

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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 cm² contains 4.5 mg of rotigotine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

Thin, matrix-type, square-shaped with rounded edges, consisting of three layers. The outside of the backing layer is tan-coloured and imprinted with Neupro 2 mg /24 h.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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.

Dosage

The dose recommendations made are in nominal dose.

A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 8 mg/24 h.

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

The maximal dose is 8 mg/24 h.

Hepatic and renal impairment: Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis (see section 4.4 and 5.2).

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

Treatment discontinuation

Neupro should be discontinued gradually. The 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).

Method of administration

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

Use and handling:

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the protective liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is fold back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch should be pressed down firmly with the palm of the hand for about 20 to 30 seconds, so that it sticks well.

In the event that a patch should fall off, a new patch should be applied for the remainder of the 24 hour dosing interval.

The patch should not be cut into pieces.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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.

Dopamine agonists are known to impair the systemic regulation of the blood pressure resulting in postural/orthostatic hypotension. These events were also observed during treatment with Neupro, however the incidence was similar to that in placebo-treated patients.
Syncope was observed in association with Neupro in patients with early stage Parkinson's disease who were not being treated with L-dopa, but also at a similar rate to patients treated with placebo.
It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of orthostatic hypotension associated with dopaminergic therapy.

Neupro has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. 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.

Compulsive disorders including pathologic gambling, hypersexuality, increased libido, repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

Although not reported with Neupro, symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore it is recommended to taper treatment (see section 4.2).

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

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

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

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

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

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

If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin color.

If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Neupro is observed, Neupro should be discontinued.

Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Neupro has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see sections 4.2 and 5.2).

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 enzyme inducing active substances (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin, St John's wort/*Hypericum perforatum*) has not been investigated.

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.

Although not indicated in combination with L-dopa for the treatment of early Parkinson's disease, in case of co-administration, 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.

4.6 Pregnancy and lactation

There are no adequate data from the use of Neupro 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.

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

4.7 Effects on ability to drive and use machines

Rotigotine may have major influence on the ability to drive and use machines.

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

4.8 Undesirable effects

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 649 Neupro- and 289 placebo-treated patients, 75.5% of the patients on Neupro and 57.1% 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.

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

In trials where the application sites were rotated as reflected in the instructions provided in SPC and package leaflet, 40.4 % of 396 patients using the Neupro transdermal patch, experienced application site reactions. The majority of these reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of treatment with Neupro in only 7 % of all subjects receiving Neupro.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following table covers adverse drug reactions from all studies in patients with early stage Parkinson's disease.

System/organ classes acc. to MedDRA	Very common >1/10	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000
Immune system disorder			hypersensitivity	
Metabolism and nutrition disorders		anorexia	decreased appetite	
Psychiatric disorders		sleep attacks ^a (see chapter below the table), hallucination (including visual and auditory), anxiety, abnormal dreams ^a , insomnia ^a	confusion state, sleep disorder, nightmares	psychotic disorder (including paranoid psychosis), increased libido (including hypersexuality), compulsive disorders (including pathologic gambling, punding)
Nervous system disorders	somnolence ^a , dizziness ^a	headache ^a , dizziness postural, dyskinesia, lethargia	tremor, balance disorder, dysgeusia, syncope, disturbance in attention, paraesthesia, memory impaired,	convulsion

			vasovagal syncope, loss of consciousness	
Eye disorders (see section 4.4)			visual disturbance, photopsia, blurred vision	
Ear and labyrinth disorders			vertigo (incl. positional)	
Cardiac disorders			palpitations, heart rate increased	
Vascular disorders		orthostatic hypotension (see section 4.4), hypertension	hypotension	
Respiratory, thoracic and mediastinal disorders		cough ^a , hiccup ^a	dyspnoea	
Gastrointestinal disorders	nausea ^a , vomiting ^a ,	constipation ^a , dry mouth ^a , diarrhoea, dyspepsia ^a	abdominal pain, stomach discomfort	
Hepato-biliary disorder			hepatic enzyme increased (including GGT, ALAT, ASAT)	
Skin and subcutaneous tissue disorders		hyperhidrosis ^a , erythema ^a , pruritus	rash (incl. allergic; macular) (see section 4.4), skin irritation, exanthema, generalized pruritus	
Musculoskeletal and connective tissue disorder			joint swelling	
Reproductive system and breast disorder			erectile dysfunction	
General disorders and administration site conditions	application site reactions ^a (including erythema, pruritus, irritation, burning, dermatitis, inflammation, papulae, vesicle, pain) (see section 4.4)	oedema peripheral, asthenic conditions (incl. fatigue ^a , asthenia, malaise),	feeling abnormal, weight decreased, gait abnormal	
Injury, poisoning and procedural complications			fall	

^a These adverse drug reactions have been reported in the pooled placebo-controlled trials 1% more frequent than in the placebo-treated patients

Neupro has been associated with somnolence including excessive daytime somnolence and sudden sleep onset episodes. In isolated cases “sudden onset of sleep” occurred while driving and resulted in motor vehicle accidents. See also section 4.4 and 4.7

4.9 Overdose

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

There is no known antidote for overdose of dopamine agonists. In case of suspected overdose, the patch(es) should immediately be removed from the patient. Levels of rotigotine decrease after patch removal. Before stopping use of rotigotine completely see section 4.2.

The patient should be monitored closely, including heart rate, heart rhythm and blood pressure.

Because rotigotine is over 90% protein bound, dialysis would not be expected to be beneficial.

Treatment of overdose may require general supportive measures to maintain the vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonists, Rotigotine; ATC code: N04BC09

Rotigotine is a non-ergolinic D₃/D₂/D₁ dopamine agonist for the treatment of Parkinson’s disease. It is believed to elicit its beneficial effect by activation of the D₃, D₂ and D₁ receptors of the caudate-putamen in the brain.

Rotigotine alleviates signs and symptoms of early-stage idiopathic Parkinson’s disease.

Clinical studies:

The effectiveness of Neupro in the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease was evaluated in a multinational drug development program consisting of two pivotal, parallel, randomized, double-blind placebo controlled studies. These trials were conducted in patients who were not receiving concomitant dopamine agonist therapy and were either L-dopa naïve or previous L-dopa treatment was ≤ 6 months. The primary outcome assessment was the score for the Activities of Daily Living (ADL) component (Part II) plus the Motor Examination component (Part III) of the Unified Parkinson’s Disease Rating Scale (UPDRS).

Efficacy was determined by the subject’s response to therapy in terms of responder and absolute points improvement in the scores of ADL and Motor Examination combined (UPDRS part II+III) In one double blind study, 177 patients received rotigotine and 96 patients received placebo. The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 6 mg/24 h. Patients in each treatment group were maintained at their optimal dose for 6 months.

At the end of the maintenance treatment in 91% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 6 mg/24 h. An improvement of 20% was seen in 48% of the subjects receiving rotigotine and in 19% of the subjects receiving placebo (Difference 29% CI_{95%} 18%; 39%, p<0.0001). With rotigotine, the mean improvement in the UPDRS score (Parts II + III) was -3.98 points (baseline 29.9 point) whereas in the placebo-treated arm a worsening of 1.31 points was observed (baseline 30.0 points) The difference was 5.28 points and statistically significant (p<0.0001).

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

At the end of the maintenance treatment in 92% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 8 mg/24 h. An improvement of 20% was seen in 52% of the

subjects receiving rotigotine, 68% of the subjects receiving ropinirole and 30% of the subjects receiving placebo (Difference rotigotine versus placebo 21.7%; CI_{95%} 11.1% ; 32.4% , difference ropinirole versus placebo 38.4% CI_{95%} 28.1% ; 48.6% , difference ropinirole versus rotigotine 16.6%; CI_{95%} .7.6% ; 25.7%). The mean improvement in the UPDRS score (Parts II + III) was 6.83 points (baseline 33.2 points) in the rotigotine arm, 10.78 point 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. The difference in effect between ropinirole and rotigotine was also statistically significant in favour of ropinirole.

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 displays a dose-proportional pharmacokinetic profile over a dose range of 2 mg/day (10 cm²) to 8 mg/day (40 cm²).

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 1% (hip versus abdomen) to 41% (shoulder versus thigh). However, there is no indication of a relevant impact on the clinical outcome.

Distribution

The *in vitro* binding of rotigotine to plasma proteins is approximately 92%.

The apparent volume of distribution in humans is approximately 84 l/kg.

Metabolism

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

The 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 elimination half-life is 5 to 7 hours.

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

Special patient groups

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

In subjects with moderate hepatic impairment or mild to severe renal impairment, no relevant increases of rotigotine plasma levels were observed. Neupro was not investigated in patients with severe hepatic impairment.

Plasma levels of conjugates of rotigotine and its desalkyl metabolites increase with impaired renal function. However, a contribution of these metabolites to clinical effects is unlikely.

5.3 Preclinical safety data

In repeated dose and long-term toxicity studies, the major effects were associated with the dopamine agonist related pharmacodynamic effects and the consequent decrease of prolactin secretion. After a single dose of rotigotine, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident, but was slowly cleared over the 14-day observation period.

Retinal degeneration was observed by transmission microscopy at a dose equivalent to 5.6 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).

Protective liner:

Transparent fluoropolymer coated polyester film.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

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

The carton contains 7, 28 or 100 transdermal patches, individually sealed in sachets.

6.6 Special precaution for disposal

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

7. MARKETING AUTHORISATION HOLDER

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

1. NAME OF THE MEDICINAL PRODUCT

Neupro 4 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 4 mg of rotigotine per 24 hours. Each patch of 20 cm² contains 9.0 mg of rotigotine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

Thin, matrix-type, square-shaped with rounded edges, consisting of three layers. The outside of the backing layer is tan-coloured and imprinted with Neupro 4 mg /24 h.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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.

Dosage

The dose recommendations made are in nominal dose.

A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 8 mg/24 h.

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

The maximal dose is 8 mg/24 h.

Hepatic and renal impairment: Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis (see section 4.4 and 5.2).

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

Treatment discontinuation

Neupro should be discontinued gradually. The 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).

Method of administration

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

Use and handling:

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the protective liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is fold back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch should be pressed down firmly with the palm of the hand for about 20 to 30 seconds, so that it sticks well.

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

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.

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Syncope was observed in association with Neupro in patients with early stage Parkinson's disease who were not being treated with L-dopa, but also at a similar rate to patients treated with placebo.
It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of orthostatic hypotension associated with dopaminergic therapy.

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Although not reported with Neupro, symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore it is recommended to taper treatment (see section 4.2).

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

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

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

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

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

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

If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin color.

If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Neupro is observed, Neupro should be discontinued.

Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Neupro has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see sections 4.2 and 5.2).

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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 enzyme inducing active substances (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin, St John's wort/*Hypericum perforatum*) has not been investigated.

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.

Although not indicated in combination with L-dopa for the treatment of early Parkinson's disease, in case of co-administration, 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.

4.6 Pregnancy and lactation

There are no adequate data from the use of Neupro 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.

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

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).

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Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 649 Neupro- and 289 placebo-treated patients, 75.5% of the patients on Neupro and 57.1% 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.

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

In trials where the application sites were rotated as reflected in the instructions provided in SPC and package leaflet, 40.4 % of 396 patients using the Neupro transdermal patch, experienced application site reactions. The majority of these reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of treatment with Neupro in only 7 % of all subjects receiving Neupro.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following table covers adverse drug reactions from all studies in patients with early stage Parkinson's disease.

