Pendaftar

1. NAME OF THE MEDICINAL PRODUCT

Neupro 2 mg/24 h transdermal patch
Neupro 4 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Neupro 2mg/24h. 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'.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. without levodopa) or in combination with levodopa, i.e. over the course

of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or 'on-off' fluctuations).

4.2 Posology and method of administration

Posology

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

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

Dose

The dose recommendations made are in nominal dose.

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

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

For doses higher than 4 mg/24 h multiple patches may be used to achieve the final dose e.g. 6 mg/24 h may be reached by combination of a 2 mg/24 h and a 4 mg/24 h patch.

Treatment Discontinuation

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

Special Populations

Hepatic and renal impairment: Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis. Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. 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 section 5.2).

Paediatric Populations

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

Method of administration

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

Use and handling: Each patch is packed in a sachet and should be applied directly after the sachet has been opened. One half of the 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.

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4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

Syncope
Syncope was observed in association with rotigotine, but at a rate that was similar to that observed in patients treated with placebo.

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

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

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

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

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

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

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

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

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

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

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

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

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

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4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy
There are no adequate data from the use of 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.

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

Fertility
For information on fertility studies, please see section 5.3.

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4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 1,307 Neupro- and 607 placebo-treated patients, 72.3% of the patients on Neupro and 57.8% of patients on placebo reported at least one adverse reaction.

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

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

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

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

seriousness.

System/organ classes acc. to MedDRA	Very common	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity	
Psychiatric disorders		Perception disturbances[a] (incl. hallucination, hallucination visual, hallucination auditory, illusion), Insomnia, Sleep disorder, Nightmare, Abnormal dreams	Sleep attacks/Sudden onset of sleep, Paranoia, Sexual desire disorders[a] (incl. hypersexuality, libido increased), Impulse control disorder[a] (incl. pathological gambling, punding), Confusional state	Psychotic disorder, Obsessive-compulsive disorder, Aggressive behaviour/ aggression[b], binge eating and compulsive eating[b]
Nervous system disorders	Somnolence, Dizziness, Headache	Disturbances in consciousness NEC[a] (incl. syncope, syncope vasovagal, loss of consciousness), Dyskinesia, Dizziness postural, Lethargy		Convulsion
Eye disorders			Vision blurred, Visual disturbance, Photopsia	
Ear and labyrinth disorders		Vertigo		
Cardiac disorders		Palpitations	Atrial fibrillation	Supraventricular tachycardia
Vascular disorders		Orthostatic hypotension, Hypertension	Hypotension	
Respiratory, thoracic and mediastinal disorders		Hiccups		
Gastrointestinal disorders	Nausea, Vomiting	Constipation, Dry mouth, Dyspepsia	Abdominal pain	
Skin and subcutaneous tissue disorders		Erythema, Hyperhidrosis, Pruritus	Pruritus generalised, Skin irritation, Dermatitis contact	Rash generalised
Reproductive system and breast disorder			Erectile dysfunction	
General disorders and administration site conditions	Application and instillation site reactions[a] (incl. erythema, pruritus, irritation, rash, dermatitis, vesicles, pain, eczema, inflammation, swelling, discolouration, papules, excoriation, urticaria, hypersensitivity)	Oedema peripheral, Asthenic conditions[a] (incl. fatigue, asthenia, malaise)		Irritability

Investigations		Weight decreased,	Hepatic enzyme increased (incl. AST, ALT, GGT), Weight increased, Heart rate increased	
Injury, poisoning and procedural complications		Fall		

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

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

Description of selected adverse reactions

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

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including rotigotine (see section 4.4 'Special warnings and precautions for use').

4.9 Overdose

The most likely adverse reactions would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hypotension, involuntary movements, hallucinations, confusion, convulsions and other signs of central dopaminergic stimulation. There is no known antidote for overdose of dopamine agonists. In case of suspected overdose, removal of the patch(es) should be considered because after removal of the patch(es) the drug input is stopped and the plasma concentration of rotigotine decreases rapidly. The patient should be monitored closely, including heart rate, heart rhythm and blood pressure. Treatment of overdose may require general supportive measures to maintain the vital signs. Dialysis would not be expected to be beneficial as rotigotine is not eliminated by dialysis.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

Clinical studies

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

Two pivotal trials investigating the effectiveness of rotigotine in the treatment of the signs and symptoms of idiopathic Parkinson's disease were conducted in patients who were not receiving concomitant dopamine agonist therapy and were either L-dopa naïve or previous L-dopa treatment was ≤ 6 months. The primary outcome assessment was the score for the Activities of Daily Living (ADL) component (Part II) plus the Motor Examination component (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS). Efficacy was determined by the subject's response to therapy in terms of responder and absolute points improvement in the scores of ADL and Motor Examination combined (UPDRS part II+III). In one double blind study, 177 patients received rotigotine and 96 patients received placebo. The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 6 mg/24 h. Patients in each treatment group were maintained at their optimal dose for 6 months.

