressure

Rare: may affect up to 1 in 1,000 people
- being aggressive
- disorientation

Not known: it is not known how often these happen
- craving large doses of medicines like Neupro – more than needed for the illness. This is known as ‘dopamine dysregulation syndrome’ and can lead to use of too much Neupro
- seeing or hearing things that are not real (hallucinations)
- nightmares
- paranoia
- confusion
- psychotic disorders
- delusion
- delirium
- feeling dizzy
- loss of consciousness, involuntary movements (dyskinesia)
- involuntary muscle spasms (convulsion)
- blurry vision
- visual disturbances such as seeing colours or lights
- vertigo (sensation of whirling motion)

- feeling of heartbeat (palpitation)
- abnormal heart rhythm
- low blood pressure
- hiccups
- constipation, dry mouth
- stomach discomfort and pain
- diarrhoea
- redness, increased sweating
- generalised itching, skin irritation
- generalised rash
- unable to achieve or maintain an erection
- weight loss, weight increase
- increased or abnormal liver function test results
- increased heart rate
- increased levels of creatine phosphokinase (CPK) (CPK is an enzyme found mainly in skeletal muscles)
- falling
- rhabdomyolysis (a rare severe muscle disorder which causes pain, tenderness and weakness of the muscles and may lead to kidney problems)

Talk to your doctor or pharmacist if you notice any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Neupro

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and box.

Do not store above 30°C.

What to do with the used and unused patches
- Used patches still contain the active substance ‘rotigotine’, 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.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Neupro contains
The active substance is rotigotine.
- 1 mg/24 h:
  Each patch releases 1 mg of rotigotine per 24 hours. Each patch of 5 cm^2 contains 2.25 mg of rotigotine.
- 3 mg/24 h:
  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 the 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 or 3 mg/24 h.

Neupro is available in the following pack-sizes:
Boxes containing 7, 14, 28, 30 or 84 (multipack containing 3 packs of 28) patches, which are individually sealed in sachets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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B-1070 Bruxelles
Belgium

Manufacturer

UCB Pharma S.A.
Chemin du Foriest
B-1420 Braine l'Alleud
Belgium

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

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Other sources of information

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 because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Neupro is and what it is used for

What Neupro is
Neupro contains the active substance rotigotine.

It belongs to a group of medicines called 'dopamine agonists'. Dopamine is a messenger in the brain which is important for movement.

What Neupro is used for
Neupro is used in adults to treat the signs and symptoms of:
- **Parkinson's disease** – Neupro can be used on its own or with another medicine called levodopa.
- **Restless Legs Syndrome (RLS)** – this can be associated with discomfort in your legs or arms, urge to move around, sleep disturbance and feeling tired or sleepy during the day. These symptoms are either reduced or their duration is shortened with Neupro treatment.

2. What you need to know before you use Neupro

Do not use Neupro if:
- you are **allergic** to **rotigotine** or any of the **other ingredients** of this medicine (listed in section 6)
- you need to have a **magnetic resonance imaging** (MRI) scan (diagnostic pictures of the inside of the body, created using magnetic rather than x-ray energy)
- you need '**cardioversion**' (specific treatment for abnormal heart beat).

You must take your Neupro patch off just before undergoing magnetic resonance imaging (MRI) or cardioversion to avoid skin burns because the patch contains aluminium. You can put a new patch on afterwards.

If any of the above apply to you, do not use Neupro. If you are not sure about this, talk to your doctor, pharmacist or nurse first.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Neupro. This is because:
- your **blood pressure** needs checking regularly while using Neupro, especially at the start of the treatment. Neupro may affect your blood pressure.
- your **eyes** need checking regularly while using Neupro. If you notice any problems with your eyesight between checks, talk to your doctor straight away.
- if you have serious **liver problems**, your doctor may need to change the dose. If your liver problems get worse during treatment, talk to your doctor straight away.
- you may get **skin problems** caused by the patch – see '**Skin problems caused by the patch**' in section 4.
- you may **feel very sleepy** or **fall asleep suddenly** – see '**Driving and using machines**' in section 2.
- your symptoms of **Restless Legs Syndrome** may start earlier than usual, be more intense and involve other limbs. If you experience such symptoms either before or after beginning treatment with Neupro, contact your doctor as your treatment may need to be adjusted.

Medicines used to treat Parkinson's disease and Restless Legs Syndrome should be reduced or stopped gradually. Tell your doctor if after stopping or reducing your Neupro treatment you experience symptoms such as depression, anxiety, fatigue, sweating or pain.

Loss of consciousness can occur
Neupro can cause loss of consciousness. This can happen especially when you start using Neupro or when your dose is increased. Tell your doctor if you lose consciousness or feel dizzy.

Changes in behaviour and abnormal thinking
Neupro can cause side effects that change your behaviour (how you act). You may find it helpful to tell a member of your family or carer that you are using this medicine and ask them to read this leaflet. This is so that your family or carer can tell you, or your doctor, if they are worried about any changes in your behaviour.

These include:
- craving for large doses of Neupro or other medicines used to treat Parkinson's disease and Restless Legs Syndrome.
- unusual urges or cravings which you cannot resist and that could harm yourself or others – the symptoms are mainly seen in patients with Parkinson's disease
- abnormal thinking or behaviour – most of the symptoms occur more frequently in patients with Parkinson's disease.

See '**Changes to your behaviour and abnormal thinking**' in section 4 for more information.

Children and adolescents
Do **not** give this medicine to **children** below 18 years of age because it is not known if it is safe or effective in this age group.

Other medicines and Neupro
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

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

Do not take the following medicines while using Neupro – because they may decrease its effect:
- 'anti-psychotic' medicines – used to treat certain mental illnesses
- metoclopramide – used to treat nausea (feeling sick) and vomiting.

Talk to your doctor before using Neupro if you are taking:
- sedating medicines such as benzodiazepines or medicines used to treat mental illness or depression.
- medicines that lower blood pressure. Neupro may decrease blood pressure when you stand up – this effect may be worsened by the medicines used to lower blood pressure.