System/organ classes acc. to MedDRA	Very common >1/10	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000
Immune system disorder			hypersensitivity	
Metabolism and nutrition disorders		anorexia	decreased appetite	
Psychiatric disorders		sleep attacks ^a (see chapter below the table), hallucination (including visual and auditory), anxiety, abnormal dreams ^a , insomnia ^a	confusion state, sleep disorder, nightmares	psychotic disorder (including paranoid psychosis), increased libido (including hypersexuality), compulsive disorders (including pathologic gambling, punding)
Nervous system disorders	somnolence ^a , dizziness ^a	headache ^a , dizziness postural, dyskinesia, lethargia	tremor, balance disorder, dysgeusia, syncope, disturbance in attention, paraesthesia, memory impaired,	convulsion

			vasovagal syncope, loss of consciousness	
Eye disorders (see section 4.4)			visual disturbance, photopsia, blurred vision	
Ear and labyrinth disorders			vertigo (incl. positional)	
Cardiac disorders			palpitations, heart rate increased	
Vascular disorders		orthostatic hypotension (see section 4.4), hypertension	hypotension	
Respiratory, thoracic and mediastinal disorders		cough ^a , hiccup ^a	dyspnoea	
Gastrointestinal disorders	nausea ^a , vomiting ^a ,	constipation ^a , dry mouth ^a , diarrhoea, dyspepsia ^a	abdominal pain, stomach discomfort	
Hepato-biliary disorder			hepatic enzyme increased (including GGT, ALAT, ASAT)	
Skin and subcutaneous tissue disorders		hyperhidrosis ^a , erythema ^a , pruritus	rash (incl. allergic; macular) (see section 4.4), skin irritation, exanthema, generalized pruritus	
Musculoskeletal and connective tissue disorder			joint swelling	
Reproductive system and breast disorder			erectile dysfunction	
General disorders and administration site conditions	application site reactions ^a (including erythema, pruritus, irritation, burning, dermatitis, inflammation, papulae, vesicle, pain) (see section 4.4)	oedema peripheral, asthenic conditions (incl. fatigue ^a , asthenia, malaise),	feeling abnormal, weight decreased, gait abnormal	
Injury, poisoning and procedural complications			fall	

^a These adverse drug reactions have been reported in the pooled placebo-controlled trials 1% more frequent than in the placebo-treated patients

Neupro has been associated with somnolence including excessive daytime somnolence and sudden sleep onset episodes. In isolated cases “sudden onset of sleep” occurred while driving and resulted in motor vehicle accidents. See also section 4.4 and 4.7

4.9 Overdose

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

There is no known antidote for overdose of dopamine agonists. In case of suspected overdose, the patch(es) should immediately be removed from the patient. Levels of rotigotine decrease after patch removal. Before stopping use of rotigotine completely see section 4.2.

The patient should be monitored closely, including heart rate, heart rhythm and blood pressure.

Because rotigotine is over 90% protein bound, dialysis would not be expected to be beneficial.

Treatment of overdose may require general supportive measures to maintain the vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonists, Rotigotine; ATC code: N04BC09

Rotigotine is a non-ergolinic D₃/D₂/D₁ dopamine agonist for the treatment of Parkinson’s disease. It is believed to elicit its beneficial effect by activation of the D₃, D₂ and D₁ receptors of the caudate-putamen in the brain.

Rotigotine alleviates signs and symptoms of early-stage idiopathic Parkinson’s disease.

Clinical studies:

The effectiveness of Neupro in the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease was evaluated in a multinational drug development program consisting of two pivotal, parallel, randomized, double-blind placebo controlled studies. These trials were conducted in patients who were not receiving concomitant dopamine agonist therapy and were either L-dopa naïve or previous L-dopa treatment was ≤ 6 months. The primary outcome assessment was the score for the Activities of Daily Living (ADL) component (Part II) plus the Motor Examination component (Part III) of the Unified Parkinson’s Disease Rating Scale (UPDRS).

Efficacy was determined by the subject’s response to therapy in terms of responder and absolute points improvement in the scores of ADL and Motor Examination combined (UPDRS part II+III) In one double blind study, 177 patients received rotigotine and 96 patients received placebo. The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 6 mg/24 h. Patients in each treatment group were maintained at their optimal dose for 6 months.

At the end of the maintenance treatment in 91% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 6 mg/24 h. An improvement of 20% was seen in 48% of the subjects receiving rotigotine and in 19% of the subjects receiving placebo (Difference 29% CI_{95%} 18%; 39%, p<0.0001). With rotigotine, the mean improvement in the UPDRS score (Parts II + III) was -3.98 points (baseline 29.9 point) whereas in the placebo-treated arm a worsening of 1.31 points was observed (baseline 30.0 points) The difference was 5.28 points and statistically significant (p<0.0001).

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

At the end of the maintenance treatment in 92% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 8 mg/24 h. An improvement of 20% was seen in 52% of the

subjects receiving rotigotine, 68% of the subjects receiving ropinirole and 30% of the subjects receiving placebo (Difference rotigotine versus placebo 21.7%; CI_{95%} 11.1% ; 32.4% , difference ropinirole versus placebo 38.4% CI_{95%} 28.1% ; 48.6% , difference ropinirole versus rotigotine 16.6%; CI_{95%} .7.6% ; 25.7%). The mean improvement in the UPDRS score (Parts II + III) was 6.83 points (baseline 33.2 points) in the rotigotine arm, 10.78 point 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. The difference in effect between ropinirole and rotigotine was also statistically significant in favour of ropinirole.

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 displays a dose-proportional pharmacokinetic profile over a dose range of 2 mg/day (10 cm²) to 8 mg/day (40 cm²).

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 1% (hip versus abdomen) to 41% (shoulder versus thigh). However, there is no indication of a relevant impact on the clinical outcome.

Distribution

The *in vitro* binding of rotigotine to plasma proteins is approximately 92%.

The apparent volume of distribution in humans is approximately 84 l/kg.

Metabolism

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

The 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 elimination half-life is 5 to 7 hours.

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

Special patient groups

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

In subjects with moderate hepatic impairment or mild to severe renal impairment, no relevant increases of rotigotine plasma levels were observed. Neupro was not investigated in patients with severe hepatic impairment.

Plasma levels of conjugates of rotigotine and its desalkyl metabolites increase with impaired renal function. However, a contribution of these metabolites to clinical effects is unlikely.

5.3 Preclinical safety data

In repeated dose and long-term toxicity studies, the major effects were associated with the dopamine agonist related pharmacodynamic effects and the consequent decrease of prolactin secretion. After a single dose of rotigotine, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident, but was slowly cleared over the 14-day observation period.

Retinal degeneration was observed by transmission microscopy at a dose equivalent to 5.6 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).

Protective liner:

Transparent fluoropolymer coated polyester film.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

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

The carton contains 7, 28 or 100 transdermal patches, individually sealed in sachets.

6.6 Special precaution for disposal

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

7. MARKETING AUTHORISATION HOLDER

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

1. NAME OF THE MEDICINAL PRODUCT

Neupro 6 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 6 mg of rotigotine per 24 hours. Each patch of 30 cm² contains 13.5 mg of rotigotine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

Thin, matrix-type, square-shaped with rounded edges, consisting of three layers. The outside of the backing layer is tan-coloured and imprinted with Neupro 6 mg /24 h.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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.

Dosage

The dose recommendations made are in nominal dose.

A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 8 mg/24 h.

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

The maximal dose is 8 mg/24 h.

Hepatic and renal impairment: Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis (see section 4.4 and 5.2).

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

Treatment discontinuation

Neupro should be discontinued gradually. The 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).

Method of administration

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

Use and handling:

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the protective liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is fold back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch should be pressed down firmly with the palm of the hand for about 20 to 30 seconds, so that it sticks well.

In the event that a patch should fall off, a new patch should be applied for the remainder of the 24 hour dosing interval.

The patch should not be cut into pieces.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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.

Dopamine agonists are known to impair the systemic regulation of the blood pressure resulting in postural/orthostatic hypotension. These events were also observed during treatment with Neupro, however the incidence was similar to that in placebo-treated patients.
Syncope was observed in association with Neupro in patients with early stage Parkinson's disease who were not being treated with L-dopa, but also at a similar rate to patients treated with placebo.
It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of orthostatic hypotension associated with dopaminergic therapy.

Neupro has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. 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.

Compulsive disorders including pathologic gambling, hypersexuality, increased libido, repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

Although not reported with Neupro, symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore it is recommended to taper treatment (see section 4.2).

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

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

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

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

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

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

If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin color.

If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Neupro is observed, Neupro should be discontinued.

Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Neupro has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see sections 4.2 and 5.2).

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 enzyme inducing active substances (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin, St John's wort/*Hypericum perforatum*) has not been investigated.

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.

Although not indicated in combination with L-dopa for the treatment of early Parkinson's disease, in case of co-administration, 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.

4.6 Pregnancy and lactation

There are no adequate data from the use of Neupro 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.

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

4.7 Effects on ability to drive and use machines

Rotigotine may have major influence on the ability to drive and use machines.

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

4.8 Undesirable effects

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 649 Neupro- and 289 placebo-treated patients, 75.5% of the patients on Neupro and 57.1% 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.

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

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Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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Nervous system disorders	somnolence ^a , dizziness ^a	headache ^a , dizziness postural, dyskinesia, lethargia	tremor, balance disorder, dysgeusia, syncope, disturbance in attention, paraesthesia, memory impaired,	convulsion

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Eye disorders (see section 4.4)			visual disturbance, photopsia, blurred vision	
Ear and labyrinth disorders			vertigo (incl. positional)	
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Vascular disorders		orthostatic hypotension (see section 4.4), hypertension	hypotension	
Respiratory, thoracic and mediastinal disorders		cough ^a , hiccup ^a	dyspnoea	
Gastrointestinal disorders	nausea ^a , vomiting ^a ,	constipation ^a , dry mouth ^a , diarrhoea, dyspepsia ^a	abdominal pain, stomach discomfort	
Hepato-biliary disorder			hepatic enzyme increased (including GGT, ALAT, ASAT)	
Skin and subcutaneous tissue disorders		hyperhidrosis ^a , erythema ^a , pruritus	rash (incl. allergic; macular) (see section 4.4), skin irritation, exanthema, generalized pruritus	
Musculoskeletal and connective tissue disorder			joint swelling	
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General disorders and administration site conditions	application site reactions ^a (including erythema, pruritus, irritation, burning, dermatitis, inflammation, papulae, vesicle, pain) (see section 4.4)	oedema peripheral, asthenic conditions (incl. fatigue ^a , asthenia, malaise),	feeling abnormal, weight decreased, gait abnormal	
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The patient should be monitored closely, including heart rate, heart rhythm and blood pressure.

Because rotigotine is over 90% protein bound, dialysis would not be expected to be beneficial.

Treatment of overdose may require general supportive measures to maintain the vital signs.

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The apparent volume of distribution in humans is approximately 84 l/kg.

Metabolism

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

The 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 elimination half-life is 5 to 7 hours.

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

Special patient groups

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

In subjects with moderate hepatic impairment or mild to severe renal impairment, no relevant increases of rotigotine plasma levels were observed. Neupro was not investigated in patients with severe hepatic impairment.

Plasma levels of conjugates of rotigotine and its desalkyl metabolites increase with impaired renal function. However, a contribution of these metabolites to clinical effects is unlikely.

