Neupro® (rotigotine) transdermal patches

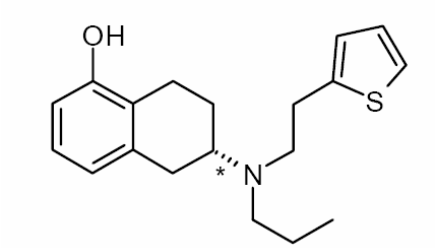
NAME OF THE MEDICINE

NEUPRO® rotigotine transdermal patch

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

Chemical name: (6S)-6-{propyl-[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol

Chemical structure:



Molecular formula: $C_{19}H_{25}NOS$
MW: 315.48

CAS number: [99755-59-6]

DESCRIPTION

The active ingredient rotigotine is a white to off-white powder. It is freely soluble in organic solvents, soluble in acidic aqueous solutions and practically insoluble in alkaline aqueous solutions.

Neupro is a thin, matrix-type transdermal patch composed of 3 layers:

1. A flexible, tan-colored backfilm that provides structural support and protection of the drug-loaded adhesive layer

2. A self-adhesive drug matrix layer. The excipients contained in the self adhesive matrix are povidone, ascorbyl palmitate, dl-alpha tocopherol and sodium metabisulfite. The adhesive matrix consists of a mixture of two proprietary silicone adhesives (BIO-PSA Q7-4301 and BIO-PSA Q7-4201).

3. A clear protective liner which is removed prior to use.

PHARMACOLOGY

Rotigotine is a non-ergolinic $D_3/D_2/D_1$ dopamine receptor agonist for the treatment of Parkinson's disease. It is believed to elicit its beneficial effect by activation of the D_3, D_2 and D_1 receptors in the brain. Several rotigotine metabolites share its pharmacological activity at dopamine receptors. Rotigotine also has agonist activity at α_{1A} adrenoceptors and 5-HT_{1D} receptors. Rotigotine improved motor deficits in animal models of Parkinson's disease.

Pharmacokinetics

Absorption

Following application, rotigotine is continuously released from the transdermal patch and absorbed through the skin. Steady-state concentrations are reached after one to two days of patch application and are maintained at a stable level by once daily application in which the patch is worn for 24 hours. Rotigotine plasma concentration increases dose-proportionally over a dose range of 2 mg/24 h to 16 mg/24 h.

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

Rotating the site of patch application may result in day-to-day differences in plasma levels. Differences in bioavailability of rotigotine ranged from 1% (hip versus abdomen) to 41% (shoulder versus thigh). However, there is no indication of a relevant impact on the clinical outcome.

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

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 extensively 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-desalkylation of rotigotine. Main metabolites are sulfates and glucuronide conjugates of the parent compound as well as N-desalkyl-metabolites.

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.

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, race 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.

CLINICAL TRIALS

The effectiveness of Neupro in the treatment for the signs and symptoms of idiopathic Parkinson's disease was evaluated in a multinational drug development program consisting of four pivotal, Phase III, parallel, randomized, double-blind placebo controlled studies.

Two trials investigating the effectiveness of Neupro for the treatment of idiopathic Parkinson's disease were conducted in patients with early stage Parkinson's disease who were not receiving concomitant dopamine agonist therapy and were either levodopa naïve or previous levodopa 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).

Two additional trials were conducted in patients with advanced idiopathic Parkinson's disease who were receiving concomitant levodopa therapy.

The primary outcome assessment was the reduction in "off" time (hours). Efficacy was determined by the subject's response to therapy in terms of responder and absolute improvement in the time spent "off".

Clinical Trials of Neupro in Early Stage Disease

In a, double blind study, 177 patients received Neupro and 96 patients received placebo. The patients were titrated to their optimal dose of Neupro 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. Onset of treatment benefits began as early as the second week of treatment. Patients were maintained at their optimal dose for 6 months.

For 91% of the subjects in the Neupro arm , the optimal dose was the maximal dose allowed i.e. 6 mg/24 h at the end of the maintenance treatment. An improvement of 20% was seen in 48% of the subjects receiving Neupro and in 19% of the subjects receiving placebo (difference 29% $CI_{95\%}$ 18%; 39%, $p<0.0001$). With Neupro, 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 from placebo was 5.28 points and statistically significant ($p<0.0001$).