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

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

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

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

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

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

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

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

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

in the pramipexole arm and 0.9 hours in the placebo arm. All differences between the active treatments and placebo were statistically significant.

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

5.2 Pharmacokinetic properties

Absorption

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

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

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

Distribution

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

Metabolism

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

Elimination

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

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

Special patient groups
Because therapy with Neupro is initiated at a low dose and gradually titrated according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the dose based on gender, weight, or age is not necessary.
In subjects with moderate hepatic impairment or mild to severe renal impairment, no relevant increases of rotigotine plasma levels were observed. Neupro was not investigated in patients with severe hepatic impairment.
Plasma levels of conjugates of rotigotine and its desalkyl metabolites increase with impaired renal function. However, a contribution of these metabolites to clinical effects is unlikely.

5.3 Preclinical safety data

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

The effects of rotigotine on reproduction have been investigated in rats, rabbits and mice. Rotigotine was not teratogenic in all three species, but was embryotoxic in rats and mice at materno-toxic doses. Rotigotine did not influence male fertility in rats, but clearly reduced female fertility in rats and mice, because of the effects on prolactin levels which are particularly significant in rodents.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Neupro 2mg/24h
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.

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Neupro 4mg/24h
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

18 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

6.5 Nature and contents of container

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

Neupro 2 mg/24 h transdermal patch,
1 carton box 28 patches which are individually sealed in sachets.
Reg. No.: DKIxxxxxxxxxxx
Neupro 4 mg/24 h transdermal patch,
1 carton box 28 patches which are individually sealed in sachets.
Reg. No.: DKIxxxxxxxxxxx

HARUS DENGAN RESEP DOKTER
Drug Prescription Only

ACC

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.

Manufactured by:
LTS Lohmann Therapie-Systeme AG,
Lohmannstr. 2, 56626 Andernach, Alemania, Germany.
for UCB Manufacturing Ireland Ltd.,
Shannon, Industrial Estate,
Co.Clare, Ireland

Imported By: PT Abbott Indonesia
Jln. Raya Jakarta Bogor KM 37
Depok 16415 - Indonesia

Pencil after

PATIENT INFORMATION LEAFLET

LEAFLET: INFORMASIUNTUK PASIEN

Neupro 2 mg/24 h

Neupro 4 mg/24 h

Rotigotine

Transdermal patch

Baca seluruh isi leaflet dengan seksama sebelum anda menggunakan obat ini karena mengandung informasi yang penting bagi anda.

- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya kembali.
- Apabila anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker atau perawat anda.
- Obat ini diresepkan hanya untuk anda. Jangan berikan obat ini kepada orang lain. Obat ini mungkin dapat membahayakan mereka, meskipun apabila mereka mengalami gejala yang sama dengan anda.
- Jika anda mengalami efek samping, sampaikan kepada dokter, apoteker atau perawat anda. Hal ini termasuk efek samping apapun yang mungkin terjadi yang tidak tercantum dalam leaflet ini. Lihat bagian 4.

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Apa yang ada dalam leaflet ini:

1. Apakah Neupro itu dan Apakah Kegunaannya

Neupro mengandung rotigotine dan tersedia sebagai patch untuk digunakan pada kulit. Neupro termasuk pada golongan obat yang disebut dopamine agonis yang menstimulasi sel-sel tipe tertentu yang terikat dengan reseptor-reseptor dopamine pada otak.

Neupro digunakan untuk mengobati:

- Tanda-tanda dan gejala-gejala penyakit **Parkinson** baik secara tunggal maupun dalam kombinasi dengan obat yang disebut levodopa.

2. Apa yang perlu diketahui sebelum anda menggunakan Neupro

Jangan menggunakan Neupro

- Apabila anda **alergi** terhadap **rotigotine** atau **komponen lain** dari Neupro (tercantum dalam bagian 6).