5.3 Preclinical safety data

In repeated dose and long-term toxicity studies, the major effects were associated with the dopamine agonist related pharmacodynamic effects and the consequent decrease of prolactin secretion. After a single dose of rotigotine, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident, but was slowly cleared over the 14-day observation period.

Retinal degeneration was observed by transmission microscopy at a dose equivalent to 5.6 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).

Protective liner:

Transparent fluoropolymer coated polyester film.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

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

The carton contains 7, 28 or 100 transdermal patches, individually sealed in sachets.

6.6 Special precaution for disposal

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

7. MARKETING AUTHORISATION HOLDER

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

1. NAME OF THE MEDICINAL PRODUCT

Neupro 8 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 8 mg of rotigotine per 24 hours. Each patch of 40 cm² contains 18.0 mg of rotigotine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

Thin, matrix-type, square-shaped with rounded edges, consisting of three layers. The outside of the backing layer is tan-coloured and imprinted with Neupro 8 mg /24 h.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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.

Dosage

The dose recommendations made are in nominal dose.

A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 8 mg/24 h.

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

The maximal dose is 8 mg/24 h.

Hepatic and renal impairment: Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis (see section 4.4 and 5.2).

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

Treatment discontinuation

Neupro should be discontinued gradually. The 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).

Method of administration

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

Use and handling:

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the protective liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is fold back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch should be pressed down firmly with the palm of the hand for about 20 to 30 seconds, so that it sticks well.

In the event that a patch should fall off, a new patch should be applied for the remainder of the 24 hour dosing interval.

The patch should not be cut into pieces.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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.

Dopamine agonists are known to impair the systemic regulation of the blood pressure resulting in postural/orthostatic hypotension. These events were also observed during treatment with Neupro, however the incidence was similar to that in placebo-treated patients.
Syncope was observed in association with Neupro in patients with early stage Parkinson's disease who were not being treated with L-dopa, but also at a similar rate to patients treated with placebo.
It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of orthostatic hypotension associated with dopaminergic therapy.

Neupro has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. 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.

Compulsive disorders including pathologic gambling, hypersexuality, increased libido, repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

Although not reported with Neupro, symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore it is recommended to taper treatment (see section 4.2).

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

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

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

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

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

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

If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin color.

If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Neupro is observed, Neupro should be discontinued.

Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Neupro has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see sections 4.2 and 5.2).

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 enzyme inducing active substances (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin, St John's wort/*Hypericum perforatum*) has not been investigated.

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.

Although not indicated in combination with L-dopa for the treatment of early Parkinson's disease, in case of co-administration, 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.

4.6 Pregnancy and lactation

There are no adequate data from the use of Neupro 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.

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

4.7 Effects on ability to drive and use machines

Rotigotine may have major influence on the ability to drive and use machines.

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

4.8 Undesirable effects

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 649 Neupro- and 289 placebo-treated patients, 75.5% of the patients on Neupro and 57.1% 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.

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

In trials where the application sites were rotated as reflected in the instructions provided in SPC and package leaflet, 40.4 % of 396 patients using the Neupro transdermal patch, experienced application site reactions. The majority of these reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of treatment with Neupro in only 7 % of all subjects receiving Neupro.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following table covers adverse drug reactions from all studies in patients with early stage Parkinson's disease.

System/organ classes acc. to MedDRA	Very common >1/10	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000
Immune system disorder			hypersensitivity	
Metabolism and nutrition disorders		anorexia	decreased appetite	
Psychiatric disorders		sleep attacks ^a (see chapter below the table), hallucination (including visual and auditory), anxiety, abnormal dreams ^a , insomnia ^a	confusion state, sleep disorder, nightmares	psychotic disorder (including paranoid psychosis), increased libido (including hypersexuality), compulsive disorders (including pathologic gambling, punding)
Nervous system disorders	somnolence ^a , dizziness ^a	headache ^a , dizziness postural, dyskinesia, lethargia	tremor, balance disorder, dysgeusia, syncope, disturbance in attention, paraesthesia, memory impaired,	convulsion

			vasovagal syncope, loss of consciousness	
Eye disorders (see section 4.4)			visual disturbance, photopsia, blurred vision	
Ear and labyrinth disorders			vertigo (incl. positional)	
Cardiac disorders			palpitations, heart rate increased	
Vascular disorders		orthostatic hypotension (see section 4.4), hypertension	hypotension	
Respiratory, thoracic and mediastinal disorders		cough ^a , hiccup ^a	dyspnoea	
Gastrointestinal disorders	nausea ^a , vomiting ^a ,	constipation ^a , dry mouth ^a , diarrhoea, dyspepsia ^a	abdominal pain, stomach discomfort	
Hepato-biliary disorder			hepatic enzyme increased (including GGT, ALAT, ASAT)	
Skin and subcutaneous tissue disorders		hyperhidrosis ^a , erythema ^a , pruritus	rash (incl. allergic; macular) (see section 4.4), skin irritation, exanthema, generalized pruritus	
Musculoskeletal and connective tissue disorder			joint swelling	
Reproductive system and breast disorder			erectile dysfunction	
General disorders and administration site conditions	application site reactions ^a (including erythema, pruritus, irritation, burning, dermatitis, inflammation, papulae, vesicle, pain) (see section 4.4)	oedema peripheral, asthenic conditions (incl. fatigue ^a , asthenia, malaise),	feeling abnormal, weight decreased, gait abnormal	
Injury, poisoning and procedural complications			fall	

^a These adverse drug reactions have been reported in the pooled placebo-controlled trials 1% more frequent than in the placebo-treated patients

Neupro has been associated with somnolence including excessive daytime somnolence and sudden sleep onset episodes. In isolated cases “sudden onset of sleep” occurred while driving and resulted in motor vehicle accidents. See also section 4.4 and 4.7

4.9 Overdose

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

There is no known antidote for overdose of dopamine agonists. In case of suspected overdose, the patch(es) should immediately be removed from the patient. Levels of rotigotine decrease after patch removal. Before stopping use of rotigotine completely see section 4.2.

The patient should be monitored closely, including heart rate, heart rhythm and blood pressure.

Because rotigotine is over 90% protein bound, dialysis would not be expected to be beneficial.

Treatment of overdose may require general supportive measures to maintain the vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonists, Rotigotine; ATC code: N04BC09

Rotigotine is a non-ergolinic D₃/D₂/D₁ dopamine agonist for the treatment of Parkinson’s disease. It is believed to elicit its beneficial effect by activation of the D₃, D₂ and D₁ receptors of the caudate-putamen in the brain.

Rotigotine alleviates signs and symptoms of early-stage idiopathic Parkinson’s disease.

Clinical studies:

The effectiveness of Neupro in the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease was evaluated in a multinational drug development program consisting of two pivotal, parallel, randomized, double-blind placebo controlled studies. These trials were conducted in patients who were not receiving concomitant dopamine agonist therapy and were either L-dopa naïve or previous L-dopa treatment was ≤ 6 months. The primary outcome assessment was the score for the Activities of Daily Living (ADL) component (Part II) plus the Motor Examination component (Part III) of the Unified Parkinson’s Disease Rating Scale (UPDRS).

Efficacy was determined by the subject’s response to therapy in terms of responder and absolute points improvement in the scores of ADL and Motor Examination combined (UPDRS part II+III) In one double blind study, 177 patients received rotigotine and 96 patients received placebo. The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 6 mg/24 h. Patients in each treatment group were maintained at their optimal dose for 6 months.

At the end of the maintenance treatment in 91% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 6 mg/24 h. An improvement of 20% was seen in 48% of the subjects receiving rotigotine and in 19% of the subjects receiving placebo (Difference 29% CI_{95%} 18%; 39%, p<0.0001). With rotigotine, the mean improvement in the UPDRS score (Parts II + III) was -3.98 points (baseline 29.9 point) whereas in the placebo-treated arm a worsening of 1.31 points was observed (baseline 30.0 points) The difference was 5.28 points and statistically significant (p<0.0001).

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

At the end of the maintenance treatment in 92% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 8 mg/24 h. An improvement of 20% was seen in 52% of the

subjects receiving rotigotine, 68% of the subjects receiving ropinirole and 30% of the subjects receiving placebo (Difference rotigotine versus placebo 21.7%; CI_{95%} 11.1% ; 32.4% , difference ropinirole versus placebo 38.4% CI_{95%} 28.1% ; 48.6% , difference ropinirole versus rotigotine 16.6%; CI_{95%} .7.6% ; 25.7%). The mean improvement in the UPDRS score (Parts II + III) was 6.83 points (baseline 33.2 points) in the rotigotine arm, 10.78 point 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. The difference in effect between ropinirole and rotigotine was also statistically significant in favour of ropinirole.

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 displays a dose-proportional pharmacokinetic profile over a dose range of 2 mg/day (10 cm²) to 8 mg/day (40 cm²).

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 1% (hip versus abdomen) to 41% (shoulder versus thigh). However, there is no indication of a relevant impact on the clinical outcome.

Distribution

The *in vitro* binding of rotigotine to plasma proteins is approximately 92%.

The apparent volume of distribution in humans is approximately 84 l/kg.

Metabolism

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

The 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 elimination half-life is 5 to 7 hours.

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

Special patient groups

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

In subjects with moderate hepatic impairment or mild to severe renal impairment, no relevant increases of rotigotine plasma levels were observed. Neupro was not investigated in patients with severe hepatic impairment.

Plasma levels of conjugates of rotigotine and its desalkyl metabolites increase with impaired renal function. However, a contribution of these metabolites to clinical effects is unlikely.

5.3 Preclinical safety data

In repeated dose and long-term toxicity studies, the major effects were associated with the dopamine agonist related pharmacodynamic effects and the consequent decrease of prolactin secretion. After a single dose of rotigotine, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident, but was slowly cleared over the 14-day observation period.

Retinal degeneration was observed by transmission microscopy at a dose equivalent to 5.6 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).

Protective liner:

Transparent fluoropolymer coated polyester film.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

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

The carton contains 7, 28 or 100 transdermal patches, individually sealed in sachets.

6.6 Special precaution for disposal

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

7. MARKETING AUTHORISATION HOLDER

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
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8. MARKETING AUTHORISATION NUMBER(S)

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10. DATE OF REVISION OF THE TEXT

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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 cm² 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 cm² 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 cm² 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 cm² contains 18.0 mg of rotigotine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.
Thin, matrix-type, square-shaped with rounded edges, consisting of three layers. The outside of the backing layer is tan-coloured and imprinted with Neupro 2 mg/24 h, 4 mg/24 h, 6 mg/24 h or 8 mg/24 h.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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.

Dosage

The dose recommendations made are in nominal dose.

A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 8 mg/24 h.

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

The maximal dose is 8 mg/24 h.

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.

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)".

Hepatic and renal impairment: Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis (see section 4.4 and 5.2).

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

Treatment discontinuation

Neupro should be discontinued gradually. The 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).

Method of administration

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

Use and handling:

Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the protective liner should be removed and the sticky side should be applied and pressed firmly to the skin. Then, the patch is fold back and the second part of the release liner is removed. The sticky side of the patch should not be touched. The patch should be pressed down firmly with the palm of the hand for about 20 to 30 seconds, so that it sticks well.

In the event that a patch should fall off, a new patch should be applied for the remainder of the 24 hour dosing interval.

The patch should not be cut into pieces.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Magnetic resonance imaging or cardioversion (see section 4.4).

4.4 Special warnings and precautions for use

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

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.