Your doctor will let you know if it is safe to keep taking these medicines while using Neupro.

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

Pregnancy and breast-feeding
Do not use Neupro if you are pregnant. This is because the effects of rotigotine on pregnancy and the unborn baby are not known.

Do not breast-feed during treatment with Neupro. This is because rotigotine may pass into your breast milk and affect your baby. It is also likely to lower the amount of milk you produce.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines
Neupro may make you feel very sleepy and you may fall asleep very suddenly. If this happens, do not drive. In isolated cases, people have fallen asleep while driving and this has caused accidents.

Also do not use tools or machines if you feel very sleepy – or do anything else which may put others or yourself at risk of serious injury.

Neupro contains sodium metabisulphite (E223)
Sodium metabisulphite (E223) may rarely cause severe hypersensitivity (allergic) reactions and bronchospasm (breathing distress caused by narrowing of the airways).

3. How to use Neupro

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Which strength patches to use
The dose of Neupro will depend on your illness – see below.

Neupro is available in different strength patches which release the medicine over 24 hours. The strengths are 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. The patches of 1 mg/24 h and 3 mg/24 h are used for the treatment of Restless Leg Syndrome, while the patches of 4 mg/24 h, 6 mg/24 h and 8 mg/24 h are used for the treatment of Parkinson's disease. The patches of 2 mg/24 h are used for the treatment of Parkinson's disease and Restless Leg Syndrome.
- You may have to use more than one patch to reach your dose, as prescribed by your doctor.
- For doses higher than 8 mg/24 h (doses prescribed by your doctor above the available strengths), multiple patches must be applied to achieve the final dose. For example the 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.
- The patches should not be cut into pieces.

Treatment of Parkinson's disease
Patients not taking levodopa – early stage of Parkinson's disease

- Your starting daily dose will be one 2 mg/24 h patch each day.
- From the second week your daily dose may be increased by 2 mg each week – until you get to the right maintenance dose for you.
- For most patients, the right dose is between 6 mg and 8 mg each day. This is normally reached within 3 to 4 weeks.
- The maximum dose is 8 mg each day.

Patients taking levodopa – advanced stage of Parkinson's disease

- Your starting daily dose will be one 4 mg/24 h patch each day.
- From the second week your daily dose will be increased by 2 mg each week – until you get to the right maintenance dose for you.
- For most patients, the right dose is between 8 mg and 16 mg each day. This is normally reached within 3 to 7 weeks.
- The maximum dose is 16 mg each day.

Treatment of Restless Legs Syndrome

- Your starting dose will be one 1 mg/24 h patch each day.
- From the second week, your daily dose may be increased by 1 mg each week – until you get to the right maintenance dose for you. This is when you and your doctor agree that the symptoms are being controlled well enough and the side effects of the medicines are acceptable.
- The maximum dose is 3 mg per day.

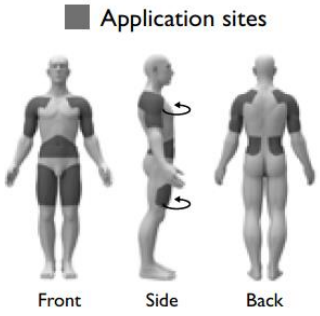
If you have to stop taking this medicine, see **'If you stop using Neupro'** in section 3.

How to use the Neupro patches:
Neupro is a patch that is put on the skin.

- Make sure that you take the old patch off before putting on a new one.
- Stick the new patch on **a different area of the skin each day**.
- Leave the patch on your skin for 24 hours, then take it off and put on a new one.
- **Change the patches** at about 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 shown in grey on the pictures opposite:

- Shoulder or upper arm.
- Belly.
- Flank (your side, between the ribs and hips).
- Thigh or hip.



To avoid skin irritation

- Stick the patch onto a **different area of skin each day**. For example, put it on the right side of your body one day, then on the left side of your body the next day. Or on your upper body one day, then on your lower body the day after that.
- 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 **'Skin problems caused by the patch'** in section 4 for more information.

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** where you will put the patch. Also do not use them 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 edges of the patch lift, the patch may be taped down with adhesive medical tape.

If the patch falls off, put on a new patch for the rest of the day – then replace the patch at the usual time.

- Do **not** let the area of the patch **get hot** – for example too much sunlight, saunas, hot baths, heating pads or hot-water bottles. This is because the medicine may be released faster. If you think that too much heat has been applied, contact your doctor or pharmacist.
- Always check that the patch has not fallen off after activities such as **bathing, showering or exercising.**
- If the patch has **irritated your skin, keep** that area **protected from direct sunlight**. This is because it may change the colour of the skin.

How to use the patch

- Each patch is packed in a separate sachet.
- Before opening the sachet decide where you are going to stick this new patch and check you have removed any old patch.
- Stick the Neupro patch onto your skin as soon as you have opened the sachet and removed the release liner.

1.
To open the sachet, hold the sachet in both hands.

2.
Peel apart the foil.

3.
Open the sachet.

4.
Take the patch out of the sachet.

5.
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.

6.

- Bend the patch in half.

This makes the S-shaped break in the liner open up.

7.

- Peel off one side of the release liner.
- Do not touch the sticky side of the patch with your fingers.

8.

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

9.
Fold back the other half of the patch and remove the other side of the release liner.

10.

- Press the patch down firmly with the palm of your hand.
- Keep it pressed for about 30 seconds.

This makes sure the patch is touching the skin and the edges stick down well.

11.

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

How to take off a used patch

- Slowly and carefully peel off the used patch.
- Gently wash the area with warm water and mild soap. This will remove any stickiness that stays on your skin. You can also use a little baby oil to remove any stickiness that will not wash off.
- Do not use alcohol or other dissolving liquids – such as nail polish remover. These may irritate your skin.

If you use more Neupro than you should

Using higher doses of Neupro than your doctor has prescribed may cause side effects such as feeling sick (nausea) or vomiting, low blood pressure, seeing or hearing things that are not real (hallucinations), feeling confused, very sleepy, having involuntary movements and convulsions.
In such cases, contact your doctor or hospital straight away. They will tell you what to do.