- Apabila anda perlu melakukan prosedur**magnetic resonance imaging** (metode untuk memvisualisasi organ-organ dan jaringan-jaringan tubuh bagian dalam) atau **cardioversion** (penanganan terhadap irama jantung yang tidak normal). Anda harus melepaskan *patch* Neupro sebelum melakukan prosedur-prosedur tersebut. Anda dapat menggunakan *patch* yang baru setelah prosedur tersebut selesai dilakukan.

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Peringatan dan Perhatian

Sampaikan kepada dokter, apoteker atau perawat sebelum menggunakan Neupro

- Obat ini dapat mempengaruhi **tekanan darah** anda, sehingga perlu dilakukan pengukuran secara teratur, terutama pada permulaan pengobatan.

- **Pemeriksaan mata** pada interval waktu tertentu direkomendasikan selama menggunakan Neupro. Namun demikian, apabila anda merasakan adanya permasalahan dengan penglihatan anda diantara jadwal pemeriksaan yang telah ditentukan, anda harus segera menghubungi dokter anda.

- Apabila anda memiliki **masalah hati (liver)** yang serius, dokter anda mungkin perlu melakukan penyesuaian dosis. Apabila selama pengobatan masalah hati (liver) anda bertambah parah, anda harus menghubungi dokter anda sesegera mungkin.

- Apabila anda **merasakan sangat mengantuk** atau mengetahui bahwa anda **tertidur secara tiba-tiba**, mohon hubungi dokter anda (baca juga bagian informasi **'Mengemudi dan mengoperasikan mesin'**).

- Hubungi dokter anda apabila keluarga/perawat anda mengetahui bahwa anda merasakan keinginan ~~yang berkembang~~ bertingkah laku yang tidak biasanya dan anda tidak dapat menahan dorongan atau godaan untuk melakukan aktifitas yang dapat membahayakan diri sendiri atau orang lain.Hal ini disebut dengan *impulse control disorder* (gangguan pengendalian keinginan) dan dapat termasuk kebiasaan seperti kecanduan judi, makan atau menggunakan uang secara berlebihan, peningkatan hasrat seksual yang abnormal, atau obsesi terhadap peningkatan perasaan-perasaan atau fikiran-pikiran seksual. Dokter anda mungkin perlu untuk meyesuaikan atau menghentikan dosisnya.

- Neupro dapat menyebabkan pikiran dan tindakan yang abnormal. Pikiran dan tindakan yang abnormal dapat terdiri dari satu macam atau lebih manifestasi termasuk pikiran abnormal tentang realitas, khayalan, halusinasi (melihat atau mendengar hal – hal yang tidak nyata), kebingungan, disorientasi, tindakan agresif, agitasi, dan mengigau. Jika anda merasakan efek tersebut, silahkan hubungi dokter anda.

- Sebagaimana halnya dengan setiap *patch* atau plester, Neupro dapat menyebabkan **reaksi-reaksi kulit**, seperti kemerahan dan gatal. Reaksi-reaksi tersebut biasanya terjadi dalam taraf ringan atau sedang, dan hanya berdampak pada area kulit tempat *patch* dilekatkan. Reaksi-reaksi tersebut biasanya akan menghilang beberapa jam setelah anda melepaskan *patch*. Apabila anda mengalami

reaksi kulit yang bertahan selama lebih dari beberapa hari, dimana sangat parah, atau menyebar diluar area kulit yang tertutupi *patch*, mohon hubungi dokter anda.
Hindari sinar matahari dan paparan matahari pada area kulit yang menunjukkan reaksi kulit jenis apapun yang disebabkan oleh Neupro. Untuk membantu menghindari reaksi-reaksi kulit, anda harus melekatkan *patch* pada area kulit yang berbeda-beda setiap hari, dan hanya melekatkannya kembali pada area yang samasetelah 14 hari.

- Neupro **tidak boleh digunakan oleh anak-anak**, karena khasiat dan keamanan pada anak-anak belum terbukti.

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Obat-obatan lain dan Neupro

Silahkan memberitahukan dokter atau apoteker anda apabila anda sedang menggunakan, baru saja telah menggunaka, atau mungkin menggunakanobat-obatan lain.

Anda tidak boleh menggunakan obat-obatan berikut selama menggunakan Neupro karena dapat menurunkan khasiat Neupro: anti-psikotik (digunakan untuk mengobati kondisi mental tertentu) atau metoklopramide (biasa digunakan untuk mengobata mual dan muntah).