Dopamine agonists are known to impair the systemic regulation of the blood pressure resulting in postural/orthostatic hypotension. These events were also observed during treatment with Neupro, however the incidence was similar to that in placebo-treated patients.

Syncope was observed in association with Neupro in patients with early stage Parkinson's disease who were not being treated with L-dopa, but also at a similar rate to patients treated with placebo.

It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of orthostatic hypotension associated with dopaminergic therapy.

Neupro has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. 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.

Compulsive disorders including pathologic gambling, hypersexuality, increased libido, repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

Although not reported with Neupro, symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore it is recommended to taper treatment (see section 4.2).

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

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

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

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

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

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

If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin color.

If a generalised skin reaction (e.g. allergic rash, including erythematous, macular, papular rash or pruritus) associated with the use of Neupro is observed, Neupro should be discontinued.

Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Neupro has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment. Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function (see sections 4.2 and 5.2).

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 enzyme inducing active substances (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin, St John's wort/*Hypericum perforatum*) has not been investigated.

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.

Although not indicated in combination with L-dopa for the treatment of early Parkinson's disease, in case of co-administration, 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.

4.6 Pregnancy and lactation

There are no adequate data from the use of Neupro 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.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 649 Neupro- and 289 placebo-treated patients, 75.5% of the patients on Neupro and 57.1% 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.

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

In trials where the application sites were rotated as reflected in the instructions provided in SPC and package leaflet, 40.4 % of 396 patients using the Neupro transdermal patch, experienced application site reactions. The majority of these reactions were mild or moderate in intensity, limited to the application areas and resulted in discontinuation of treatment with Neupro in only 7 % of all subjects receiving Neupro.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following table covers adverse drug reactions from all studies in patients with early stage Parkinson's disease.

System/organ classes acc. to MedDRA	Very common >1/10	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000
Immune system disorder			hypersensitivity	
Metabolism and nutrition disorders		anorexia	decreased appetite	
Psychiatric disorders		sleep attacks ^a (see chapter below the table), hallucination (including visual and auditory), anxiety, abnormal dreams ^a , insomnia ^a	confusion state, sleep disorder, nightmares	psychotic disorder (including paranoid psychosis), increased libido (including hypersexuality), compulsive disorders (including pathologic gambling, punding)
Nervous system disorders	somnolence ^a , dizziness ^a	headache ^a , dizziness postural, dyskinesia, lethargia	tremor, balance disorder, dysgeusia, syncope, disturbance in attention, paraesthesia, memory impaired, vasovagal syncope, loss of consciousness	convulsion
Eye disorders (see section 4.4)			visual disturbance, photopsia, blurred vision	
Ear and labyrinth disorders			vertigo (incl. positional)	
Cardiac disorders			palpitations, heart rate increased	
Vascular disorders		orthostatic hypotension (see section 4.4), hypertension	hypotension	
Respiratory, thoracic and mediastinal disorders		cough ^a , hiccup ^a	dyspnoea	
Gastrointestinal disorders	nausea ^a , vomiting ^a ,	constipation ^a , dry mouth ^a , diarrhoea, dyspepsia ^a	abdominal pain, stomach discomfort	
Hepato-biliary disorder			hepatic enzyme increased (including GGT, ALAT, ASAT)	
Skin and		hyperhidrosis ^a ,	rash (incl. allergic;	

subcutaneous tissue disorders		erythema ^a ; pruritus	macular) (see section 4.4), skin irritation, exanthema, generalized pruritus	
Musculoskeletal and connective tissue disorder			joint swelling	
Reproductive system and breast disorder			erectile dysfunction	
General disorders and administration site conditions	application site reactions ^a (including erythema, pruritus, irritation, burning, dermatitis, inflammation, papulae, vesicle, pain) (see section 4.4)	oedema peripheral, asthenic conditions (incl. fatigue ^a , asthenia, malaise),	feeling abnormal, weight decreased, gait abnormal	
Injury, poisoning and procedural complications			fall	

^a These adverse drug reactions have been reported in the pooled placebo-controlled trials 1% more frequent than in the placebo-treated patients

Neupro has been associated with somnolence including excessive daytime somnolence and sudden sleep onset episodes. In isolated cases “sudden onset of sleep” occurred while driving and resulted in motor vehicle accidents. See also section 4.4 and 4.7

4.9 Overdose

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

There is no known antidote for overdose of dopamine agonists. In case of suspected overdose, the patch(es) should immediately be removed from the patient. Levels of rotigotine decrease after patch removal. Before stopping use of rotigotine completely see section 4.2.

The patient should be monitored closely, including heart rate, heart rhythm and blood pressure. Because rotigotine is over 90% protein bound, dialysis would not be expected to be beneficial. Treatment of overdose may require general supportive measures to maintain the vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonists, Rotigotine; ATC code: N04BC09

Rotigotine is a non-ergolinic D₃/D₂/D₁ dopamine agonist for the treatment of Parkinson’s disease. It is believed to elicit its beneficial effect by activation of the D₃, D₂ and D₁ receptors of the caudate-putamen in the brain.

Rotigotine alleviates signs and symptoms of early-stage idiopathic Parkinson’s disease.

Clinical studies:

The effectiveness of Neupro in the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease was evaluated in a multinational drug development program consisting of two pivotal, parallel, randomized, double-blind placebo controlled studies. These trials were conducted in patients who were not receiving concomitant dopamine agonist therapy and were either L-dopa naïve or previous L-dopa treatment was ≤ 6 months. The primary outcome assessment was the score for the Activities of Daily Living (ADL) component (Part II) plus the Motor Examination component (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS).

Efficacy was determined by the subject's response to therapy in terms of responder and absolute points improvement in the scores of ADL and Motor Examination combined (UPDRS part II+III) In one double blind study, 177 patients received rotigotine and 96 patients received placebo. The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 6 mg/24 h. Patients in each treatment group were maintained at their optimal dose for 6 months.

At the end of the maintenance treatment in 91% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 6 mg/24 h. An improvement of 20% was seen in 48% of the subjects receiving rotigotine and in 19% of the subjects receiving placebo (Difference 29% CI_{95%} 18%; 39%, $p < 0.0001$). With rotigotine, the mean improvement in the UPDRS score (Parts II + III) was -3.98 points (baseline 29.9 point) whereas in the placebo-treated arm a worsening of 1.31 points was observed (baseline 30.0 points) The difference was 5.28 points and statistically significant ($p < 0.0001$).

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

At the end of the maintenance treatment in 92% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 8 mg/24 h. An improvement of 20% was seen in 52% of the subjects receiving rotigotine, 68% of the subjects receiving ropinirole and 30% of the subjects receiving placebo (Difference rotigotine versus placebo 21.7%; CI_{95%} 11.1% ; 32.4% , difference ropinirole versus placebo 38.4% CI_{95%} 28.1% ; 48.6% , difference ropinirole versus rotigotine 16.6%; CI_{95%} .7.6% ; 25.7%). The mean improvement in the UPDRS score (Parts II + III) was 6.83 points (baseline 33.2 points) in the rotigotine arm, 10.78 point 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. The difference in effect between ropinirole and rotigotine was also statistically significant in favour of ropinirole.

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 displays a dose-proportional pharmacokinetic profile over a dose range of 2 mg/day (10 cm²) to 8 mg/day (40 cm²).

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 1% (hip versus abdomen) to 41% (shoulder versus thigh). However, there is no indication of a relevant impact on the clinical outcome.

Distribution

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

Metabolism

Rotigotine is metabolised to a great extent. Rotigotine is metabolised by N-dealkylation as well as direct and secondary conjugation. In vitro results indicate that different CYP isoforms are able to catalyse the N-dealkylation of rotigotine. Main metabolites are sulfates and glucuronide conjugates of the parent compound as well as N-desalkyl-metabolites, which are biologically inactive. The 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 elimination half-life is 5 to 7 hours.

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

Special patient groups

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

In subjects with moderate hepatic impairment or mild to severe renal impairment, no relevant increases of rotigotine plasma levels were observed. Neupro was not investigated in patients with severe hepatic impairment.

Plasma levels of conjugates of rotigotine and its desalkyl metabolites increase with impaired renal function. However, a contribution of these metabolites to clinical effects is unlikely.

5.3 Preclinical safety data

In repeated dose and long-term toxicity studies, the major effects were associated with the dopamine agonist related pharmacodynamic effects and the consequent decrease of prolactin secretion.

After a single dose of rotigotine, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident, but was slowly cleared over the 14-day observation period.

Retinal degeneration was observed by transmission microscopy at a dose equivalent to 5.6 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).

Protective liner:

Transparent fluoropolymer coated polyester film.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

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

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

6.6 Special precaution for disposal

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

7. MARKETING AUTHORISATION HOLDER

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Schwarz Pharma Ltd.
Shannon Industrial Estate
Shannon, Co.Clare
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

Medicinal product subject to medical prescription.

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

Not applicable.

• **OTHER CONDITIONS**

The MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

The MAH commits to performing the study detailed in the Pharmacovigilance Plan.

An updated Risk Management Plan should be provided as per the CHMP Guideline on Risk Management Systems for medicinal products for human use.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 7 [28] [100] 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 cm² 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)

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
28 transdermal patches
100 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package.

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

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/001 [7 transdermal patches]
EU/0/00/000/002 [28 transdermal patches]
EU/0/00/000/003 [100 transdermal patches]

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupro 2 mg/24h

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

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 7 [28] [100] 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 cm² 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)

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
28 transdermal patches
100 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package.

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

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/001 [7 transdermal patches]
EU/0/00/000/002 [28 transdermal patches]
EU/0/00/000/003 [100 transdermal patches]

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupro 4 mg/24h

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

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 7 [28] [100] 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 cm² 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)

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
28 transdermal patches
100 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package.

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

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/001 [7 transdermal patches]
EU/0/00/000/002 [28 transdermal patches]
EU/0/00/000/003 [100 transdermal patches]

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupro 6 mg/24h

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

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

BOX OF 7 [28] [100] 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 cm² 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)

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
28 transdermal patches
100 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package.

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

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/001 [7 transdermal patches]
EU/0/00/000/002 [28 transdermal patches]
EU/0/00/000/003 [100 transdermal patches]

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupro 8 mg/24h

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

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch.

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 cm² 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 cm² 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 cm² 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 cm² 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)

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package.

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

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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

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 cm² 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)

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches.
Week 1.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package.

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

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupro 2 mg/24h

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

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch.

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 cm² 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)

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches.
Week 2.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package.

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

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupro 4 mg/24h

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

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch.

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 cm² 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)

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches.
Week 3.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package.

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

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupro 6 mg/24h

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

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch.

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 cm² 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)

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches.
Week 4

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package.

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

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupro 8 mg/24h

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

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 2 mg/24 h transdermal patch Rotigotine

Read all of this leaflet carefully before you start using this medicine.

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

In this leaflet:

1. What Neupro is and what it is used for
2. Before you use Neupro
3. How to use Neupro
4. Possible side effects
5. How to store Neupro
6. Further information

1. WHAT Neupro IS AND WHAT IT IS USED FOR

Rotigotine, the active substance of Neupro, belongs to a group of medicines called dopamine agonists which stimulate dopamine receptors in the brain.

Neupro is used to treat the signs and symptoms of early-stage Parkinson's disease as monotherapy (i.e. without levodopa).