If you forget to change the patch at your usual time

- If you have forgotten to change the patch at your usual time, change it as soon as you remember Take off 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, use a new patch at the usual time on the following day. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro

Do not stop using Neupro without talking to your doctor. A sudden stop could lead to a medical condition called 'neuroleptic malignant syndrome' which could be life-threatening. The signs include: loss of muscle movement (akinesia), rigid muscles, fever, unstable blood pressure, increased heart rate (tachycardia), confusion, low level of consciousness (such as a coma).

If your doctor says you should stop Neupro, the **daily dose** should be **lowered gradually**:

- **Parkinson's disease** – lowered by 2 mg every other day.
- **Restless Legs Syndrome** – lowered by 1 mg every other day.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor, pharmacist or nurse if you notice any side effects.

Side effects more likely at the start of treatment
You may **feel sick** (nausea) and **vomit at the start of treatment**. These effects are usually mild or moderate and only last for a short time. **Talk to your doctor** if they last for a long time or if you are worried about them.

Skin problems caused by the patch
- You may get redness and itching on the skin where the patch has been – these reactions are usually mild or moderate.
- The reactions normally go away after a few hours – once you remove the patch.
- **Talk to your doctor** if you have a skin reaction that lasts longer than a few days or is severe. Also do this if it spreads outside the area of skin that was covered by the patch.
- Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by the patch.
- 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.

Loss of consciousness can occur
Neupro can cause loss of consciousness. This can happen especially when you start using Neupro or when your dose is increased. Tell your doctor if you lose consciousness or feel dizzy.

Changes in behaviour and abnormal thinking
Tell your doctor if you notice any changes in behaviour, thinking or both, that are listed below. They will discuss ways of managing or reducing symptoms.

You may find it helpful to also tell a member of your family or carer that you are using this medicine and ask them to read this leaflet. This is so that your family or carer can tell you, or your doctor, if they are worried about any changes in your behaviour. Neupro can cause unusual urges or cravings which you cannot resist such as the impulse, drive or temptation to do things that could harm yourself or others – the symptoms are mainly seen in patients with Parkinson's disease.

These may include:
- strong impulse to gamble too much – even if this seriously affects you or your family
- altered or increased sexual interest and behaviour which causes significant concern to you or others – for example, an increased sex drive
- uncontrolled shopping or spending too much
- 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).

Neupro may cause other behaviours and abnormal thinking. These may include:
- abnormal thoughts about reality
- delusions and hallucinations (seeing or hearing things that are not real)
- confusion
- disorientation
- aggressive behaviour
- agitation
- delirium.

Tell your doctor if you notice any changes in behaviour, thinking or both that are listed above. They will discuss ways of managing or reducing symptoms.

Allergic reactions
Contact your doctor if you notice signs of an allergic reaction – these can include swelling of the face, tongue or lips.

Side effects when using Neupro for Parkinson's disease
Tell your doctor, pharmacist or nurse if you get any of the following side effects:

Very common: may affect more than 1 in 10 people
- headache
- feeling sleepy or dizzy
- feeling sick (nausea), vomiting
- skin reactions under the patch such as redness and itching

Common: may affect up to 1 in 10 people
- falling
- hiccups
- weight loss
- swelling of legs and feet
- feeling weak (fatigue), feeling tired
- feeling of heartbeat (palpitation)
- constipation, dry mouth, heartburn
- redness, increased sweating, itching
- vertigo (sensation of whirling motion)
- seeing or hearing things that are not real (hallucinations)
- low blood pressure when standing up, high blood pressure
- difficulty falling asleep, sleep disorder, difficulty sleeping, nightmare, unusual dreams
- movements you cannot control related to Parkinson's disease (dyskinesia)
- fainting, feeling dizzy when standing up because of fall in blood pressure
- unable to resist the impulse to perform an action that is harmful involving excessive gambling, repetitive meaningless actions, uncontrolled shopping or spending too much
- binge eating (eating large amount of food in a short period of time), compulsive eating (eating more food than normal and more than needed to satisfy hunger)

Uncommon: may affect up to 1 in 100 people
- blurred vision
- weight increase
- allergic reaction
- low blood pressure
- increased heart rate
- increased sex drive
- abnormal heart beat
- stomach discomfort and pain
- generalised itching, skin irritation
- falling asleep suddenly without warning
- unable to achieve or maintain an erection
- feeling agitated, disorientated, confused or paranoid
- increased or abnormal liver test results
- sight problems such as seeing colours or lights
- increased levels of creatine phosphokinase (CPK) (CPK is an enzyme found mainly in skeletal muscles).

Rare: may affect up to 1 in 1,000 people
- delusion
- delirium
- feeling irritable
- being aggressive
- psychotic disorders
- rash over larger parts of the body
- involuntary muscle spasms (convulsion)

Not known: it is not known how often these happen
- craving large doses of medicines like Neupro – more than needed for the illness. This is known as 'dopamine dysregulation syndrome' and can lead to use of too much Neupro.
- diarrhoea
- dropped head syndrome
- rhabdomyolysis (a rare severe muscle disorder which causes pain, tenderness and weakness of the muscles and may lead to kidney problems)

Tell your doctor, pharmacist or nurse if you notice any of the side effects listed above.