In a second double-blind study, 213 patients received Neupro, 227 received ropinirole and 117 patients received placebo. The patients were titrated to their optimal dose of Neupro 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 Neupro arm the optimal dose was the maximal dose allowed i.e. 8 mg/24 h at the end of the maintenance treatment. An improvement over baseline of 20% was seen in 52% of the subjects receiving Neupro, 68% of the subjects receiving ropinirole and 30% of the subjects receiving placebo (difference Neupro 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 Neupro arm, 10.78 points in the ropinirole arm (baseline 32.2 points) and -2.33 points in the placebo arm (baseline 31.3 points). All differences between the active treatments and placebo were statistically significant.

Clinical Trials of Neupro in Advanced Disease

In a double blind study, 113 patients received Neupro in conjunction with levodopa up to a maximum dose of 8 mg/24 h, 109 patients received Neupro up to a maximum dose of 12 mg/24 h and 119 patients received placebo. The patients were titrated to their optimal doses of Neupro or placebo in weekly increments of 2 mg/24 h starting at 4 mg/24h. Patients in each treatment group were maintained at their optimal dose for 6 months.

At the end of the maintenance period an improvement of at least 30% was seen in 57% and 55% of the subjects receiving Neupro 8 mg/24 h and 12 mg/24 h, respectively and in 34% of the subjects receiving placebo (Differences 22% and 21%, respectively $CI_{95\%}$ 10%; 35% and 8%; 33%, respectively, $p<0.001$ for both Neupro groups). With Neupro, the mean reductions in “off” time were 2.7 and 2.1 hours, respectively whereas in the placebo-treated arm a reduction of 0.9 hours was observed. The differences were statistically significant ($p<0.001$ and $p=0.003$, respectively).

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

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

INDICATIONS

Neupro is indicated as monotherapy, or in combination with levodopa, for the treatment of idiopathic Parkinson's disease from early stage to advanced disease.

CONTRAINDICATIONS

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

Magnetic resonance imaging or cardioversion (see PRECAUTIONS).

PRECAUTIONS

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 Rotigotine, but also at a similar rate in patients treated with placebo.

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

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.

Placebo-controlled trials have shown a higher incidence of visual disturbance and eye conditions in the rotigotine groups in comparison with controls. Similar events have been observed in open-label trials. Ophthalmologic monitoring is recommended at regular intervals or if visual abnormalities occur.

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 DOSAGE AND ADMINISTRATION).

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

Neuroleptics given as antiemetic should not be given to patients taking dopamine agonists (see PRECAUTIONS – Interactions with other medicines).

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 PHARMACOLOGY – Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Fibrotic complications: Neupro is a non-ergot derived dopaminergic agent.

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.

Cardiac valve abnormalities have been observed in open-label trials of rotigotine, however in placebo-controlled clinical trials, the incidence of these adverse events was similar between treatment groups. Regular cardiac review as part of physical examination should be performed. Echo-cardiograph monitoring may be advisable in accordance with clinical judgement. (see ADVERSE EFFECTS)

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.

Effects on fertility

Subcutaneous administration of rotigotine to male rats prior to and through mating did not affect fertility, although epididymal sperm motility was reduced at a plasma rotigotine concentration 11-fold the clinical plasma C_{max} at the maximal recommended dose; the no-effect dose was 4-fold the clinical C_{max}. In female mice and rats, rotigotine disrupted implantation and prevented pregnancy, probably due to hypoprolactinaemia. These effects are considered not clinically relevant because, in humans, chorionic gonadotropin rather than prolactin is essential for implantation.

Use in Pregnancy

Category : B3

There are no adequate data on the use of Neupro in pregnant women. Subcutaneous administration of rotigotine to mice, rats and rabbits during the period of organogenisis did not produce teratogenicity. Maternotoxic doses were associated with embryofetal toxicity. Administration to rats from early gestation to weaning was associated with effects in offspring (impaired auditory startle reflex during lactation, delays in some developmental indices). The potential risk for humans is unknown. Rotigotine should not be used during pregnancy.

Use in lactation

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. Subcutaneous administration to rats from early gestation to weaning was associated with adverse effects in offspring (see **Use in Pregnancy**). In the absence of human data, breast-feeding should be discontinued.

Paediatric use

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

Use in the elderly

No dosage adjustment is necessary in the elderly because therapy with Neupro is initiated at a low dose and gradually titrated according to clinical tolerability to obtain the optimum therapeutic effect (see PHARMACOLOGY – Pharmacokinetics)

Carcinogenicity

Two-year subcutaneous carcinogenicity studies with rotigotine were conducted in mice and rats, achieving respective systemic exposures (plasma AUC) up to 5- and 2-fold the clinical plasma AUC at the maximal recommended dose. There was no evidence of carcinogenicity in mice. Rats developed Leydig cell adenomas and uterine tumours (adenocarcinomas,

squamous cell carcinomas), but the findings are of questionable significance because the endocrine mechanisms are not considered relevant to humans.