Apabila anda diobati dengan Neupro dan levodopa pada saat bersamaan, beberapa efek samping dapat menjadi lebih serius, seperti melihat atau mendengar hal-hal yang tidak nyata (halusinasi), gerakan-gerakan tidak terkontrolterkait dengan penyakit Parkinson (diskinesia), dan pembengkakan pada tungkai dan kaki.

Silahkan tanyakan kepada dokter anda apakah aman bagi anda untuk:

- minum alkohol atau
- menggunakan obat-obatan yang memiliki efek sedatif (contohnya benzodiazepine, obat-obatan yang digunakan untuk mengobati kondisi mental atau depresi) sementara anda mengunakan Neupro.

MenggunakanNeuprodengan makanan, minuman dan alkohol

Karena rotigotine memasuki aliran darah melalui kulit anda, makanan dan minuman tidak mempengaruhi cara kerja obat. Anda harus berdiskusi dengan dokter anda mengenai keamanannya apabila anda minum alkohol sementara menggunakan Neupro.

Kehamilan, menyusui dan fertilitas

Anda tidak boleh menggunakan Neupro apabila anda sedang hamil, karena efek rotigotine pada kehamilan dan terhadap bayi yang belum lahir tidak diketahui.Menyusui tidak direkomendasikan selama pengobatan dengan Neupro. Rotigotine dapat keluar melalui air susu anda dan mempengaruhi bayi anda dan mungkin juga dapat mengurangi jumlah air susu yang diproduksi.

Beritahukan dokter anda apabila anda sedang hamil atau menyusui, memperkirakan bahwa anda mungkin hamil atau sedang merencanakan kehamilan, mintalah saran kepada dokter atau apoteker anda sebelum menggunakan obat ini.

Mengemudi dan mengoperasikan mesin

Neupro dapat membuat anda merasa sangat mengantuk, dan anda mungkin dapat tertidur dengan sangat tiba-tiba. Apabila hal ini terjadi pada anda, anda tidak boleh mengemudi atau turut andil dalam aktifitas dimana ketidakwaspadaan dapat menyebabkan anda atau orang lain beresiko cedera serius, contohnya mengoperasikan mesin.

Pada beberapa kasus, orang tertidur saat mengemudi dan hal ini menyebabkan kecelakaan.

Neupro mengandung *sodium metabisulphite*(E223)

Sodium metabisulphite (E223), jarang menyebabkan reaksi hipersensitif berat dan *bronchospasme*.

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3. Bagaimana Cara Menggunakan Neupro

Selalu gunakan Neupro persis seperti yang telah diberitahukan oleh dokter atau apoteker anda.Anda harus memastikan kepada dokter atau apoteker anda apabila anda merasa tidak yakin.

Neupro umumnya digunakan sebagai pengobatan jangka panjang. Biasanya, anda akan memulai pengobatan dengan dosis rendah dan, bila perlu, dosis ditingkatkan dari minggu ke minggu, sebagaimana yang dianjurkan oleh dokter anda, sampai mencapai dosis yang tepat untuk anda. Kemudian anda akan melanjutkan pengobatan dengan dosis ini, yang disebut sebagai dosis pemeliharaan.

Anda harus mengganti *patch* Neupro sekali dalam sehari. Untuk mencapai dosis yang diperlukan, beberapa *patch* dengan kekuatan yang berbeda telah tersedia, setiap patch melepaskan jumlah zat aktif yang berbeda per hari: 2 mg/24 jam dan 4 mg/24 jam. Untuk dosis yang lebih tinggi, harus digunakan beberapa *patch*. Sebagai contoh, untuk pemakaian dosis harian sebanyak 6 mg dapat diperoleh dengan menggunakan satu *patch* dengan kekuatan 2 mg/24 jam dan satu *patch* dengan kekuatan 4 mg/24 jam.

Pengobatan penyakit Parkinson

Penderita yang tidak menggunakan levodopa (Penyakit Parkinson tahap awal)

Anda akan mulai dengan menggunakan satu *patch* Neupro 2 mg/24 jam setiap hari. Mulai minggu kedua, dosis harian akan ditingkatkan sebanyak 2 mg, dalam periode mingguan, sehingga mencapai dosis yang tepat (dosis pemeliharaan) untuk anda. Untuk sebagain besar penderita, dosis yang tepat adalah antara 6 mg dan 8 mg per hari (dicapai dalam kurun waktu 3 sampai 4 minggu).

Dosis maksimum adalah 8 mg per hari.