Side effects when using Neupro for Restless Legs Syndrome
Tell your doctor or pharmacist if you notice any of the following side effects:

Very common: may affect more than 1 in 10 people
- headache
- feeling sick (nausea)
- feeling weak (fatigue)
- skin irritations under the patch such as redness and itching

Common: may affect up to 1 in 10 people
- itching
- feeling irritable
- allergic reaction
- increased sex drive
- high blood pressure
- vomiting, heartburn
- swelling of legs and feet
- feeling sleepy, falling asleep suddenly without warning, difficulty in sleeping, sleep problems, having unusual dreams
- unable to resist the impulse to perform an action that is harmful involving excessive gambling, repetitive meaningless actions, uncontrolled shopping or spending too much
- binge eating (eating large amount of food in a short period of time) or compulsive eating (eating more food than normal and more than needed to satisfy hunger)

Uncommon: may affect up to 1 in 100 people
- feeling agitated
- feeling dizzy when standing up because of a fall in blood pressure

Rare: may affect up to 1 in 1,000 people
- being aggressive
- disorientation

Not known: it is not known how often these happen
- craving large doses of medicines like Neupro – more than needed for the illness. This is known as 'dopamine dysregulation syndrome' and can lead to use of too much Neupro
- seeing or hearing things that are not real (hallucinations)
- nightmares
- paranoia
- confusion
- psychotic disorders
- delusion
- delirium
- feeling dizzy
- loss of consciousness, involuntary movements (dyskinesia)
- involuntary muscle spasms (convulsion)

- blurry vision
- visual disturbances such as seeing colours or lights
- vertigo (sensation of whirling motion)
- feeling of heartbeat (palpitation)
- abnormal heart rhythm
- low blood pressure
- hiccups
- constipation, dry mouth
- stomach discomfort and pain
- diarrhoea
- redness, increased sweating
- generalised itching, skin irritation
- generalised rash
- unable to achieve or maintain an erection
- weight loss, weight increase
- increased or abnormal liver function test results
- increased heart rate
- increased levels of creatine phosphokinase (CPK) (CPK is an enzyme found mainly in skeletal muscles)
- falling
- rhabdomyolysis (a rare severe muscle disorder which causes pain, tenderness and weakness of the muscles and may lead to kidney problems)

Talk to your doctor or pharmacist if you notice any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Neupro

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and box.

Do not store above 30°C.

What to do with the used and unused patches
- Used patches still contain the active substance ‘rotigotine’, 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.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other 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 the 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:
Boxes containing 7, 14, 28, 30 or 84 (multipack containing 3 packs of 28) patches, which are individually sealed in sachets.

Not all pack sizes may be marketed.

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This leaflet was last revised in {MM/YYYY}

Other sources of information

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
Neupro 6 mg/24 h transdermal patch
Neupro 8 mg/24 h transdermal patch
Rotigotine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Neupro is and what it is used for

What Neupro is
Neupro contains the active substance rotigotine.

It belongs to a group of medicines called 'dopamine agonists'. Dopamine is a messenger in the brain which is important for movement

What Neupro is used for
Neupro is used in adults to treat the signs and symptoms of:
- **Parkinson's disease** – Neupro can be used on its own or with another medicine called levodopa.

2. What you need to know before you use Neupro

Do not use Neupro if:
- you are **allergic** to **rotigotine** or any of the **other ingredients** of this medicine (listed in section 6)
- you need to have a **magnetic resonance imaging** (MRI) scan (diagnostic pictures of the inside of the body, created using magnetic rather than x-ray energy)
- you need '**cardioversion**' (specific treatment for abnormal heart beat).

You must take your Neupro patch off just before undergoing magnetic resonance imaging (MRI) or cardioversion to avoid skin burns because the patch contains aluminium. You can put a new patch on afterwards.

If any of the above apply to you, do not use Neupro. If you are not sure about this, talk to your doctor or pharmacist or nurse first.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Neupro. This is because:
- your **blood pressure** needs checking regularly while using Neupro, especially at the start of the treatment. Neupro may affect your blood pressure.
- your **eyes** need checking regularly while using Neupro. If you notice any problems with your eyesight between checks, talk to your doctor straight away.
- if you have serious **liver problems**, your doctor may need to change the dose. If your liver problems get worse during treatment, talk to your doctor straight away.
- you may get **skin problems** caused by the patch – see '**Skin problems caused by the patch**' in section 4.
- you may **feel very sleepy** or **fall asleep suddenly** – see '**Driving and using machines**' in section 2.

If you experience these symptoms after beginning treatment with Neupro, contact your doctor.

Medicines used to treat Parkinson's disease should be reduced or stopped gradually. Tell your doctor if after stopping or reducing your Neupro treatment you experience symptoms such as depression, anxiety, fatigue, sweating or pain.

Loss of consciousness can occur
Neupro can cause loss of consciousness. This can happen especially when you start using Neupro or when your dose is increased. Tell your doctor if you lose consciousness or feel dizzy.

Changes in behaviour and abnormal thinking

Neupro can cause side effects that change your behaviour (how you act). You may find it helpful to tell a member of your family or carer that you are using this medicine and ask them to read this leaflet. This is so that your family or carer can tell you, or your doctor, if they are worried about any changes in your behaviour.
These include:
- craving for large doses of Neupro or other medicines used to treat Parkinson's disease.
- unusual urges or cravings which you cannot resist and that could harm yourself or others
- abnormal thinking or behaviour.

See '**Changes to your behaviour and abnormal thinking**' in section 4 for more information.

Children and adolescents
Do **not** give this medicine to **children** below 18 years of age because it is not known if it is safe or effective in this age group.

Other medicines and Neupro
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

If you are treated with Neupro and levodopa at the same time, some side effects may get more serious. This includes seeing or hearing things that are not real (hallucinations), movements you cannot control related to Parkinson's disease ('dyskinesia'), and swelling of legs and feet.
Do not take the following medicines while using Neupro – because they may decrease its effect:
- 'anti-psychotic' medicines – used to treat certain mental illnesses
- metoclopramide – used to treat nausea (feeling sick) and vomiting.

Talk to your doctor before using Neupro if you are taking:
- sedating medicines such as benzodiazepines or medicines used to treat mental illness or depression.
- medicines that lower blood pressure. Neupro may decrease blood pressure when you stand up – this effect may be worsened by the medicines used to lower blood pressure.

Your doctor will let you know if it is safe to keep taking these medicines while using Neupro.

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

Pregnancy and breast-feeding
Do not use Neupro if you are pregnant. This is because the effects of rotigotine on pregnancy and the unborn baby are not known.

Do not breast-feed during treatment with Neupro. This is because rotigotine may pass into your breast milk and affect your baby. It is also likely to lower the amount of milk you produce.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines
Neupro may make you feel very sleepy, and you may fall asleep very suddenly. If this happens, do not drive. In isolated cases, people have fallen asleep while driving and this has caused accidents.