2. BEFORE YOU USE Neupro

Do not use Neupro

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

Take special care with Neupro

- This medicine may affect your blood pressure, so it should be measured regularly, especially at the beginning of your treatment.
- If you feel very drowsy or find that you fall asleep suddenly, please contact your doctor (see also Section 2, '**Driving and using machines**').
- Like with every patch or bandage, Neupro can cause skin reactions. These are normally mild and usually affect only the area of skin the patch has been on. We recommend that you put the patch in a different place every day. You should not use the same area of skin within 14 days. If you have a skin reaction which lasts for more than a few days, if a skin reaction becomes serious, or if the skin reaction spreads outside the area covered by the patch, please contact your

doctor. Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro.

- Regular eye examinations are recommended or if problems seeing occur.
- If you have severe liver problems, you may need to get a lower dose. Please contact your doctor, if your liver problems get worse.
- Compulsive behaviours including excessive gambling, hypersexuality (increased sex drive), increased libido (increased sexual interest), repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

Taking other medicines

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

Neuroleptics (medicines which affect how your brain works) or metoclopramide (used to treat nausea and vomiting) may make Neupro less effective. You should not take these medicines while you are using Neupro.

Please ask your doctor whether it is safe for you to drink alcohol or take sedating medicines (for example, benzodiazepine, medicines to treat mental disorders and medicines to treat depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect it. Before drinking alcohol please consult your doctor.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant or planning to become pregnant. The effects of rotigotine on pregnancy and the unborn baby are not known; therefore Neupro should not be used during pregnancy.

Neupro is not recommended if you are breast-feeding, as it is likely to reduce the amount of milk you produce. Rotigotine may also pass into your breast milk and affect your baby. If your doctor says you need to take Neupro, you should stop breast-feeding.

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

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.

In isolated cases people have fallen asleep while driving and this has caused accidents.

3. HOW TO USE Neupro

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

At the beginning of treatment you will start by using Neupro 2 mg/24 h daily. This dose will be increased weekly in steps of 2 mg/24 h until the right (maintenance) dose for your needs is reached.

The maximum dose is 8 mg/24 h, which is reached within 4 weeks. Strengths of 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h are available to reach the respective doses.

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, 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.

Do not cut Neupro into pieces.

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

Special patient groups

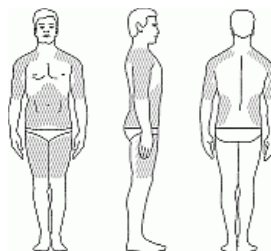
It is not necessary to adjust the dose depending on your sex, weight or age. Neupro should not be used by children.

Follow these instructions when using Neupro:

Where to stick the patch

Put the sticky side of the patch onto clean, dry, healthy skin on the following areas:

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



To help avoid skin irritation, stick Neupro onto a different area of skin each day (for example, on the right side of your body one day, then on the left side the next day and on your upper body one day, then on your lower body). You should not stick Neupro on the same area of skin twice within 14 days.

NOTE

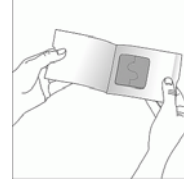
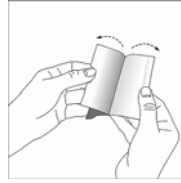
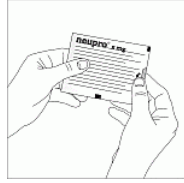
- You should put the patch where it will not be rubbed by tight clothing which could make it fall off.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least three days before sticking the patch there.
- Do not stick the patch on broken skin or on skin that is red, irritated or damaged.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing. The patch may become loose.
- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off after such activities.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area of skin covered from the sun, as it may cause changes in the colour of the skin.

How to use the patch

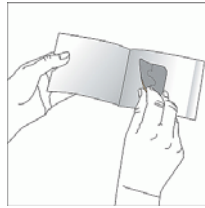
Each patch is packed in a sachet containing the medicine. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the protective liner.

You should stick a Neupro patch onto the skin once a day. You should leave the patch on your skin for 24 hours and then replace it with a new one. Make sure that you take the old patch off before sticking on the new one. You should replace the patch at around the same time every day.

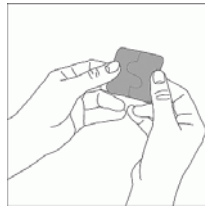
- 1.**
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.



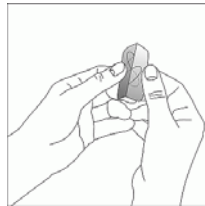
- 2.**
Take the patch out of the sachet.



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



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



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



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



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



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



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

How to change the patch

Before you put on a new patch, slowly and carefully peel off the used patch.

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

Do not use alcohol or other dissolving liquids such as nail polish remover or other solvents as these may irritate your skin.

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

What to do with the used and unused patches

Used patches still contain active ingredient, which may be harmful to others. Fold the used patch with the sticky inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.

You should follow local guidelines for domestic waste when throwing away used or unused patches or return them to the pharmacy. Do not flush them down the toilet, nor place them in liquid waste disposal systems.

Skin reactions

You may get skin reactions from the patch. These are usually mild or moderate and only affect the area of the skin where the patch has been. The reactions normally disappear after a few hours when you remove the patch.

If you have a skin reaction that lasts longer than a few days, a severe reaction, or a skin reaction that spreads outside the area of skin covered by the patch, you should talk to your doctor.

If you use more Neupro than you should

Taking higher dosages of Neupro than your doctor has prescribed may cause nausea, vomiting, low blood pressure, fast heart beats, hallucinations, confusion or extreme sleepiness. If you have used more patches than your doctor told you to, remove the extra patches.

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

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

If you stop using Neupro

Although not reported with Neupro, if you are on a dose of Neupro higher than 2 mg, and you stop using the patches suddenly, you could have symptoms like fever, rigid joints, increased heart rate or disturbance of consciousness. So, your dose of Neupro should be reduced gradually by 2 mg every other day.

4. POSSIBLE SIDE EFFECTS

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

Very common side effects (happening in more than 1 in 10 patients)

You may have nausea and vomiting at the beginning of therapy. These effects are usually mild or moderate and transient even if you continue with your treatment. Other very common side effects are dizziness, feeling sleepy, and skin irritations under the patch such as redness and itching.

Common side effects (happening in 1 in 100 to 1 in 10 patients)

Common side effects are falling asleep suddenly without warning, seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), feeling dizzy when standing up after sitting or lying down because of reduced blood pressure, increased blood pressure, anxiety, diarrhoea, headache, having unusual dreams, being unable to sleep, feeling weak (conditions including fatigue, debility and feeling of discomfort), swelling of legs and feet, lethargy, decreased appetite (anorexia), constipation, hiccups, cough, heartburn, dry mouth, increased sweating,

Uncommon side effects (happening in 1 in 1,000 to 1 in 100 patients)

Uncommon side effects are fainting, fainting due to a drop in blood pressure when standing up, loss of consciousness, increased or abnormal liver function test results, increased heart rate, reduced blood pressure, shortness of breath, rash, generalised itching, feeling of abnormal motion (vertigo), poor balance, being unable to walk properly, falling, tremors, confusion, visual disturbances such as seeing colours or lights or blurred vision, reduced concentration, loss of memory, sleep disorders, nightmares, numbness or tingling sensation, feeling of increased heart rate (palpitations), weight loss, stomach discomfort and pain, swelling of the joints, impotence in men (being unable to achieve or maintain an erection), feeling abnormal, food and drink tasting different.

Rare side effects (happening in 1 in 10,000 to 1 in 1,000 patients)

Rare side effects are psychotic disorders including abnormal thinking about reality and behaviour (paranoid psychosis), or an unusual urge to carry out a certain activity including increased sex drive, and involuntary muscle spasms (seizure, convulsion), Compulsive disorders (e.g. excessive gambling, repetitive meaningless actions (punding) have been observed in subjects treated with Neupro.

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

5. HOW TO STORE Neupro

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

- Store in the original package.

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.
Each patch releases 2 mg of rotigotine per 24 hours. Each patch of 10 cm² 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).
Protective liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

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

Neupro is available in the following pack-sizes:

Cartons containing 7, 28 or 100 patches, which are individually sealed in sachets.

Marketing Authorisation Holder and Manufacturer

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

This leaflet was last approved in {MM/YYYY}

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 4 mg/24 h transdermal patch Rotigotine

Read all of this leaflet carefully before you start using this medicine.

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

In this leaflet:

1. What Neupro is and what it is used for
2. Before you use Neupro
3. How to use Neupro
4. Possible side effects
5. How to store Neupro
6. Further information

1. WHAT Neupro IS AND WHAT IT IS USED FOR

Rotigotine, the active substance of Neupro, belongs to a group of medicines called dopamine agonists which stimulate dopamine receptors in the brain.

Neupro is used to treat the signs and symptoms of early-stage Parkinson's disease as monotherapy (i.e. without levodopa).

2. BEFORE YOU USE Neupro

Do not use Neupro

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

Take special care with Neupro

- This medicine may affect your blood pressure, so it should be measured regularly, especially at the beginning of your treatment.
- If you feel very drowsy or find that you fall asleep suddenly, please contact your doctor (see also Section 2, '**Driving and using machines**').
- Like with every patch or bandage, Neupro can cause skin reactions. These are normally mild and usually affect only the area of skin the patch has been on. We recommend that you put the patch in a different place every day. You should not use the same area of skin within 14 days. If you have a skin reaction which lasts for more than a few days, if a skin reaction becomes serious, or if the skin reaction spreads outside the area covered by the patch, please contact your

doctor. Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro.

- Regular eye examinations are recommended or if problems seeing occur.
- If you have severe liver problems, you may need to get a lower dose. Please contact your doctor, if your liver problems get worse.
- Compulsive behaviours including excessive gambling, hypersexuality (increased sex drive), increased libido (increased sexual interest), repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

Taking other medicines

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

Neuroleptics (medicines which affect how your brain works) or metoclopramide (used to treat nausea and vomiting) may make Neupro less effective. You should not take these medicines while you are using Neupro.

Please ask your doctor whether it is safe for you to drink alcohol or take sedating medicines (for example, benzodiazepine, medicines to treat mental disorders and medicines to treat depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect it. Before drinking alcohol please consult your doctor.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant or planning to become pregnant. The effects of rotigotine on pregnancy and the unborn baby are not known; therefore Neupro should not be used during pregnancy.

Neupro is not recommended if you are breast-feeding, as it is likely to reduce the amount of milk you produce. Rotigotine may also pass into your breast milk and affect your baby. If your doctor says you need to take Neupro, you should stop breast-feeding.

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

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.

In isolated cases people have fallen asleep while driving and this has caused accidents.

3. HOW TO USE Neupro

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

At the beginning of treatment you will start by using Neupro 2 mg/24 h daily. This dose will be increased weekly in steps of 2 mg/24 h until the right (maintenance) dose for your needs is reached.

The maximum dose is 8 mg/24 h, which is reached within 4 weeks. Strengths of 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h are available to reach the respective doses.

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, 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.

Do not cut Neupro into pieces.

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

Special patient groups

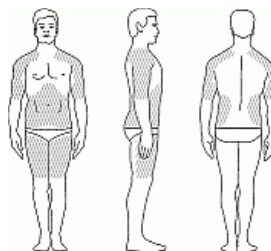
It is not necessary to adjust the dose depending on your sex, weight or age. Neupro should not be used by children.