Ocular Toxicity

After a single dose of rotigotine, binding to melanin-containing tissues (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 following subcutaneous administration of rotigotine to albino rats for 3 months. The effects were more pronounced in females. 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.

Genotoxicity

There was no evidence of genotoxicity in assays for bacterial gene mutation and unscheduled DNA synthesis in rat hepatocytes. A positive result was obtained in the *in vitro* mouse lymphoma assay, but there was no evidence of clastogenicity in the *in vivo* mouse micronucleus assay.

Interactions with other medicines

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 Neupro.

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 levodopa and carbidopa with rotigotine had no effect on the pharmacokinetics of rotigotine, and rotigotine had no effect on the pharmacokinetics of levodopa and carbidopa.

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

The incidence of some dopaminergic adverse effects, such as hallucinations, dyskinesia, and peripheral oedema generally is higher when given in combination with levodopa.

Rotigotine is primarily metabolized by, and also inhibits to a degree, CYP2C19. Co-administration of rotigotine and drugs that are metabolised by CYP2C19 may lead to an increase systemic exposure to these drugs. This has not been fully characterised, however some *in vitro* and *in vivo* studies suggest that the inhibition of CYP2C19 may only be clinically relevant at supra-therapeutic doses. 50% inhibition was observed in one *in vitro* study at concentrations 80-fold higher than maximum plasma concentrations observed for the

dose of 16 mg/24 h. Possible interaction should be borne in mind when co-administering other drugs metabolized by CYP2C19.

Effect on laboratory tests

As seen in other dopamine agonists, clinical trials revealed a decrease of prolactin plasma concentrations after exposure to rotigotine.

Effects on ability to drive and use machines

Neupro may have a major influence on the ability to drive and use machines (see ADVERSE EFFECTS).

Neupro has been associated with somnolence including excessive daytime somnolence and sudden sleep onset episodes. Patients being treated with Neupro 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 PRECAUTIONS).

ADVERSE EFFECTS

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 1083 Neupro- and 508 placebo-treated patients, 73.0% of the patients on Neupro and 56.3% of patients on placebo reported at least one adverse reaction.

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

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

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

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

The following table covers adverse drug reactions from all rotigotine studies in patients with Parkinson’s disease.

System/organ classes (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		Perception disturbances[b] (hallucination[a], visual hallucination[a], auditory hallucination[a], illusion) confused state, abnormal dreams[a], insomnia[a]	sleep attacks[a], psychotic disorder (including paranoid psychosis), compulsive disorders (including pathologic gambling, punding), increased libido (including hypersexuality), anxiety, sleep disorder[a], nightmares, disorientation	
Nervous system disorders	somnolence[a], dizziness[a]	dyskinesia[a] headache[a] , dizziness postural, headache[a]	Syncope,vasovagal syncope, dystonia, hypersomnia, lethargia, disturbance in attention, memory impaired, paraesthesia dysgeusia, balance disorder, tremor.	Convulsion, loss of consciousness
Eye disorders			visual disturbance, photopsia, blurred vision	
Ear and labyrinth disorders			vertigo (incl. positional)	
Cardiac disorders			Atrial fibrillation, heart rate increased, palpitations	Supraventricular tachycardia
Vascular disorders		orthostatic hypotension, (see PRECAUTIONS)	Hypertension, hypotension	

System/organ classes (MedDRA)	Very common >1/10	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000
Respiratory, thoracic and mediastinal disorders			cough, hiccup[a] dyspnoea	
Gastrointestinal disorders	nausea[a],	vomiting[a], diarrhoea, constipation[a], dyspepsia[a] dry mouth[a],	abdominal pain (incl upper abdominal pain), stomach discomfort	
Hepato-biliary disorder		hepatic enzyme increased (including GGT, ALAT, ASAT)		
Skin and subcutaneous tissue disorders		rash (incl. allergic; macular exanthema) (see PRECAUTIONS), erythema[a] pruritus hyperhydrosis[a],	Generalised pruritus, dermatitis contact, skin irritation,	
Musculoskeletal and connective tissue disorder			joint swelling	
Reproductive system and breast disorder			erectile dysfunction	
General disorders and administration site conditions	application site reactions[b] (including erythema[a], pruritus[a], irritation[a], burning[a], dermatitis[a], inflammation, papulae,vesicle,blister, pain, hypersensitivity) (see PRECAUTIONS)	oedema peripheral[a], asthenic conditions[b] (incl. fatigue[a], asthenia, malaise), weight decrease	Gait disturbance[a,] feeling abnormal, weight increased[a]	
Injury, poisoning and procedural complications			Fall	