Also do not use tools or machines if you feel very sleepy – or do anything else which may put others or yourself at risk of serious injury.

Neupro contains sodium metabisulphite (E223)
Sodium metabisulphite (E223) may rarely cause severe hypersensitivity (allergic) reactions and bronchospasm (breathing distress caused by narrowing of the airways).

3. How to use Neupro

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Which strength patches to use
The dose of Neupro will depend on your illness – see below.

Neupro is available in different strength patches which release the medicine over 24 hours. The strengths are 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h for the treatment of Parkinson's disease.

- You may have to use more than one patch to reach your dose, as prescribed by your doctor.
- For doses higher than 8 mg/24 h (doses prescribed by your doctor above the available strengths), multiple patches must be applied to achieve the final dose. For example a daily dose of 10 mg/24 h may be reached by applying one patch of 6 mg/24 h and one patch of 4 mg/24 h.
- The patches should not be cut into pieces.

Treatment of Parkinson's disease
Patients not taking levodopa – early stage of Parkinson's disease
- Your starting daily dose will be one 2 mg/24 h patch each day.
- From the second week your daily dose may be increased by 2 mg each week – until you get to the right maintenance dose for you.
- For most patients, the right dose is between 6 mg and 8 mg each day. This is normally reached within 3 to 4 weeks.
- The maximum dose is 8 mg each day.

Patients taking levodopa – advanced stage of Parkinson's disease

- Your starting daily dose will be one 4 mg/24 h patch each day.
- From the second week your daily dose will be increased by 2 mg each week – until you get to the right maintenance dose for you.
- For most patients, the right dose is between 8 mg and 16 mg each day. This is normally reached within 3 to 7 weeks.
- The maximum dose is 16 mg each day.

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

How to use the Neupro patches

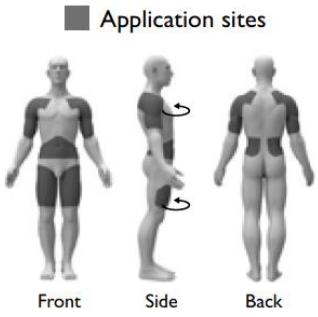
Neupro is a patch that is put on the skin.

- Make sure that you take the old patch off before putting on a new one.
- Stick the new patch on **a different area of the skin each day**.
- Leave the patch on your skin for 24 hours, then take it off and put on a new one.
- **Change the patches** at about 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 shown in grey on the pictures opposite:

- Shoulder or upper arm.
- Belly.
- Flank (your side, between the ribs and hips).
- Thigh or hip.



To avoid skin irritation

- Stick the patch onto a **different area of skin each day**. For example, put it on the right side of your body one day, then on the left side of your body the next day. Or on your upper body one day, then on your lower body the day after that.
- 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 **Skin problems caused by the patch'** in section 4 for more information.

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** where you will put the patch. Also do not use them 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 edges of the patch lift, the patch may be taped down with adhesive medical tape.

If the patch falls off, put on a new patch for the rest of the day – then replace the patch at the usual time.

- Do **not** let the area of the patch **get hot** – for example too much sunlight, saunas, hot baths, heating pads or hot-water bottles. This is because the medicine may be released faster. If you think that too much heat has been applied, contact your doctor or pharmacist.
- Always check that the patch has not fallen off after activities such as **bathing, showering or exercising.**
- If the patch has **irritated your skin, keep** that area **protected from direct sunlight**. This is because it may change the colour of the skin.

How to use the patch
- Each patch is packed in a separate sachet.
- Before opening the sachet decide where you are going to stick this new patch and check you have removed any old patch.
- Stick the Neupro patch onto your skin as soon as you have opened the sachet and removed the release liner.

1.
To open the sachet, hold the sachet in both hands.

2.
Peel apart the foil.

3.
Open the sachet.

4.
Take the patch out of the sachet.

5.
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.

6.

- Bend the patch in half.

This makes the S-shaped break in the liner open up.

7.

- Peel off one side of the release liner.
- Do not touch the sticky side of the patch with your fingers.

8.

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

9.

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

10.

- Press the patch down firmly with the palm of your hand.
- Keep it pressed for about 30 seconds.

This makes sure the patch is touching the skin and the edges stick down well.

11.

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

How to take off a used patch

- Slowly and carefully peel off the used patch.
- Gently wash the area with warm water and mild soap. This will remove any stickiness that stays on your skin. You can also use a little baby oil to remove any stickiness that will not wash off.
- Do not use alcohol or other dissolving liquids – such as nail polish remover. These may irritate your skin.

If you use more Neupro than you should
Using higher doses of Neupro than your doctor has prescribed may cause side effects such as feeling sick (nausea) or vomiting, low blood pressure, seeing or hearing things that are not real (hallucinations), feeling confused, very sleepy, having involuntary movements and convulsions. In such cases, contact your doctor or hospital straight away. They will tell you what to do.

If you forget to change the patch at your usual time
- If you have forgotten to change the patch at your usual time, change it as soon as you remember. Take off 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, use a new patch at the usual time on the following day. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro
Do not stop using Neupro without talking to your doctor. A sudden stop could lead to a medical condition called 'neuroleptic malignant syndrome' which could be life-threatening. The signs include: loss of muscle movement (akinesia), rigid muscles, fever, unstable blood pressure, increased heart rate (tachycardia), confusion, low level of consciousness (such as a coma).

If your doctor says you should stop Neupro, the **daily dose** should be **lowered gradually:**
- **Parkinson's disease** – lowered by 2 mg every other day.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor or pharmacist or nurse if you notice any side effects.

Side effects more likely at the start of treatment
You may **feel sick** (nausea) and **vomit at the start of treatment**. These effects are usually mild or moderate and only last for a short time. **Talk to your doctor** if they last for a long time or if you are worried about them.