Penderita yang menggunakan levodopa (Penyakit Parkinson tahap lanjut)

Anda akan mulai dengan menggunakan satu *patch* Neupro 4 mg/24 jam setiap hari. Mulai minggu kedua, dosis harian akan ditingkatkan sebanyak 2 mg, dalam periode mingguan, sampai mencapai dosis yang tepat (dosis pemeliharaan) untuk anda. Untuk sebagian besar penderita, dosis yang tepat adalah antara 8 mg dan 16 mg per hari (dicapai dalam kurun waktu 3 sampai 7 minggu)

Dosis maksimum adalah 16 mg per hari.

Apabila anda harus menghentikan penggunaan obat ini, lihat bagian 3, **'Apabila anda berhenti menggunakan Neupro'**.

Ikutilah Instruksi-instruksi berikut ketika menggunakan Neupro:

Neupro digunakan secara transdermal, sebuah patch yang dipakai pada kulit.Anda harus melekatkan patch Neupro yang baru pada kulit **sekali dalam sehari**. Biarkan patch tersebut pada kulit anda selama 24 jam, kemudian lepaskan patch tersebut dan gunakan lagi yang baru. Pastikan bahwa anda melepaskan patch yang lama sebelum menggunakan yang baru, lekatkan patch baru pada area kulit yangberbeda.

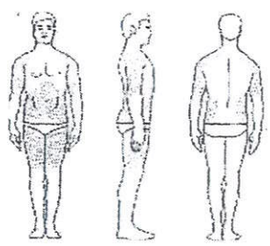
Anda harus **mengganti patch anda pada kisaran waktu yang sama setiap hari**.

Jangan menggunting patch Neupro menjadi beberapa bagian.

Tempat untuk melekatkan patch

Letakan sisi lengket dari patch pada area kulit yang bersih, kering dan sehat dibagian tubuh berikut (area yang ditandai dengan warna kelabu pada gambar di samping):

- bahu
- lengan bagian atas
- perut
- paha
- pinggul
- panggul (daerah antara tulang rusuk dan pinggulanda).



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Untuk **membantu menghindari iritasi kulit**:

- Lekatkan patch pada area kulit yang berbeda setiap hari, sebagai contoh: satu hari pada bagian sebelah kanan tubuh anda, kemudian hari berikutnya pada bagian sebelah kiri; satu hari pada bagian tubuh sebelah atas, kemudian pada bagian tubuh sebelah bawah.
- Jangan melekatkan Neupro pada area kulit yang sama dua kali dalam jangka waktu 14 hari.
- Jangan melekatkan patch pada kulit yang terkoyak atau luka atau pada kulit yang memerah atau teriritasi.

Apabila anda masih mengalami masalah dengan kulit anda karena penggunaan patch, silahkan lihat informasi detil pada Bagian 4 **'Efek-efek samping yang mungkin terjadi'** mengenai tindakan yang harus anda lakukan.

Untuk mencegah patch menjadi longgar atau terlepas

- Jangan melekatkan patch pada area yang dapat tergesekoleh pakaian ketat.
- Jangan menggunakan krim, minyak, losion, bedak atau produk-produk perawatan kulit lain pada area kulit yang akan digunakan untuk melekatkan patch atau berdekatan dengan patch yang telah anda gunakan.
- Apabila anda akan melekat patch pada area kulit yang berambut, anda harus mencukur area tersebut paling tidak 3 hari sebelum melekatkan patch pada area tersebut.

Apabila patch terlepas, patch baru harus digunakan selama sisa waktu di hari tersebut, kemudian ganti patch pada waktu yang sama seperti biasanya.

CATATAN

- Mandi berendam, mandi *shower* dan olah raga semestinya tidak mengganggu kerja Neupro. Namun demikian, lakukan pemeriksaan untuk memastikan patch tidak terlepas setelahnya.
- Anda harus menghindari panas eksternal (contohnya: sinar matahari berlebih, sauna, berendam air panas, bantalan pemanas atau botol air panas) pada area tempat patch melekat.
- Apabila patch mengiritasi kulit anda, anda harus menjaga area tersebut terlindung dari sinar matahari langsung, karena hal tersebut dapat menyebabkan perubahan warna kulit.

Bagaimana cara menggunakan patch

Tiap patch dikemas dalam sachet tersendiri. Anda harus melekatkan Neupro pada kulit anda sesegera mungkin setelah membuka sachet dan melepaskan lapisan pengaman.

