AUSTRALIAN PRODUCT INFORMATION

NEUPRO® (ROTIGOTINE) TRANSDERMAL PATCHES

1 NAME OF THE MEDICINE

Rotigotine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Neupro 1 mg: 5 cm^2 patch containing 2.25 mg rotigotine with a nominal release rate of 1 mg rotigotine per 24 hours.
Neupro 2 mg: 10 cm^2 patch containing 4.5 mg rotigotine with a nominal release rate of 2 mg rotigotine per 24 hours.
Neupro 3 mg: 15 cm^2 patch containing 6.75 mg rotigotine with a nominal release rate of 3 mg rotigotine per 24 hours.
Neupro 4 mg: 20 cm^2 patch containing 9.0 mg rotigotine with a nominal release rate of 4 mg rotigotine per 24 hours.
Neupro 6 mg: 30 cm^2 patch containing 13.5 mg rotigotine with a nominal release rate of 6 mg rotigotine per 24 hours.
Neupro 8 mg: 40 cm^2 patch containing 18.0 mg rotigotine with a nominal release rate of 8 mg rotigotine per 24 hours.

The active ingredient rotigotine is a white to light brownish powder. It is very slightly soluble to freely soluble in organic solvents, sparingly soluble in acidic aqueous solutions and practically insoluble in alkaline aqueous solutions.

The formulation contains sodium metabisulfite.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

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

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

2. A self-adhesive drug matrix layer.

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

Thin, matrix type transdermal patch that is square shaped with rounded edges. The backing layer comprises a polyester film, siliconized, aluminized, colour coated with a tan coloured pigment (titanium dioxide (E171), pigment yellow 95, pigment red 166) layer and imprinted (pigment red 144, pigment yellow 95, pigment black 7). The protective liner comprises a transparent fluoropolymer coated polyester film. The outside of the tan coloured backing layer is imprinted with Neupro 1 mg/24 h, Neupro 2 mg/24 h, Neupro 3 mg/24 h, Neupro 4 mg/24 h, Neupro 6 mg/24 h or Neupro 8 mg/24 h respectively.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

Restless legs syndrome
Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome in adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

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

Neupro can be applied irrespective of the timing of meals.

Dosage
The dose recommendations made below are in nominal dose.

Parkinson's disease
Dosing in patients with early stage Parkinson's disease
A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 8 mg/24 h.

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

The maximal dose is 8 mg/24 h.

Dosing in patients with advanced stage Parkinson's disease
A single daily dose should be initiated at 4 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 16 mg/24 h.

4 mg/24 h or 6 mg/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 up to a maximum dose of 16 mg/24 h.

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

Restless legs syndrome
A single daily dose should be initiated at 1 mg/24 h. Depending on the individual patient response, the dose may be increased in weekly increments of 1 mg/24 h to a maximal dose of 3 mg/24 h. The need for treatment continuation should be reconsidered every 6 months for risk/benefit analysis.

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 (see Section 4.4 Special Warnings and Precautions for Use and Section 5.2 Pharmacokinetic Properties). Rotigotine has not been investigated in patients with severe hepatic impairment.

Children and adolescents

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

Treatment discontinuation

Parkinson's disease

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

Restless legs syndrome

Neupro should be discontinued gradually. The daily dose should be reduced in steps of 1 mg/24 h with a dose reduction preferably every other day, until complete withdrawal of Neupro (see Section 4.4 Special Warnings and Precautions for Use). Following this procedure, rebound (worsening of symptoms beyond initial intensity after discontinuation of treatment) was not observed.

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 Special Warnings and Precautions for Use).

Use and handling

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

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

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

The patch should not be cut into pieces.

4.3 CONTRAINDICATIONS

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

Magnetic resonance imaging or cardioversion (see Section 4.4 Special Warnings and Precautions for Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Orthostatic hypotension
Dopamine agonists are known to impair the systemic regulation of the blood pressure resulting in postural/orthostatic hypotension. These events were also observed during treatment with Neupro, 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.

Elevation of blood pressure and heart rate
Some patients treated with Neupro exhibited increases in systolic blood pressure (greater than 180 mmHg) and/or diastolic blood pressure (greater than 105 mmHg) while supine or standing. Some patients treated with Neupro exhibited increased pulse (greater than 100 beats per minute) while supine and/or standing. These findings of blood pressure and heart rate elevations should be considered when treating patients with cardiovascular disease.

Syncope
Syncope was observed in association with rotigotine, but also at a similar rate in patients treated with placebo. Patients with severe cardiovascular disease should be asked about symptoms of syncope and pre-syncope.

Somnolence and sudden onset of sleep
Patients treated with Neupro have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on Neupro, some perceived no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as one year after initiation of treatment.