Skin problems caused by the patch
- You may get redness and itching on the skin where the patch has been – these reactions are usually mild or moderate.
- The reactions normally go away after a few hours – once you remove the patch.
- **Talk to your doctor** if you have a skin reaction that lasts longer than a few days or is severe. Also do this if it spreads outside the area of skin that was covered by the patch.
- Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by the patch.
- 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.

Loss of consciousness can occur
Neupro can cause loss of consciousness. This can happen especially when you start using Neupro or when your dose is increased. Tell your doctor if you lose consciousness or feel dizzy.

Changes in behaviour and abnormal thinking
Tell your doctor if you notice any changes in behaviour, thinking or both, that are listed below. They will discuss ways of managing or reducing symptoms.

You may find it helpful to also tell a member of your family or carer that you are using this medicine and ask them to read this leaflet. This is so that your family or carer can tell you, or your doctor, if they are worried about any changes in your behaviour. Neupro can cause unusual urges or cravings which you cannot resist such as the impulse, drive or temptation to do things that could harm yourself or others.

These may include:
- strong impulse to gamble too much – even if this seriously affects you or your family
- altered or increased sexual interest and behaviour which causes significant concern to you or others – for example, an increased sex drive
- uncontrolled shopping or spending too much
- 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).

Neupro may cause other behaviours and abnormal thinking. These may include:
- abnormal thoughts about reality
- delusions and hallucinations (seeing or hearing things that are not real)
- confusion
- disorientation
- aggressive behaviour
- agitation
- delirium.

Tell your doctor if you notice any changes in behaviour, thinking or both that are listed above. They will discuss ways of managing or reducing symptoms.

Allergic reactions
Contact your doctor if you notice signs of an allergic reaction – these can include swelling of the face, tongue or lips.

Side effects when using Neupro for Parkinson's disease
Tell your doctor, pharmacist or nurse if you get any of the following side effects:

Very common: may affect more than 1 in 10 people
- headache
- feeling sleepy or dizzy
- feeling sick (nausea), vomiting
- skin reactions under the patch such as redness and itching

Common: may affect up to 1 in 10 people
- falling
- hiccups
- weight loss
- swelling of legs and feet
- feeling weak (fatigue), feeling tired
- feeling of heartbeat (palpitation)
- constipation, dry mouth, heartburn
- redness, increased sweating, itching
- vertigo (sensation of whirling motion)
- seeing or hearing things that are not real (hallucinations)
- low blood pressure when standing up, high blood pressure
- difficulty falling asleep, sleep disorder, difficulty sleeping, nightmare, unusual dreams
- movements you cannot control related to Parkinson's disease (dyskinesia)
- fainting, feeling dizzy when standing up because of fall in blood pressure

- unable to resist the impulse to perform an action that is harmful involving excessive gambling, repetitive meaningless actions, uncontrolled shopping or spending too much
- binge eating (eating large amount of food in a short period of time), compulsive eating (eating more food than normal and more than needed to satisfy hunger)

Uncommon: may affect up to 1 in 100 people
- blurred vision
- weight increase
- allergic reaction
- low blood pressure
- increased heart rate
- increased sex drive
- abnormal heart beat
- stomach discomfort and pain
- generalised itching, skin irritation
- falling asleep suddenly without warning
- unable to achieve or maintain an erection
- feeling agitated, disorientated, confused or paranoid
- increased or abnormal liver test results
- sight problems such as seeing colours or lights
- increased levels of creatine phosphokinase (CPK) (CPK is an enzyme found mainly in skeletal muscles).

Rare: may affect up to 1 in 1,000 people
- delusion
- delirium
- feeling irritable
- being aggressive
- psychotic disorders
- rash over larger parts of the body
- involuntary muscle spasms (convulsion)

Not known: it is not known how often these happen
- craving large doses of medicines like Neupro – more than needed for the illness. This is known as 'dopamine dysregulation syndrome' and can lead to use of too much Neupro.
- diarrhoea
- dropped head syndrome
- rhabdomyolysis (a rare severe muscle disorder which causes pain, tenderness and weakness of the muscles and may lead to kidney problems)

Tell your doctor, pharmacist or nurse if you notice any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Neupro

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and box.

Do not store above 30°C.

What to do with the used and unused patches
- Used patches still contain the active substance ‘rotigotine’, 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.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Neupro contains
The active substance is rotigotine.
- 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.

- 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.

- 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 the 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 6 mg/24 h or Neupro 8 mg/ 24 h.

Neupro is available in the following pack-sizes:
Boxes containing 7, 14, 28, 30 or 84 (multipack containing 3 packs of 28) patches, which are individually sealed in sachets.

Not all pack sizes may be marketed.

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Other sources of information

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 because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Neupro is and what it is used for

What Neupro is
Neupro contains the active substance rotigotine.

It belongs to a group of medicines called 'dopamine agonists'. Dopamine is a messenger in the brain which is important for movement.

What Neupro is used for
Neupro is used in adults to treat the signs and symptoms of:
- **Parkinson's disease** – Neupro can be used on its own or with another medicine called levodopa.

2. What you need to know before you use Neupro

Do not use Neupro if:
- you are **allergic** to **rotigotine** or any of the **other ingredients** of this medicine (listed in section 6)
- you need to have a **magnetic resonance imaging** (MRI) scan (diagnostic pictures of the inside of the body, created using magnetic rather than x-ray energy)
- you need '**cardioversion**' (specific treatment for abnormal heart beat).

You must take your Neupro patch off just before undergoing magnetic resonance imaging (MRI) or cardioversion to avoid skin burns because the patch contains aluminium. You can put a new patch on afterwards.

If any of the above apply to you, do not use Neupro. If you are not sure about this, talk to your doctor or pharmacist or nurse first.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Neupro. This is because

- your **blood pressure** needs checking regularly while using Neupro, especially at the start of the treatment. Neupro may affect your blood pressure.
- your **eyes** need checking regularly while using Neupro. If you notice any problems with your eyesight between checks, talk to your doctor straight away.
- if you have serious **liver problems**, your doctor may need to change the dose. If your liver problems get worse during treatment, talk to your doctor straight away.
- you may get **skin problems** caused by the patch – see '**Skin problems caused by the patch**' in section 4.
- you may **feel very sleepy** or **fall asleep suddenly** – see '**Driving and using machines**' in section 2.