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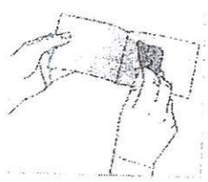
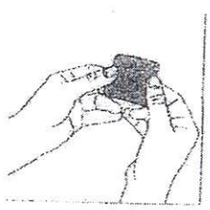
1.
Untuk membuka sachet, pegangkedua sisi dari sachet. Kelupas bagian foil dan buka sachet.

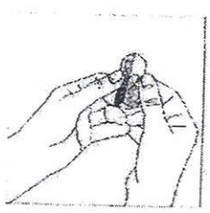
2.
Ambil patch keluar dari sachet.



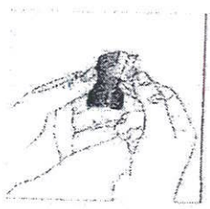
3.
Bagian lengket dari patch dilindungi oleh lapisan transparan.Pegang patch menggunakan kedua tangan dengan lapisan pelindung menghadap anda.



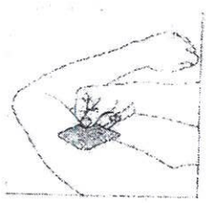
4.
Tekuk patch menjadi dua sehingga garis potong berbentuk S pada lapisan pelindung terbuka.



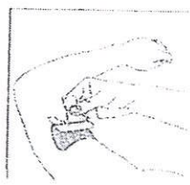
5.
Kelupas satu sisi dari lapisan pelindung. Jangan menyentuh bagian lengket pada patch dengan jari-jari anda.



6.
Pegang setengah bagian lapisan yang kaku dan letakan permukaan lengket dari patch pada kulit anda. Tekan sisi lengket dari patch sampai melekat kuat.



7.
Lipat balik setengah bagian lain dari patch dan lepaskan lapisan pelindung yang tersisa.



8.
Tekan patch dengan kuat menggunakan telapak tangan sekitar 20 sampai 30 detik untuk memastikan bahwa patch menyentuh kulit dan pinggiran patch melekat dengan baik.

Cuci tangan anda dengan sabun dan air segera setelah menangani patch.

Bagaimana cara melepaskan patch yang telah digunakan

Kelupas patch yang telah digunakan secara perlahan dan seksama.

Cuci bagian kulit tersebut dengan perlahan menggunakan air hangat dan sabun yang lembut untuk menghilangkan perekat yang masih tersisa pada kulit setelah anda melepaskan patch.Anda dapat juga menggunakan sedikit baby oil untuk mnghilangkan perekat yang tidak dapat tercuci.

Jangan menggunakan alkohol atau cairan pelarut lainnya seperti penghapus cat kuku, karena dapat menyebabkan iritasi kulit.

Pilih bagian kulit yang baru dimana anda akan melekatkan patch baru, kemudian ikuti instruksi yang telah diberikan di atas.

Apabila anda menggunakan Neupro lebih dari yang seharusnya

Menggunakan dosis Neupro yang lebih tinggi dari yang telah diresepkan oleh dokter anda dapat menyebabkan efek-efek samping seperti mual, muntah, tekanan darah rendah, halusinasi (melihat atau mendengar hal-hal yang tidak nyata), kebingungan atau rasa kantuk yang sangat berat, gerakan tidak terkontrol dan konvulsi

Apabila anda menggunakan patch berlebih dari yang telah dianjurkan oleh dokter anda, lepaskan kelebihan *patch*dan hubungi dokter anda atau rumah sakit dengan segera untuk mendapatkan saran.

Apabila anda lupa untuk mengganti patch pada waktu yang ditentukan

Apabila anda lupa untuk mengganti patch pada waktu yang telah ditentukan, gantilah sesegera mungkin ketika anda ingat: lepaskan patch yang lama dan gunakan patch yang baru. Bila anda lupa untuk melekatkan patch yang baru setelah melepaskan patch yang lama, gunakan patch yang baru sesegera mungkin ketika anda ingat.

Dalam kedua kasus di atas, pada hari berikutnya anda harus menggunakan patch baru pada waktu yang lazim digunakan. Jangan menggunakan dosis ganda untuk menggantikan dosis yang terlupakan.

Apabila anda berhenti menggunakan Neupro

Jangan berhenti menggunakan Neupro secara tiba-tiba tanpa memberitahukan dokter anda, penghentian yang tiba-tiba dapat menyebabkan anda mengalami kondisi medis yang disebut *neuroleptic malignant syndrome* yang dapat memperlihatkan risiko yang besar terhadap kesehatan. Gejala-gejalanya termasuk: akinesia (kehilangan gerakan otot), kekakuan otot-otot, demam, tekanan darah yang tidak stabil, *tachycardia* (peningkatan detak jantung), kebingungan, penurunan tingkat kesadaran (misal: koma).