Follow these instructions when using Neupro:

Where to stick the patch

Put the sticky side of the patch onto clean, dry, healthy skin on the following areas:

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



To help avoid skin irritation, stick Neupro onto a different area of skin each day (for example, on the right side of your body one day, then on the left side the next day and on your upper body one day, then on your lower body). You should not stick Neupro on the same area of skin twice within 14 days.

NOTE

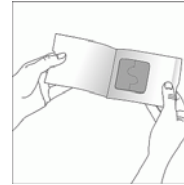
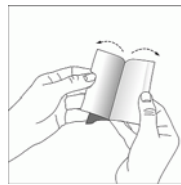
- You should put the patch where it will not be rubbed by tight clothing which could make it fall off.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least three days before sticking the patch there.
- Do not stick the patch on broken skin or on skin that is red, irritated or damaged.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing. The patch may become loose.
- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off after such activities.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area of skin covered from the sun, as it may cause changes in the colour of the skin.

How to use the patch

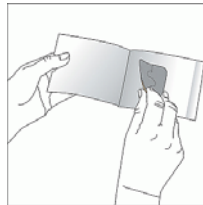
Each patch is packed in a sachet containing the medicine. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the protective liner.

You should stick a Neupro patch onto the skin once a day. You should leave the patch on your skin for 24 hours and then replace it with a new one. Make sure that you take the old patch off before sticking on the new one. You should replace the patch at around the same time every day.

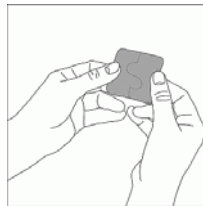
1.
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.



2.
Take the patch out of the sachet.



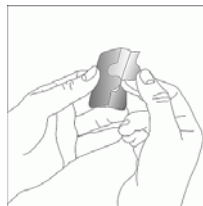
3.
The sticky side of the patch is covered by a transparent protective liner. Hold the patch in both hands with the protective liner facing you.



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



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



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



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



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



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

How to change the patch

Before you put on a new patch, slowly and carefully peel off the used patch.

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

Do not use alcohol or other dissolving liquids such as nail polish remover or other solvents as these may irritate your skin.

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

What to do with the used and unused patches

Used patches still contain active ingredient, which may be harmful to others. Fold the used patch with the sticky inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.

You should follow local guidelines for domestic waste when throwing away used or unused patches or return them to the pharmacy. Do not flush them down the toilet, nor place them in liquid waste disposal systems.

Skin reactions

You may get skin reactions from the patch. These are usually mild or moderate and only affect the area of the skin where the patch has been. The reactions normally disappear after a few hours when you remove the patch.

If you have a skin reaction that lasts longer than a few days, a severe reaction, or a skin reaction that spreads outside the area of skin covered by the patch, you should talk to your doctor.

If you use more Neupro than you should

Taking higher dosages of Neupro than your doctor has prescribed may cause nausea, vomiting, low blood pressure, fast heart beats, hallucinations, confusion or extreme sleepiness. If you have used more patches than your doctor told you to, remove the extra patches.

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

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

If you stop using Neupro

Although not reported with Neupro, if you are on a dose of Neupro higher than 2 mg, and you stop using the patches suddenly, you could have symptoms like fever, rigid joints, increased heart rate or disturbance of consciousness. So, your dose of Neupro should be reduced gradually by 2 mg every other day.

4. POSSIBLE SIDE EFFECTS

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

Very common side effects (happening in more than 1 in 10 patients)

You may have nausea and vomiting at the beginning of therapy. These effects are usually mild or moderate and transient even if you continue with your treatment. Other very common side effects are dizziness, feeling sleepy, and skin irritations under the patch such as redness and itching.

Common side effects (happening in 1 in 100 to 1 in 10 patients)

Common side effects are falling asleep suddenly without warning, seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), feeling dizzy when standing up after sitting or lying down because of reduced blood pressure, increased blood pressure, anxiety, diarrhoea, headache, having unusual dreams, being unable to sleep, feeling weak (conditions including fatigue, debility and feeling of discomfort), swelling of legs and feet, lethargy, decreased appetite (anorexia), constipation, hiccups, cough, heartburn, dry mouth, increased sweating,

Uncommon side effects (happening in 1 in 1,000 to 1 in 100 patients)

Uncommon side effects are fainting, fainting due to a drop in blood pressure when standing up, loss of consciousness, increased or abnormal liver function test results, increased heart rate, reduced blood pressure, shortness of breath, rash, generalised itching, feeling of abnormal motion (vertigo), poor balance, being unable to walk properly, falling, tremors, confusion, visual disturbances such as seeing colours or lights or blurred vision, reduced concentration, loss of memory, sleep disorders, nightmares, numbness or tingling sensation, feeling of increased heart rate (palpitations), weight loss, stomach discomfort and pain, swelling of the joints, impotence in men (being unable to achieve or maintain an erection), feeling abnormal, food and drink tasting different.

Rare side effects (happening in 1 in 10,000 to 1 in 1,000 patients)

Rare side effects are psychotic disorders including abnormal thinking about reality and behaviour (paranoid psychosis), or an unusual urge to carry out a certain activity including increased sex drive, and involuntary muscle spasms (seizure, convulsion), Compulsive disorders (e.g. excessive gambling, repetitive meaningless actions (punding) have been observed in subjects treated with Neupro.

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

5. HOW TO STORE Neupro

- Keep out of the reach and sight of children.
- Do not use Neupro after the expiry date which is stated on the label and carton.

- Do not store above 25°C.
- Store in the original package.

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.
Each patch releases 4 mg of rotigotine per 24 hours. Each patch of 20 cm² contains 9.0 mg of rotigotine.
- The other ingredients are poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, sodium metabisulphite (E223), ascorbyl palmitate (E304) and DL- α -tocopherol (E307).
Backing layer: Polyester film, siliconized, aluminized, colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7).
Protective liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

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

Neupro is available in the following pack-sizes:

Cartons containing 7, 28 or 100 patches, which are individually sealed in sachets.

Marketing Authorisation Holder and Manufacturer

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

This leaflet was last approved in {MM/YYYY}

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 6 mg/24 h transdermal patch Rotigotine

Read all of this leaflet carefully before you start using this medicine.

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

In this leaflet:

1. What Neupro is and what it is used for
2. Before you use Neupro
3. How to use Neupro
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1. WHAT Neupro IS AND WHAT IT IS USED FOR

Rotigotine, the active substance of Neupro, belongs to a group of medicines called dopamine agonists which stimulate dopamine receptors in the brain.

Neupro is used to treat the signs and symptoms of early-stage Parkinson's disease as monotherapy (i.e. without levodopa).

2. BEFORE YOU USE Neupro

Do not use Neupro

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

Take special care with Neupro

- This medicine may affect your blood pressure, so it should be measured regularly, especially at the beginning of your treatment.
- If you feel very drowsy or find that you fall asleep suddenly, please contact your doctor (see also Section 2, '**Driving and using machines**').
- Like with every patch or bandage, Neupro can cause skin reactions. These are normally mild and usually affect only the area of skin the patch has been on. We recommend that you put the patch in a different place every day. You should not use the same area of skin within 14 days. If you have a skin reaction which lasts for more than a few days, if a skin reaction becomes serious, or if the skin reaction spreads outside the area covered by the patch, please contact your

doctor. Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro.

- Regular eye examinations are recommended or if problems seeing occur.
- If you have severe liver problems, you may need to get a lower dose. Please contact your doctor, if your liver problems get worse.
- Compulsive behaviours including excessive gambling, hypersexuality (increased sex drive), increased libido (increased sexual interest), repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

Taking other medicines

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

Neuroleptics (medicines which affect how your brain works) or metoclopramide (used to treat nausea and vomiting) may make Neupro less effective. You should not take these medicines while you are using Neupro.

Please ask your doctor whether it is safe for you to drink alcohol or take sedating medicines (for example, benzodiazepine, medicines to treat mental disorders and medicines to treat depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect it. Before drinking alcohol please consult your doctor.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant or planning to become pregnant. The effects of rotigotine on pregnancy and the unborn baby are not known; therefore Neupro should not be used during pregnancy.

Neupro is not recommended if you are breast-feeding, as it is likely to reduce the amount of milk you produce. Rotigotine may also pass into your breast milk and affect your baby. If your doctor says you need to take Neupro, you should stop breast-feeding.

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

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.

In isolated cases people have fallen asleep while driving and this has caused accidents.

3. HOW TO USE Neupro

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

At the beginning of treatment you will start by using Neupro 2 mg/24 h daily. This dose will be increased weekly in steps of 2 mg/24 h until the right (maintenance) dose for your needs is reached.

The maximum dose is 8 mg/24 h, which is reached within 4 weeks. Strengths of 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h are available to reach the respective doses.

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, 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.

Do not cut Neupro into pieces.

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

Special patient groups

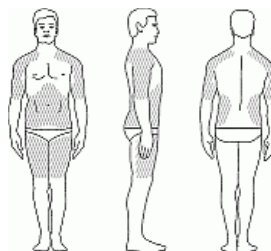
It is not necessary to adjust the dose depending on your sex, weight or age. Neupro should not be used by children.

Follow these instructions when using Neupro:

Where to stick the patch

Put the sticky side of the patch onto clean, dry, healthy skin on the following areas:

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



To help avoid skin irritation, stick Neupro onto a different area of skin each day (for example, on the right side of your body one day, then on the left side the next day and on your upper body one day, then on your lower body). You should not stick Neupro on the same area of skin twice within 14 days.

NOTE

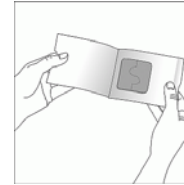
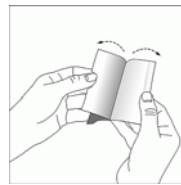
- You should put the patch where it will not be rubbed by tight clothing which could make it fall off.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least three days before sticking the patch there.
- Do not stick the patch on broken skin or on skin that is red, irritated or damaged.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing. The patch may become loose.
- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off after such activities.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area of skin covered from the sun, as it may cause changes in the colour of the skin.

How to use the patch

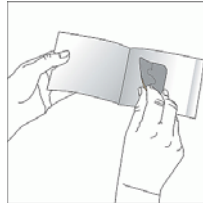
Each patch is packed in a sachet containing the medicine. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the protective liner.

You should stick a Neupro patch onto the skin once a day. You should leave the patch on your skin for 24 hours and then replace it with a new one. Make sure that you take the old patch off before sticking on the new one. You should replace the patch at around the same time every day.

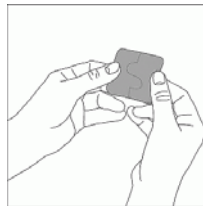
1.
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.



2.
Take the patch out of the sachet.



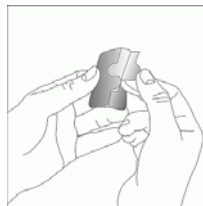
3.
The sticky side of the patch is covered by a transparent protective liner. Hold the patch in both hands with the protective liner facing you.



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



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



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



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



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



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

How to change the patch

Before you put on a new patch, slowly and carefully peel off the used patch.

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

Do not use alcohol or other dissolving liquids such as nail polish remover or other solvents as these may irritate your skin.

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

What to do with the used and unused patches

Used patches still contain active ingredient, which may be harmful to others. Fold the used patch with the sticky inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.

You should follow local guidelines for domestic waste when throwing away used or unused patches or return them to the pharmacy. Do not flush them down the toilet, nor place them in liquid waste disposal systems.