If you experience these symptoms after beginning treatment with Neupro, contact your doctor.

Medicines used to treat Parkinson's disease should be reduced or stopped gradually. Tell your doctor if after stopping or reducing your Neupro treatment you experience symptoms such as depression, anxiety, fatigue, sweating or pain

Loss of consciousness can occur
Neupro can cause loss of consciousness. This can happen especially when you start using Neupro or when your dose is increased. Tell your doctor if you lose consciousness or feel dizzy.

Changes in behaviour and abnormal thinking
Neupro can cause side effects that change your behaviour (how you act). You may find it helpful to tell a member of your family or carer that you are using this medicine and ask them to read this leaflet. This is so that your family or carer can tell you, or your doctor, if they are worried about any changes in your behaviour.

These include:

- craving for large doses of Neupro or other medicines used to treat Parkinson's disease.
- unusual urges or cravings which you cannot resist and that could harm yourself or others
- abnormal thinking or behaviour.

See '**Changes to your behaviour and abnormal thinking**' in section 4 for more information.

Children and adolescents
Do **not** give this medicine to **children** below 18 years of age because it is not known if it is safe or effective in this age group.

Other medicines and Neupro
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

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

Do not take the following medicines while using Neupro – because they may decrease its effect:

- 'anti-psychotic' medicines – used to treat certain mental illnesses
- metoclopramide – used to treat nausea (feeling sick) and vomiting.

Talk to your doctor before using Neupro if you are taking:
- sedating medicines such as benzodiazepines or medicines used to treat mental illness or depression.
- medicines that lower blood pressure. Neupro may decrease blood pressure when you stand up – this effect may be worsened by the medicines used to lower blood pressure.

Your doctor will let you know if it is safe to keep taking these medicines while using Neupro.

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

Pregnancy and breast-feeding
Do not use Neupro if you are pregnant. This is because the effects of rotigotine on pregnancy and the unborn baby are not known.

Do not breast-feed during treatment with Neupro. This is because rotigotine may pass into your breast milk and affect your baby. It is also likely to lower the amount of milk you produce.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines
Neupro may make you feel very sleepy and you may fall asleep very suddenly. If this happens, do not drive. In isolated cases people have fallen asleep while driving and this has caused accidents.

Also do not use tools or machines if you feel very sleepy – or do anything else which may put others or yourself at risk of serious injury.

Neupro contains sodium metabisulphite (E223)
Sodium metabisulphite (E223) may rarely cause severe hypersensitivity (allergic) reactions and bronchospasm (breathing distress caused by narrowing of the airways).

3. How to use Neupro

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Which strength patches to use
The dose of Neupro will depend on your illness – see below.

Neupro is available in different strength patches which release the medicine over 24 hours. The strengths are 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h for the treatment of Parkinson's disease. You may have to use more than one patch to reach your dose, as prescribed by your doctor.

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**").

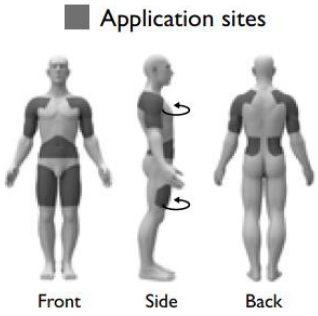
At the beginning of the fourth week, you should take Neupro 8 mg (package marked with "**Week 4**").

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. For doses higher than 8 mg/24 h (doses prescribed by your doctor above the available strengths), multiple patches must be applied to achieve the final dose. For example, a daily dose of 14 mg can be reached by applying one patch of 6 mg/24 h and one patch of 8 mg/24 h and likewise, a daily dose of 16 mg can be reached by applying two patches of 8 mg/24 h.

If you have to stop taking this medicine see **'If you stop using Neupro'** in section 3.

How to use the Neupro patches
Neupro is a patch that is put on the skin.
- Make sure that you take the old patch off before putting on a new one.
- Stick the new patch on **a different area of the skin each day**.
- Leave the patch on your skin for 24 hours, then take it off and put on a new one.
- **Change the patch** at about 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 shown in grey on the pictures opposite:
- Shoulder or upper arm.
- Belly.
- Flank (your side, between the ribs and hips).
- Thigh or hip.



To avoid skin irritation
- Stick the patch onto a **different area of skin each day**. For example, put it on the right side of your body one day, then on the left side of your body the next day. Or on your upper body one day, then on your lower body the day after that.
- 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 **'Skin problems caused by the patch'** in section 4 for more information.

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** where you will put the patch. Also do not use them 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 edges of the patch lift, the patch may be taped down with adhesive medical tape.

If the patch falls off, put on a new patch for the rest of the day – then replace the patch at the usual time.

- Do **not** let the area of the patch **get hot** – for example too much sunlight, saunas, hot baths, heating pads or hot-water bottles. This is because the medicine may be released faster. If you think that too much heat has been applied, contact your doctor or pharmacist.
- Always check that the patch has not fallen off after activities such as **bathing, showering or exercising.**
- If the patch has **irritated your skin, keep** that area **protected from direct sunlight**. This is because it may change the colour of the skin.

How to use the patch

- Each patch is packed in a separate sachet.
- Before opening the sachet decide where you are going to stick this new patch and check you have removed any old patch.
- Stick the Neupro patch onto your skin as soon as you have opened the sachet and removed the release liner.

1.
To open the sachet, hold the sachet in both hands.

2.
Peel apart the foil.

3.
Open the sachet.

4.
Take the patch out of the sachet.

5.
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.

6.

- Bend the patch in half.

This makes the S-shaped break in the liner open up.

7.

- Peel off one side of the release liner.
- Do not touch the sticky side of the patch with your fingers.

8.

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

9.

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

10.

- Press the patch down firmly with the palm of your hand.
- Keep it pressed for about 30 seconds.

This makes sure the patch is touching the skin and the edges stick down well.

11.