Dosis harian Neupro harus dikurangi secara bertahap

- Sebanyak 2 mg setiap dua hari – apabila anda menggunakan Neupro **untuk penyakit parkinson**

Apabila anda memiliki pertanyaan lebih lanjut mengenai penggunaan produk ini, tanyakan kepada dokter, apotekeratau perawat anda.

ACC

4. Efek Samping yang mungkin terjadi

Seperti halnya obat-obatan lain, Neupro dapat menimbulkan efek samping, walaupun tidak semua orang akan mengalaminya.

Anda mungkin akan mengalami **mual**(merasa tidak nyaman) dan **muntah pada permulaan pengobatan**. Efek-efek samping tersebut biasanya muncul secara ringan sampai sedang dan hanya terjadi untuk waktu yang pendek.Anda harus menghubungi dokter anda apabila efek-efek samping tersebut bertahan untuk waktu yang cukup lama atau apabila anda merasa khawatirmengenai hal tersebut.

Masalah-masalah kulit yang disebabkan oleh patch

Anda mungkin akan mengalami reaksi kulit yang diakibatkan oleh pemakaian patch, seperti kemerahan dan gatal. Reaksi-reaksi tersebut biasanya muncul secara ringan atau sedang dan hanya terjadi pada area kulit dimana patch melekat. Reaksi-reaksi tersebut biasanya akan menghilang beberapa jam setelah anda melepaskan patch.

Apabila anda mengalami reaksi kulit yang bertahan selama lebih dari beberapa hari, dimana sangat parah, atau menyebar diluar area kullit yang tertutupi *patch*, anda harus menghubungi dokter anda.

Anda mungkin mengalami efek samping berikut ini:

Ketidakmampuan untuk menahan keinginan, dorongan, atau godaan untuk melakukan tindakan yang membahayakan anda atau orang lain, dimana mungkin termasuk:

- Keinginan kuat untuk berjudi secara berlebihan meskipun mengakibatkan hal yang serius terhadap pribadi atau keluarga.
- Gangguan atau peningkatan keinginan dan kebiasaan seksual yang signifikan berpengaruh terhadap anda dan orang lain, sebagai contoh peningkatan dorongan seks
- Penggunaan uang atau pembelanjaan yang berlebih tak terkendali

- Makan yang berlebihan (makan dengan jumlah yang besar dalam waktu yang singkat) atau dorongan makan (makan yang banyak melebihi normal dan lebih dari yang diperlukan untuk memuaskan rasa lapar)

Hubungi dokter anda jika anda mengalami salah satu kebiasaan diatas; mereka akan mendiskusikan cara mengatur dan mengurangi gejala-gejala tersebut.

Anda mungkin mengalami pembengkakan pada wajah, lidah dan/atau bibir.Jika gejala ini berkembang, silahkan menghubungi dokter anda.

Apabila anda menggunakan Neupro untuk penyakit Parkinson efek-efek samping berikut dapat terjadi:

Efek samping yang sangat umum dapat terjadi pada lebih dari 1 pengguna dari 10 pengguna

- Rasa kantuk, pusing, sakit kepala
- Merasa tidak nyaman (mual), muntah
- Iritasi pada kulit dibawah permukaan patch, seperti kemerahan dan gatal

Efek samping yang umumdapat terjadi pada 1 dalam 10 orang

- melihat atau mendengar hal-hal yang tidak nyata (halusinasi),
- kesulitan untuk tertidur, gangguan tidur, kesulitan tidur, mimpi buruk, mimpi yang tidak biasa, kehilangan kesadaran, gerakan tidak terkendali terkait dengan penyakit Parkinson (dyskinesia), merasakan pusing ketika berdiri karena penurunan tekanan darah,
- vertigo (perasaan seperti mengalami gerakan berputar-putar)
- merasakan jantung berdegup (palpitasi)
- tekanan darah rendah ketika berdiri, tekanan darah tinggi
- cegukan
- konstipasi, mulut kering, nyeri ulu hati
- kemerahan, peningkatan keringat, gatal
- pembengkakan pada tungkai dan kaki
- merakan lemah, merasakan letih
- terjatuh
- penurunan berat badan
- Ketidakmampuan menahan dorongan untuk melakukan tindakan yang berbahaya yang berkaitan dengan judi yang berlebihan, pengulangan tindakan yang tidak bermakna dan belanja berlebihan.