Skin reactions

You may get skin reactions from the patch. These are usually mild or moderate and only affect the area of the skin where the patch has been. The reactions normally disappear after a few hours when you remove the patch.

If you have a skin reaction that lasts longer than a few days, a severe reaction, or a skin reaction that spreads outside the area of skin covered by the patch, you should talk to your doctor.

If you use more Neupro than you should

Taking higher dosages of Neupro than your doctor has prescribed may cause nausea, vomiting, low blood pressure, fast heart beats, hallucinations, confusion or extreme sleepiness. If you have used more patches than your doctor told you to, remove the extra patches.

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

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

If you stop using Neupro

Although not reported with Neupro, if you are on a dose of Neupro higher than 2 mg, and you stop using the patches suddenly, you could have symptoms like fever, rigid joints, increased heart rate or disturbance of consciousness. So, your dose of Neupro should be reduced gradually by 2 mg every other day.

4. POSSIBLE SIDE EFFECTS

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

Very common side effects (happening in more than 1 in 10 patients)

You may have nausea and vomiting at the beginning of therapy. These effects are usually mild or moderate and transient even if you continue with your treatment. Other very common side effects are dizziness, feeling sleepy, and skin irritations under the patch such as redness and itching.

Common side effects (happening in 1 in 100 to 1 in 10 patients)

Common side effects are falling asleep suddenly without warning, seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), feeling dizzy when standing up after sitting or lying down because of reduced blood pressure, increased blood pressure, anxiety, diarrhoea, headache, having unusual dreams, being unable to sleep, feeling weak (conditions including fatigue, debility and feeling of discomfort), swelling of legs and feet, lethargy, decreased appetite (anorexia), constipation, hiccups, cough, heartburn, dry mouth, increased sweating,

Uncommon side effects (happening in 1 in 1,000 to 1 in 100 patients)

Uncommon side effects are fainting, fainting due to a drop in blood pressure when standing up, loss of consciousness, increased or abnormal liver function test results, increased heart rate, reduced blood pressure, shortness of breath, rash, generalised itching, feeling of abnormal motion (vertigo), poor balance, being unable to walk properly, falling, tremors, confusion, visual disturbances such as seeing colours or lights or blurred vision, reduced concentration, loss of memory, sleep disorders, nightmares, numbness or tingling sensation, feeling of increased heart rate (palpitations), weight loss, stomach discomfort and pain, swelling of the joints, impotence in men (being unable to achieve or maintain an erection), feeling abnormal, food and drink tasting different.

Rare side effects (happening in 1 in 10,000 to 1 in 1,000 patients)

Rare side effects are psychotic disorders including abnormal thinking about reality and behaviour (paranoid psychosis), or an unusual urge to carry out a certain activity including increased sex drive, and involuntary muscle spasms (seizure, convulsion), Compulsive disorders (e.g. excessive gambling, repetitive meaningless actions (punding) have been observed in subjects treated with Neupro.

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

5. HOW TO STORE Neupro

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

- Store in the original package.

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.
Each patch releases 6 mg of rotigotine per 24 hours. Each patch of 30 cm² contains 13.5 mg of rotigotine.
- The other ingredients are poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, sodium metabisulphite (E223), ascorbyl palmitate (E304) and DL- α -tocopherol (E307).
Backing layer: Polyester film, siliconized, aluminized, colour coated with a pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7).
Protective liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

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

Neupro is available in the following pack-sizes:

Cartons containing 7, 28 or 100 patches, which are individually sealed in sachets.

Marketing Authorisation Holder and Manufacturer

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

This leaflet was last approved in {MM/YYYY}

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupro 8 mg/24 h transdermal patch Rotigotine

Read all of this leaflet carefully before you start using this medicine.

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

In this leaflet:

1. What Neupro is and what it is used for
2. Before you use Neupro
3. How to use Neupro
4. Possible side effects
5. How to store Neupro
6. Further information

1. WHAT Neupro IS AND WHAT IT IS USED FOR

Rotigotine, the active substance of Neupro, belongs to a group of medicines called dopamine agonists which stimulate dopamine receptors in the brain.

Neupro is used to treat the signs and symptoms of early-stage Parkinson's disease as monotherapy (i.e. without levodopa).

2. BEFORE YOU USE Neupro

Do not use Neupro

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

Take special care with Neupro

- This medicine may affect your blood pressure, so it should be measured regularly, especially at the beginning of your treatment.
- If you feel very drowsy or find that you fall asleep suddenly, please contact your doctor (see also Section 2, '**Driving and using machines**').
- Like with every patch or bandage, Neupro can cause skin reactions. These are normally mild and usually affect only the area of skin the patch has been on. We recommend that you put the patch in a different place every day. You should not use the same area of skin within 14 days. If you have a skin reaction which lasts for more than a few days, if a skin reaction becomes serious, or if the skin reaction spreads outside the area covered by the patch, please contact your

doctor. Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro.

- Regular eye examinations are recommended or if problems seeing occur.
- If you have severe liver problems, you may need to get a lower dose. Please contact your doctor, if your liver problems get worse.
- Compulsive behaviours including excessive gambling, hypersexuality (increased sex drive), increased libido (increased sexual interest), repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

Taking other medicines

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

Neuroleptics (medicines which affect how your brain works) or metoclopramide (used to treat nausea and vomiting) may make Neupro less effective. You should not take these medicines while you are using Neupro.

Please ask your doctor whether it is safe for you to drink alcohol or take sedating medicines (for example, benzodiazepine, medicines to treat mental disorders and medicines to treat depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect it. Before drinking alcohol please consult your doctor.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant or planning to become pregnant. The effects of rotigotine on pregnancy and the unborn baby are not known; therefore Neupro should not be used during pregnancy.

Neupro is not recommended if you are breast-feeding, as it is likely to reduce the amount of milk you produce. Rotigotine may also pass into your breast milk and affect your baby. If your doctor says you need to take Neupro, you should stop breast-feeding.

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

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.

In isolated cases people have fallen asleep while driving and this has caused accidents.

3. HOW TO USE Neupro

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

At the beginning of treatment you will start by using Neupro 2 mg/24 h daily. This dose will be increased weekly in steps of 2 mg/24 h until the right (maintenance) dose for your needs is reached.

The maximum dose is 8 mg/24 h, which is reached within 4 weeks. Strengths of 2 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h are available to reach the respective doses.

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, 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.

Do not cut Neupro into pieces.

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

Special patient groups

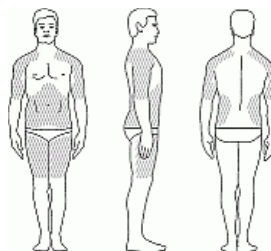
It is not necessary to adjust the dose depending on your sex, weight or age. Neupro should not be used by children.

Follow these instructions when using Neupro:

Where to stick the patch

Put the sticky side of the patch onto clean, dry, healthy skin on the following areas:

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



To help avoid skin irritation, stick Neupro onto a different area of skin each day (for example, on the right side of your body one day, then on the left side the next day and on your upper body one day, then on your lower body). You should not stick Neupro on the same area of skin twice within 14 days.

NOTE

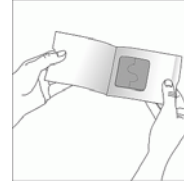
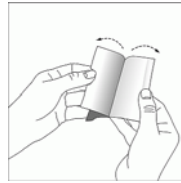
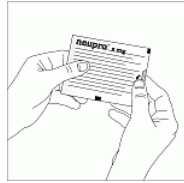
- You should put the patch where it will not be rubbed by tight clothing which could make it fall off.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least three days before sticking the patch there.
- Do not stick the patch on broken skin or on skin that is red, irritated or damaged.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing. The patch may become loose.
- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off after such activities.
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area of skin covered from the sun, as it may cause changes in the colour of the skin.

How to use the patch

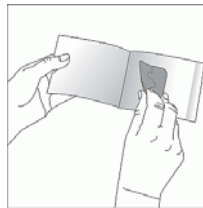
Each patch is packed in a sachet containing the medicine. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the protective liner.

You should stick a Neupro patch onto the skin once a day. You should leave the patch on your skin for 24 hours and then replace it with a new one. Make sure that you take the old patch off before sticking on the new one. You should replace the patch at around the same time every day.

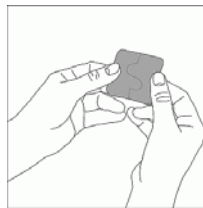
- 1.**
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.



- 2.**
Take the patch out of the sachet.



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



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



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



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



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



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



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

How to change the patch

Before you put on a new patch, slowly and carefully peel off the used patch.

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

Do not use alcohol or other dissolving liquids such as nail polish remover or other solvents as these may irritate your skin.

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

What to do with the used and unused patches

Used patches still contain active ingredient, which may be harmful to others. Fold the used patch with the sticky inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.

You should follow local guidelines for domestic waste when throwing away used or unused patches or return them to the pharmacy. Do not flush them down the toilet, nor place them in liquid waste disposal systems.

Skin reactions

You may get skin reactions from the patch. These are usually mild or moderate and only affect the area of the skin where the patch has been. The reactions normally disappear after a few hours when you remove the patch.

If you have a skin reaction that lasts longer than a few days, a severe reaction, or a skin reaction that spreads outside the area of skin covered by the patch, you should talk to your doctor.

If you use more Neupro than you should

Taking higher dosages of Neupro than your doctor has prescribed may cause nausea, vomiting, low blood pressure, fast heart beats, hallucinations, confusion or extreme sleepiness. If you have used more patches than your doctor told you to, remove the extra patches.

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

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

If you stop using Neupro

Although not reported with Neupro, if you are on a dose of Neupro higher than 2 mg, and you stop using the patches suddenly, you could have symptoms like fever, rigid joints, increased heart rate or disturbance of consciousness. So, your dose of Neupro should be reduced gradually by 2 mg every other day.

4. POSSIBLE SIDE EFFECTS

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

Very common side effects (happening in more than 1 in 10 patients)

You may have nausea and vomiting at the beginning of therapy. These effects are usually mild or moderate and transient even if you continue with your treatment. Other very common side effects are dizziness, feeling sleepy, and skin irritations under the patch such as redness and itching.

Common side effects (happening in 1 in 100 to 1 in 10 patients)

Common side effects are falling asleep suddenly without warning, seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), feeling dizzy when standing up after sitting or lying down because of reduced blood pressure, increased blood pressure, anxiety, diarrhoea, headache, having unusual dreams, being unable to sleep, feeling weak (conditions including fatigue, debility and feeling of discomfort), swelling of legs and feet, lethargy, decreased appetite (anorexia), constipation, hiccups, cough, heartburn, dry mouth, increased sweating,

Uncommon side effects (happening in 1 in 1,000 to 1 in 100 patients)

Uncommon side effects are fainting, fainting due to a drop in blood pressure when standing up, loss of consciousness, increased or abnormal liver function test results, increased heart rate, reduced blood pressure, shortness of breath, rash, generalised itching, feeling of abnormal motion (vertigo), poor balance, being unable to walk properly, falling, tremors, confusion, visual disturbances such as seeing colours or lights or blurred vision, reduced concentration, loss of memory, sleep disorders, nightmares, numbness or tingling sensation, feeling of increased heart rate (palpitations), weight loss, stomach discomfort and pain, swelling of the joints, impotence in men (being unable to achieve or maintain an erection), feeling abnormal, food and drink tasting different.

