

## 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<sup>2</sup> contains 4.5 mg of rotigotine.

Each patch releases 4 mg of rotigotine per 24 hours. Each patch of 20 cm<sup>2</sup> contains 9.0 mg of rotigotine.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Neupro 2 mg/24 h. 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 4 mg/24 h. 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.

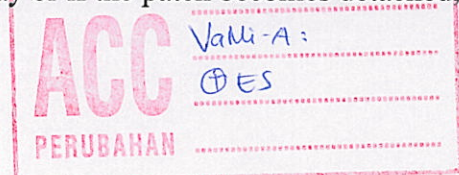
#### Dose

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

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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. 4mg/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/24h 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.

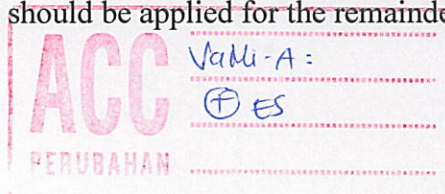
#### Method of administration

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.





### 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

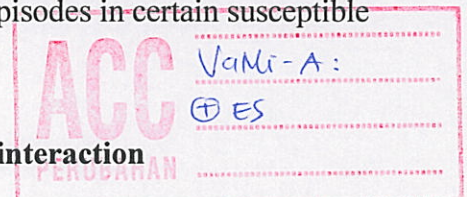
In clinical studies in Parkinson's patients, the 6 month-specific rates of peripheral edema remained at about 4% through the entire observation period up to 36 months.

#### 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.

### **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

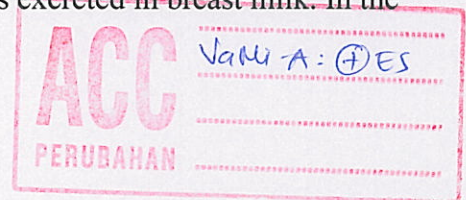
Because rotigotine decreases prolactin secretion in humans, inhibition of lactation is expected. Studies in rats have shown that rotigotine and/or its metabolite(s) is excreted in breast milk. In the absence of human data, breast-feeding should be discontinued.

##### Fertility

For information on fertility studies, please see section 5.3.

#### **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

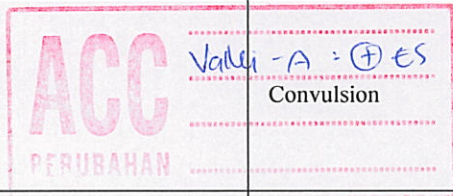
Based on the analysis of pooled placebo-controlled clinical trials comprising a total of 1,307 Neupro- and 607 placebo-treated patients, 72.3% of the patients on Neupro and 57.8% of patients on placebo reported at least one adverse reaction.

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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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 <sup>a</sup> (incl. hallucination, hallucination visual, hallucination auditory, illusion), Insomnia, Sleep disorder, Nightmare, Abnormal dreams, Impulse-control disorders <sup>a</sup> (incl. pathological gambling, punding)	Sleep attacks/Sudden onset of sleep, Paranoia, Sexual desire disorders <sup>a</sup> (incl. hypersexuality, libido increased), Confusional state, Disorientation, Agitation	Psychotic disorder, Obsessive-compulsive disorder, aggressive behaviour/aggression <sup>b</sup> , binge eating and compulsive eating <sup>b</sup>
Nervous system disorders	Somnolence, Dizziness, Headache	Disturbances in consciousness NEC <sup>a</sup> (incl. syncope, syncopal vasovagal, loss of consciousness), Dyskinesia, Dizziness postural, Lethargy		
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 <sup>a</sup> (incl. erythema, pruritus, irritation, rash, dermatitis, vesicles, pain, eczema, inflammation, swelling, discolouration, papules, excoriation, urticaria, hypersensitivity)	Oedema peripheral, Asthenic conditions <sup>a</sup> (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		

<sup>a</sup> High Level Term<sup>b</sup> 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<sub>2</sub> and D<sub>3</sub> receptor agonist acting also on D<sub>1</sub>, D<sub>4</sub> and D<sub>5</sub> 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<sub>3</sub>, D<sub>2</sub> and D<sub>1</sub> 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  $\leq 6$  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<sub>95%</sub> 18%; 39%,  $p < 0.0001$ ). With rotigotine, the mean improvement in the UPDRS score (Parts II + III) was -3.98 points (baseline 29.9 point) whereas in the placebo-treated arm a worsening of 1.31 points was observed (baseline 30.0 points). The difference was 5.28 points and statistically significant ( $p < 0.0001$ ).