Efek samping yang tidak umumdapat terjadi pada 1 dalam 100 orang

- reaksi alergi
- tertidur secara tiba-tiba tanpa ada tanda-tanda terlebih dahulu
- paranoid
- disorientasi
- Agitasi
- Peningkatan dorongan seks
- kebingungan
- pandangan kabur
- gangguan-gangguan penglihatan, seperti melihat warna atau cahaya
- irama jantung tidak normal
- tekanan darah rendah
- ketidaknyamanan pada perut dan nyeri
- gatal yang menyebar, iritasi kulit

- tidak mampu untuk mencapai atau menjaga ereksi
- Hasil pengujian fungsi hati meningkat atau tidak normal
- penambahan berat badan
- peningkatan detak jantung

Efek samping yang jarangdapat terjadi pada 1 dalam 1,000 orang

- gangguan psikotik
- Tindakan agresif/ agresi
- Makan berlebihan dan dorongan makan yang berlebihan
- spasme otot yang tidak terkendali (konvulsi)
- ruam yang menyebar
- iritabilitas

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Pelaporan efek samping

Jika anda mengalami efek samping sampaikan kepada dokter, apotekeratau perawat anda.. Hal ini termasuk efek samping apapun yang mungkin terjadi yang tidak tercantum dalam leaflet ini.Dengan melaporkan efek samping anda dapat membantu menyediakan informasi keamanan obat ini.

5. Bagaimana Cara Menyimpan Neupro

Jauhkan dari jangkauan dan penglihatan anak-anak.
Jangan menggunakan Neupro setelah waktu kadaluarsa yang tercantum pada label dan dus.
Simpan dalam lemari pendingin (2°C – 8°C).

Apa yang harus dilakukan terhadap patch bekas pakai dan yang tidak terpakai.

Patch bekas pakai masih mengandung zat berkhasiat, yang dapat membahayakan orang lain. Lipat patch bekas pakai dengan permukaan lengket dibagian dalam. Taruh patch pada sachet aslinya dan buang di tempat aman, jauh dari jangkauan anak-anak.

Jangan membuang obat apapun melalui saluran air limbah atau limbah rumah tangga. Tanyakan kepada apoteker anda mengenai cara membuang obat-obatan yang sudah tidak diperlukan lagi. Hal ini akan membantu menjaga lingkungan.

6. Isi kemasan dan Informasi lain

Apa yang terkandung dalam Neupro

- Zat berkhasiatnya adalah rotigotine.

Neupro 2 mg/24 h

Tiap patch melepaskan 2 mg rotigotine per 24 jam. Tiap patch berukuran 10 cm^2mengandung 4.5 mg rotigotine.

Neupro 4 mg/24 h

Tiap patch melepaskan 4 mg rotigotine per 24 jam. Tiap patch berukuran 20 cm^2mengandung 9.0 mg rotigotine.

- Komponen zat tambahan lainnya adalah *poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidoneK90, sodium metabisulphite (E223), ascorbyl palmitate (E304) dan DL-α-tocopherol (E307).*
  Lapisan belakang: *Polyester film, siliconized, aluminized,* salut warna denganlapisan pigment *(titanium dioxide (E171), pigment yellow 95, pigment red 166)* and cetakan *(pigment red 144, pigment yellow 95, pigment black 7).*
  Lapisan pelindung: *Transparent fluoropolymer coated polyester film.*

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Bagaimana penampilan Neupro dan isi dari kemasan

Neupro merupakan patch transdermal. Patch tersebut tipis dan memiliki tiga lapisan. Patch berbentuk kotak dengan sudut membulat. Bagian luar berwarna dan tercetak informasi Neupro 2 mg/24 h, 4 mg/24 h, ~~6 mg/24 h atau 8 mg/24 h.~~ 6

Neupro tersedia dalam kemasan dus berisi 28 patch yang dikemas tersendiri dalam sachet.

Neupro 2 mg/24 h transdermal patch, 1 dus karton isi 28 patch yang masing-masing dikemas dalam sachet.
Reg. No.: DKIxxxxxxxxxxxx
Neupro 4 mg/24 h transdermal patch, 1 dus karton isi 28 patch yang masing-masing dikemas dalam sachet.Reg. No.: DKIxxxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

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