[a] These adverse drug reactions have been reported in the pooled placebo-controlled trials at a frequency of 1% more than in the placebo-treated patients. See PRECAUTIONS and Effects on ability to drive and use machines

[b] High level term.

Adverse events that might be indicative of fibrosis reported in the advanced-stage PD clinical trial program are summarized below.

Rotigotine treatment-emergent adverse events related to fibrosis – Advanced-stage Parkinson's disease

MedDRA® version 8.1 High Level Term Preferred Term	**Placebo-Controlled Studies**		**All studies (including open label studies*)**
	Placebo N=219 n (%)	**Rotigotine N=434 n (%)**	**Rotigotine N=1151 n (%)**
Hydronephrosis	1 (0.5)	0	1 (<0.1)
Pleural effusion	1 (0.5)	0	1 (<0.1)
Cardiac valve disease	0	1 (0.2)	1 (<0.1)
Cardiac murmur	0	1 (0.2)	3 (0.3)
Mitral valve incompetence	0	0	5 (0.4)
Aortic valve incompetence	0	0	2 (0.2)
Aortic valve sclerosis	0	0	1 (<0.1)
Tricuspid valve incompetence	0	0	2 (0.2)

MedDRA®=Medical Dictionary for Regulatory Activities
* Patients in open label studies were on concomitant Parkinson's disease medications.

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

Patients treated with dopamine agonists for treatment of Parkinson's disease, including Rotigotine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

DOSAGE AND ADMINISTRATION

Dosage

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.

Neupro can be applied irrespective of the timing of meals.

The dose recommendations made below are in nominal dose.

Dosing in patients with early stage Parkinson's disease:

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

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

The maximal dose is 8 mg/24 h.

Dosing in patients with advanced stage Parkinson's disease:

A single daily dose should be initiated at 4 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 16 mg/24 h.

4 mg/24 h or 6 mg/24h may be effective doses in some patients. For most patients an effective dose is reached within 3 to7 weeks at doses of 8 up to a maximum dose of 16 mg/24 h.

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

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 PHARMACOLOGY – Pharmacokinetics and PRECAUTIONS). Rotigotine has not been investigated in patients with severe hepatic impairment.

Children and adolescents: Rotigotine 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 PRECAUTIONS).

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 PRECAUTIONS).

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 folded back and the second part of the protective 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.

Neupro does not need to be removed for bathing or swimming.

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

The patch should not be cut into pieces.

OVERDOSAGE

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 DOSAGE AND ADMINISTRATION – treatment discontinuation.

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.

PRESENTATION AND STORAGE CONDITIONS

Thin, matrix type transdermal patch that is square shaped with rounded edges. The backing layer comprises a polyester film, siliconized, aluminized, colour coated with a tan coloured pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7). The protective liner comprises a transparent fluoropolymer coated polyester film. The outside of the tan coloured backing layer is imprinted with Neupro 2 mg/24 h, Neupro 4 mg/24 h, Neupro 6 mg/24 h or Neupro 8 mg/24 h respectively. Available in the following presentations:

Neupro 2 mg: 10 cm^2 patch containing 4.5 mg rotigotine with a nominal release rate of 2 mg rotigotine per 24 hours. Pack size: 28s.
Neupro 4 mg: 20 cm^2 patch containing 9.0 mg rotigotine with a nominal release rate of 4 mg rotigotine per 24 hours. Pack size 28s.
Neupro 6 mg: 30 cm^2 patch containing 13.5 mg rotigotine with a nominal release rate of 6 mg rotigotine per 24 hours. Pack size 28s.
Neupro 8 mg: 40 cm^2 patch containing 18.0 mg rotigotine with a nominal release rate of 8 mg rotigotine per 24 hours. Pack size 28s.

Each patch is individually sealed in a sachet.

Store below 25°C.

Store in the original package

NAME AND ADDRESS OF THE SPONSOR

UCB Pharma
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Level 1, 1155 Malvern Road
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POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (S4)

DATE OF APPROVAL

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