Somnolence is a common occurrence in patients receiving Neupro. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients should be advised to exercise caution while driving, operating machines, or working at heights during treatment with Neupro. Patients who have already experienced somnolence and/or an episode of sudden sleep onset should not participate in these activities during treatment with Neupro.

Before initiating treatment with Neupro, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with Neupro such as concomitant sedating medications and the presence of sleep disorders. If a patient develops meaningful daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g. conversations, eating, etc.), Neupro should ordinarily be discontinued (see Section 4.2 Dose and Method of Administration, Treatment discontinuation for guidance on discontinuing Neupro). If a decision is made to continue Neupro, patients should be advised not to drive and to

avoid other potentially dangerous activities. There is insufficient information to establish whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Sedating medicinal products or other CNS (central nervous system) depressants
Because of possible additive effects, patients should be advised to exercise caution when taking sedating medicinal products or other CNS (central nervous system) depressants (e.g. benzodiazepines, antipsychotics, antidepressants) or alcohol in combination with Neupro (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Ophthalmologic monitoring
Placebo controlled trials have shown a higher incidence of visual disturbance and eye conditions (see Section 4.8 Adverse Effects (Undesirable Effects)) in the rotigotine groups in comparison with controls. Similar events have been observed in open label trials. It is important to carry out ophthalmological monitoring at regular intervals for early detection of visual abnormalities.

Impulse control and related disorders
Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money or buying, binge eating, compulsive eating, and/or other intense urges, and the inability to control these urges while taking one or more medications, including Neupro, that increase central dopaminergic tone and are generally used for the treatment of Parkinson's disease. In some patients, dopamine dysregulation syndrome was observed under the treatment with rotigotine. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognise these behaviours as abnormal, it is important for prescribers to specifically ask their patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with Neupro. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Neupro.

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 Dose and Method of Administration).

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

Hallucinations / psychotic-like behaviour
Abnormal thinking and behaviour have been reported with Neupro. This abnormal thinking and behaviour can consist of one or more of a variety of manifestations including paranoid ideation, hallucinations, confusion, psychotic-like behaviour, disorientation, aggressive behaviour, agitation, delusions and delirium. Other drugs prescribed to improve the symptoms of Parkinson's disease can have similar effects on thinking and behaviour.

Patients with a major psychotic disorder should ordinarily not be treated with Neupro because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of Neupro (see Section 4.5

Interactions with Other Medicines and Other Forms of Interactions). Patients should be informed that hallucinations, abnormal thinking and behaviours can occur.

Neuroleptics
Neuroleptics given as antiemetic should not be given to patients taking dopamine agonists (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Augmentation
Reports in the literature indicate that treatment of restless legs syndrome with dopaminergic medicinal products can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in severity of symptoms, and spread of symptoms to involve other body parts.

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.

Sulfite sensitivity
Neupro transdermal patches contain sodium metabisulfite, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people.

Peripheral oedema
As with other dopamine agonists, rotigotine has been associated with the development of peripheral oedema in some patients with Parkinson's disease. Peripheral oedema has also been observed in clinical studies conducted in patients with RLS.

Weight gain and fluid retention
Patients taking Neupro for early stage and advanced stage Parkinson's disease had a higher incidence of substantial weight gain (more than 10% of baseline weight) than patients taking placebo. The weight gain was frequently associated with the development of peripheral oedema in patients with Parkinson's disease, suggesting that Neupro may cause fluid retention in some Parkinson's patients. Monitor for weight gain and fluid retention when treating patients with concomitant illnesses such as congestive heart failure or renal insufficiency.

Fibrotic complications
Neupro is a nonergot derived dopaminergic agent.

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

Cardiac valve abnormalities have been observed in open label trials of rotigotine, however, in placebo controlled clinical trials, the incidence of these adverse events was similar between treatment groups. Regular cardiac review as part of physical examination should be performed. Echocardiograph monitoring may be advisable in accordance with clinical judgment (see Section 4.8 Adverse Effects (Undesirable Effects)).

Ocular toxicity
After a single dose of rotigotine, binding to melanin containing tissues (eyes) in the pigmented rat and monkey was evident, but was slowly cleared over the 14 day observation period. Retinal degeneration was observed by transmission microscopy following subcutaneous administration of rotigotine to albino rats for 3 months. The effects were more pronounced in females. Additional studies to further evaluate the specific pathology have not been performed. Retinal degeneration was not observed during the routine histopathological evaluation of the eyes in any of the toxicology studies in any species used. The relevance of these findings to humans is not known.

Use in hepatic impairment
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 4.2 Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties).

Use in the elderly
No dosage adjustment is necessary in the elderly because therapy with Neupro is initiated at a low dose and gradually titrated according to clinical tolerability to obtain the optimum therapeutic effect (see Section 5.2 Pharmacokinetic Properties).