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

How to take off a used patch

- Slowly and carefully peel off the used patch.
- Gently wash the area with warm water and mild soap. This will remove any stickiness that stays on your skin. You can also use a little baby oil to remove any stickiness that will not wash off.
- Do not use alcohol or other dissolving liquids – such as nail polish remover. These may irritate your skin.

If you use more Neupro than you should
Using higher doses of Neupro than your doctor has prescribed may cause side effects such as feeling sick (nausea) or vomiting, low blood pressure, seeing or hearing things that are not real (hallucinations), feeling confused, very sleepy, having involuntary movements and convulsions. In such cases, contact your doctor or hospital straight away. They will tell you what to do.

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 forget to change the patch at your usual time
- If you have forgotten to change the patch at your usual time, change it as soon as you remember. Take off 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, use a new patch at the usual time on the following day. Do not use a double dose to make up for a forgotten dose.

If you stop using Neupro
Do not stop using Neupro without talking to your doctor. A sudden stop could lead to a medical condition called 'neuroleptic malignant syndrome' which could be life-threatening. The signs include: loss of muscle movement (akinesia), rigid muscles, fever, unstable blood pressure, increased heart rate (tachycardia), confusion, low level of consciousness (such as a coma).

If your doctor says you should stop Neupro, the **daily dose** of Neupro should be **lowered gradually:**
- **Parkinson's disease** – lowered by 2 mg every other day.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor or pharmacist or nurse if you notice any side effects.

Side effects more likely at the start of treatment
You may **feel sick** (nausea) and **vomit at the start of treatment**. These effects are usually mild or moderate and only last for a short time. **Talk to your doctor** if they last for a long time or if you are worried about them.

Skin problems caused by the patch
- You may get redness and itching on the skin where the patch has been – these reactions are usually mild or moderate.
- The reactions normally go away after a few hours – once you remove the patch.
- **Talk to your doctor** if you have a skin reaction that lasts longer than a few days or is severe. Also do this if it spreads outside the area of skin that was covered by the patch.
- Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by the patch.
- 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.

Loss of consciousness can occur
Neupro can cause loss of consciousness. This can happen especially when you start using Neupro or when your dose is increased. Tell your doctor if you lose consciousness or feel dizzy.

Changes in behaviour and abnormal thinking
Tell your doctor if you notice any changes in behaviour, thinking or both, that are listed below. They will discuss ways of managing or reducing symptoms.

You may find it helpful to also tell a member of your family or carer that you are using this medicine and ask them to read this leaflet. This is so that your family or carer can tell you, or your doctor, if they are worried about any changes in your behaviour. Neupro can cause unusual urges or cravings which you cannot resist such as the impulse, drive or temptation to do things that could harm yourself or others.

These may include:
- strong impulse to gamble too much – even if this seriously affects you or your family
- altered or increased sexual interest and behaviour which causes significant concern to you or others – for example, an increased sex drive
- uncontrolled shopping or spending too much
- 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).

Neupro may cause other behaviours and abnormal thinking. These may include:
- abnormal thoughts about reality
- delusions and hallucinations (seeing or hearing things that are not real)
- confusion
- disorientation
- aggressive behaviour
- agitation
- delirium.

Tell your doctor if you notice any changes in behaviour, thinking or both that are listed above. They will discuss ways of managing or reducing symptoms.

Allergic reactions
Contact your doctor if you notice signs of an allergic reaction – these can include swelling of the face, tongue or lips.

Side effects when using Neupro for Parkinson's disease
Tell your doctor, pharmacist or nurse if you get any of the following side effects:

Very common: may affect more than 1 in 10 people
- headache
- feeling sleepy or dizzy
- feeling sick (nausea), vomiting
- skin reactions under the patch such as redness and itching

Common: may affect up to 1 in 10 people
- falling
- hiccups
- weight loss
- swelling of legs and feet
- feeling weak (fatigue), feeling tired
- feeling of heartbeat (palpitation)
- constipation, dry mouth, heartburn
- redness, increased sweating, itching
- vertigo (sensation of whirling motion)
- seeing or hearing things that are not real (hallucinations)
- low blood pressure when standing up, high blood pressure

- difficulty falling asleep, sleep disorder, difficulty sleeping, nightmare, unusual dreams
- movements you cannot control related to Parkinson's disease (dyskinesia)
- fainting, feeling dizzy when standing up because of fall in blood pressure
- unable to resist the impulse to perform an action that is harmful involving excessive gambling, repetitive meaningless actions, uncontrolled shopping or spending too much
- binge eating (eating large amount of food in a short period of time), compulsive eating (eating more food than normal and more than needed to satisfy hunger)

Uncommon: may affect up to 1 in 100 people
- blurred vision
- weight increase
- allergic reaction
- low blood pressure
- increased heart rate
- increased sex drive
- abnormal heart beat
- stomach discomfort and pain
- generalised itching, skin irritation
- falling asleep suddenly without warning
- unable to achieve or maintain an erection
- feeling agitated, disorientated, confused or paranoid
- increased or abnormal liver test results
- sight problems such as seeing colours or lights
- increased levels of creatine phosphokinase (CPK) (CPK is an enzyme found mainly in skeletal muscles).

Rare: may affect up to 1 in 1,000 people
- delusion
- delirium
- feeling irritable
- being aggressive
- psychotic disorders
- rash over larger parts of the body
- involuntary muscle spasms (convulsion)

Not known: it is not known how often these happen
- craving large doses of medicines like Neupro – more than needed for the illness. This is known as 'dopamine dysregulation syndrome' and can lead to use of too much Neupro.
- diarrhoea
- dropped head syndrome
- rhabdomyolysis (a rare severe muscle disorder which causes pain, tenderness and weakness of the muscles and may lead to kidney problems)

Tell your doctor, pharmacist or nurse if you notice any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Neupro

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton.

Do not store above 30°C.

What to do with the used and unused patches
- Used patches still contain the active substance ‘rotigotine’, 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
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Neupro contains
The active substance is rotigotine.
- 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.

- 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.

- 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.

- 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 the 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.

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Manufacturer

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Other sources of information

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