Rare side effects (happening in 1 in 10,000 to 1 in 1,000 patients)

Rare side effects are psychotic disorders including abnormal thinking about reality and behaviour (paranoid psychosis), or an unusual urge to carry out a certain activity including increased sex drive, and involuntary muscle spasms (seizure, convulsion), Compulsive disorders (e.g. excessive gambling, repetitive meaningless actions (punding) have been observed in subjects treated with Neupro.

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

5. HOW TO STORE Neupro

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

- Store in the original package.

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.
Each patch releases 8 mg of rotigotine per 24 hours. Each patch of 40 cm² 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).
Protective liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

Neupro is a transdermal patch. It is thin and has three layers. It is square-shaped with rounded edges. The outside is tan-coloured and is imprinted with Neupro 8 mg /24 h.

Neupro is available in the following pack-sizes:

Cartons containing 7, 28 or 100 patches, which are individually sealed in sachets.

Marketing Authorisation Holder and Manufacturer

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

This leaflet was last approved in {MM/YYYY}

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you start using this medicine.

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

In this leaflet:

1. What Neupro is and what it is used for
2. Before you use Neupro
3. How to use Neupro
4. Possible side effects
5. How to store Neupro
6. Further information

1. WHAT Neupro IS AND WHAT IT IS USED FOR

Rotigotine, the active substance of Neupro, belongs to a group of medicines called dopamine agonists which stimulate dopamine receptors in the brain.

Neupro is used to treat the signs and symptoms of early-stage Parkinson's disease as monotherapy (i.e. without levodopa).

2. BEFORE YOU USE Neupro

Do not use Neupro

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

Take special care with Neupro

- This medicine may affect your blood pressure, so it should be measured regularly, especially at the beginning of your treatment.
- If you feel very drowsy or find that you fall asleep suddenly, please contact your doctor (see also Section 2, '**Driving and using machines**').
- Like with every patch or bandage, Neupro can cause skin reactions. These are normally mild and usually affect only the area of skin the patch has been on. We recommend that you put the

patch in a different place every day. You should not use the same area of skin within 14 days. If you have a skin reaction which lasts for more than a few days, if a skin reaction becomes serious, or if the skin reaction spreads outside the area covered by the patch, please contact your doctor. Avoid sunlight and solarium exposure on areas of skin showing any kind of skin reaction caused by Neupro.

- Regular eye examinations are recommended or if problems seeing occur.
- If you have severe liver problems, you may need to get a lower dose. Please contact your doctor, if your liver problems get worse.
- Compulsive behaviours including excessive gambling, hypersexuality (increased sex drive), increased libido (increased sexual interest), repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

Taking other medicines

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

Neuroleptics (medicines which affect how your brain works) or metoclopramide (used to treat nausea and vomiting) may make Neupro less effective. You should not take these medicines while you are using Neupro.

Please ask your doctor whether it is safe for you to drink alcohol or take sedating medicines (for example, benzodiazepine, medicines to treat mental disorders and medicines to treat depression) while you are using Neupro.

Using Neupro with food and drink

Because rotigotine enters your bloodstream through your skin, food or drink does not affect it. Before drinking alcohol please consult your doctor.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant or planning to become pregnant. The effects of rotigotine on pregnancy and the unborn baby are not known; therefore Neupro should not be used during pregnancy.

Neupro is not recommended if you are breast-feeding, as it is likely to reduce the amount of milk you produce. Rotigotine may also pass into your breast milk and affect your baby. If your doctor says you need to take Neupro, you should stop breast-feeding.

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

Driving and using machines

Neupro may make you feel very drowsy, and you may fall asleep very suddenly. If this affects you, you should not drive or take part in activities where not being alert may put you or others at risk of serious injury, for example, using machines.

In isolated cases people have fallen asleep while driving and this has caused accidents.

3. HOW TO USE Neupro

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

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.

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, 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.

Do not cut Neupro into pieces.

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

Special patient groups

It is not necessary to adjust the dose depending on your sex, weight or age.

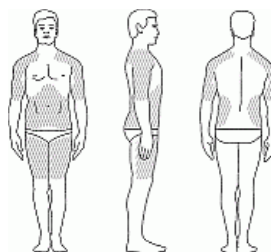
Neupro should not be used by children.

Follow these instructions when using Neupro:

Where to stick the patch

Put the sticky side of the patch onto clean, dry, healthy skin on the following areas:

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



To help avoid skin irritation, stick Neupro onto a different area of skin each day (for example, on the right side of your body one day, then on the left side the next day and on your upper body one day, then on your lower body). You should not stick Neupro on the same area of skin twice within 14 days.

NOTE

- You should put the patch where it will not be rubbed by tight clothing which could make it fall off.
- If you need to stick the patch to a hairy area of skin, you must shave the area at least three days before sticking the patch there.
- Do not stick the patch on broken skin or on skin that is red, irritated or damaged.
- Do not use creams, oils, lotions, powders or other skin products on the area of skin you will be sticking the patch on or near a patch you are already wearing. The patch may become loose.
- Bathing, showering and exercising should not affect how Neupro works. Nevertheless, check that the patch has not fallen off after such activities.

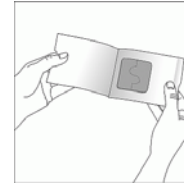
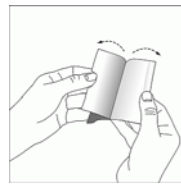
- You should avoid external heat (for example excessive sunlight, saunas, hot baths heating pads or hot-water bottles) on the area of the patch.
- If the patch has irritated your skin, you should keep that area of skin covered from the sun, as it may cause changes in the colour of the skin.

How to use the patch

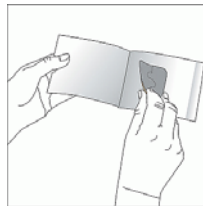
Each patch is packed in a sachet containing the medicine. You should stick Neupro onto your skin as soon as you have opened the sachet and removed the protective liner.

You should stick a Neupro patch onto the skin once a day. You should leave the patch on your skin for 24 hours and then replace it with a new one. Make sure that you take the old patch off before sticking on the new one. You should replace the patch at around the same time every day.

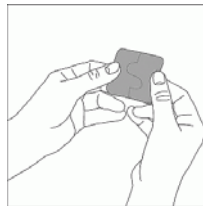
- 1.**
To open the sachet, hold the two sides of the sachet. Peel apart the foil and open the sachet.



- 2.**
Take the patch out of the sachet.



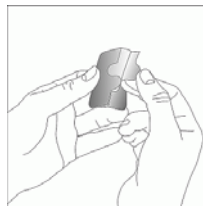
- 3.**
The sticky side of the patch is covered by a transparent protective liner. Hold the patch in both hands with the protective liner facing you.



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



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



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



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



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



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

How to change the patch

Before you put on a new patch, slowly and carefully peel off the used patch.

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

Do not use alcohol or other dissolving liquids such as nail polish remover or other solvents as these may irritate your skin.

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

What to do with the used and unused patches

Used patches still contain active ingredient, which may be harmful to others. Fold the used patch with the sticky inwards. Put the patch in the original sachet and then throw it away safely, out of the reach of children.

You should follow local guidelines for domestic waste when throwing away used or unused patches or return them to the pharmacy. Do not flush them down the toilet, nor place them in liquid waste disposal systems.

Skin reactions

You may get skin reactions from the patch. These are usually mild or moderate and only affect the area of the skin where the patch has been. The reactions normally disappear after a few hours when you remove the patch.

If you have a skin reaction that lasts longer than a few days, a severe reaction, or a skin reaction that spreads outside the area of skin covered by the patch, you should talk to your doctor.

If you use more Neupro than you should

Taking higher dosages of Neupro than your doctor has prescribed may cause nausea, vomiting, low blood pressure, fast heart beats, hallucinations, confusion or extreme sleepiness. If you have used more patches than your doctor told you to, remove the extra patches.

If you have used a different patch (e.g. Neupro 4 mg/24 h instead of Neupro 2 mg/24 h) than your doctor told you to, remove the different patch and apply the accurate one.

If you have any unpleasant reactions, contact your doctor.

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

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

If you stop using Neupro

Although not reported with Neupro, if you are on a dose of Neupro higher than 2 mg, and you stop using the patches suddenly, you could have symptoms like fever, rigid joints, increased heart rate or disturbance of consciousness. So, your dose of Neupro should be reduced gradually by 2 mg every other day.

4. POSSIBLE SIDE EFFECTS

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

Very common side effects (happening in more than 1 in 10 patients)

You may have nausea and vomiting at the beginning of therapy. These effects are usually mild or moderate and transient even if you continue with your treatment. Other very common side effects are dizziness, feeling sleepy, and skin irritations under the patch such as redness and itching.

Common side effects (happening in 1 in 100 to 1 in 10 patients)

Common side effects are falling asleep suddenly without warning, seeing or hearing things that are not real (hallucinations), involuntary movements related to Parkinson's disease (dyskinesia), feeling dizzy when standing up after sitting or lying down because of reduced blood pressure, increased blood pressure, anxiety, diarrhoea, headache, having unusual dreams, being unable to sleep, feeling weak (conditions including fatigue, debility and feeling of discomfort), swelling of legs and feet, lethargy, decreased appetite (anorexia), constipation, hiccups, cough, heartburn, dry mouth, increased sweating,

Uncommon side effects (happening in 1 in 1,000 to 1 in 100 patients)

Uncommon side effects are fainting, fainting due to a drop in blood pressure when standing up, loss of consciousness, increased or abnormal liver function test results, increased heart rate, reduced blood pressure, shortness of breath, rash, generalised itching, feeling of abnormal motion (vertigo), poor balance, being unable to walk properly, falling, tremors, confusion, visual disturbances such as seeing colours or lights or blurred vision, reduced concentration, loss of memory, sleep disorders, nightmares, numbness or tingling sensation, feeling of increased heart rate (palpitations), weight loss, stomach discomfort and pain, swelling of the joints, impotence in men (being unable to achieve or maintain an erection), feeling abnormal, food and drink tasting different.

Rare side effects (happening in 1 in 10,000 to 1 in 1,000 patients)

Rare side effects are psychotic disorders including abnormal thinking about reality and behaviour (paranoid psychosis), or an unusual urge to carry out a certain activity including increased sex drive, and involuntary muscle spasms (seizure, convulsion), Compulsive disorders (e.g. excessive gambling, repetitive meaningless actions (punding) have been observed in subjects treated with Neupro.

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

5. HOW TO STORE Neupro

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

6. FURTHER INFORMATION

What Neupro contains

- The active substance is rotigotine.

Neupro 2 mg/24 h

Each patch releases 2 mg of rotigotine per 24 hours. Each patch of 10 cm² 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 cm² 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 cm² 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 cm² 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).

Protective liner: Transparent fluoropolymer coated polyester film.

What Neupro looks like and contents of pack

Neupro is a transdermal patch. It is thin and has three layers. It is square-shaped with rounded edges. The outside is tan-coloured and is imprinted with Neupro 2 mg/24 h, 4 mg/24 h, 6 mg/24 h or 8 mg/24 h.

Neupro is available in the following pack-sizes:

One treatment initiation pack contains 28 transdermal patches in 4 cartons with 7 patches of 2 mg, 4 mg, 6 mg, and 8 mg each, which are individually sealed in sachets.

Marketing Authorisation Holder and Manufacturer

SCHWARZ PHARMA Ltd.
Shannon, Industrial Estate,
Co.Clare, Ireland

This leaflet was last approved in {MM/YYYY}