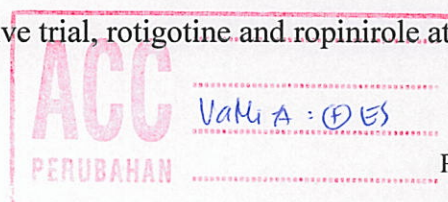
**In a second double-blind study**, 213 patients received rotigotine, 227 received ropinirole and 117 patients received placebo. The patients were titrated to their optimal dose of rotigotine in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 8 mg/24 h over 4 weeks. In the ropinirole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

At the end of the maintenance treatment in 92% of the subjects in the rotigotine arm, the optimal dose was the maximal dose allowed i.e. 8 mg/24 h. An improvement of 20% was seen in 52% of the subjects receiving rotigotine, 68% of the subjects receiving ropinirole and 30% of the subjects receiving placebo (Difference rotigotine *versus* placebo 21.7%; CI<sub>95%</sub> 11.1% ; 32.4% , difference ropinirole *versus* placebo 38.4% CI<sub>95%</sub> 28.1% ; 48.6% , difference ropinirole *versus* rotigotine 16.6%; CI<sub>95%</sub> -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  $6.3 \pm 1.3$  points in rotigotine-treated patients, and by  $5.9 \pm 1.3$  points in the ropinirole-group after 4 weeks of maintenance. Sleep (PDSS) improved by  $4.1 \pm 13.8$  points for rotigotine-treated patients, and by  $2.5 \pm 13.5$  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”.

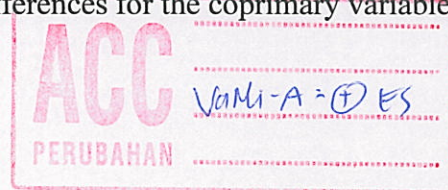
**In one double blind study**, 113 patients received rotigotine up to a maximum dose of 8 mg/24 h, 109 patients received rotigotine up to a maximum dose of 12 mg/24 h and 119 patients received placebo. The patients were titrated to their optimal doses of rotigotine or placebo in weekly increments of 2mg/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 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. 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/m<sup>2</sup> 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- $\alpha$ -tocopherol (E307).

##### *Protective liner:*

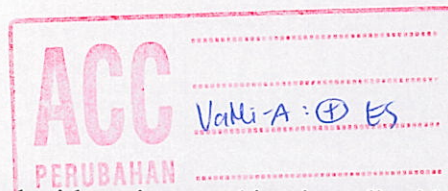
Transparent fluoropolymer coated polyester film.

#### 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- $\alpha$ -tocopherol (E307).

*Protective liner:*

Transparent fluoropolymer coated polyester film.

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

<sup>24</sup>/<sub>18</sub> 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.: DKI1441300155A1

Neupro 4 mg/24 h transdermal patch,  
1 carton box 28 patches which are individually sealed in sachets.  
Reg. No.: DKI1441300155B1

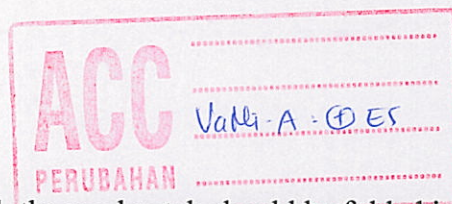
HARUS DENGAN RESEP DOKTER  
Drug Prescription Only

## 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



DRAFT