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

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

Patients with early stage Parkinson's disease receiving Neupro had an increased risk for low haemoglobin and low haemocrit below the normal reference range.

There was an increased risk for low serum glucose below the normal reference range in patients with early stage and advanced stage Parkinson's disease receiving Neupro.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 coadministration should be avoided. Because of possible additive effects, caution should be advised when patients are taking sedating medicinal products or other CNS (central nervous system) depressants (e.g. benzodiazepines, antipsychotics, antidepressants) or alcohol in combination with Neupro.

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

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

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

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

Coadministration of domperidone with rotigotine had no effect on the pharmacokinetics of rotigotine.

Rotigotine is metabolised by CYP2C19, and also weakly inhibits CYP2C19 at high concentrations. Coadministration of omeprazole (inhibitor of CYP2C19), in doses of 40 mg/day, had no effect on the pharmacokinetics and metabolism of rotigotine in healthy volunteers.

Coadministration 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

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

Use in pregnancy
Category: B3

There are no adequate data on the use of Neupro in pregnant women. Studies in rats have shown that rotigotine and/or its metabolites cross the placenta. There was no evidence of teratogenicity following subcutaneous administration of rotigotine to mice, rats and rabbits during the period of organogenesis; the exposure (plasma AUC) in rabbits was more than 100-fold the maximal clinical exposure. Maternotoxic doses were associated with embryofetal toxicity. Administration to rats from early gestation to weaning was associated with effects in offspring (impaired auditory startle reflex during lactation, delays in some developmental indices). The potential risk for humans is unknown. Rotigotine should not be used during pregnancy.

Use in lactation
Because rotigotine decreases prolactin secretion in humans, inhibition of lactation is expected. Studies in rats have shown that rotigotine and/or its metabolite(s) is excreted in breast milk. Subcutaneous administration to rats from early gestation to weaning was associated with adverse effects in offspring (see Use in pregnancy). In the absence of human data, breastfeeding should be discontinued.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Neupro may have a major influence on the ability to drive and use machines (see Section 4.8 Adverse Effects (Undesirable Effects)).

Neupro has been associated with somnolence including excessive daytime somnolence and sudden sleep onset episodes. Patients being treated with Neupro and presenting with somnolence and/or sudden sleep episodes must be informed not to drive or engage in activities (e.g. operating machines) where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved (see Section 4.4 Special Warnings and Precautions for Use).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

Parkinson's disease
Based on the analysis of pooled placebo controlled clinical trials comprising a total of 1307 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.

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

Table 1 covers adverse drug reactions from all rotigotine studies in patients with Parkinson's disease. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse Drug Reactions from all Parkinson's Disease Studies

System/organ classes (MedDRA)	Very common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1,000, <1/100	Rare ≥1/10,000, <1/1,000
Immune system disorders			Hypersensitivity which may include angioedema, lip oedema and tongue oedema	
Psychiatric disorders		Perception disturbances[a] (incl. hallucination,	Sleep attacks/Sudden onset of sleep, Paranoia, Sexual	Psychotic disorder, Obsessive-compulsive disorders,

System/organ classes (MedDRA)	Very common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1,000, <1/100	Rare ≥1/10,000, <1/1,000
		hallucination visual, hallucination auditory, illusion), Insomnia, Sleep disorder, Nightmare, Abnormal dreams, Impulse control disorder[a] (incl. pathological gambling, stereotypy/punding, compulsive shopping)	desire disorders[a] (incl. hypersexuality, libido increased), Confusional state, disorientation, agitation	binge eating[b] / eating disorder, aggressive behaviour/ aggression[b], delusions, delirium
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 impairment, Photopsia	
Ear and labyrinth disorders		Vertigo		
Cardiac disorders		Palpitations	Atrial fibrillation	Supraventricular tachycardia, 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, exfoliation, urticaria, hypersensitivity	Oedema peripheral, Asthenic conditions (incl. fatigue, asthenia, malaise)		Irritability

System/organ classes (MedDRA)	Very common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1,000, <1/100	Rare ≥1/10,000, <1/1,000
Investigations		Weight decreased, CPK increased (see *Special populations)*	Hepatic enzyme increased (inc. AST, ALT, GGT), Weight increased, Heart rate increased	
Injury, poisoning and procedural complications		Fall		

[a]High level term.
[b]Observed in open-label studies

In addition, the following potentially important adverse drug reactions have been identified as being reported in clinical trials:

- Fluid retention (see Section 4.4 Special Warnings and Precautions for Use).

Adverse events that might be indicative of fibrosis reported in the advanced stage PD clinical trial program are summarised in Table 2.

Table 2: Rotigotine treatment-emergent adverse events related to fibrosis – Advanced-stage Parkinson's disease

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

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

Restless legs syndrome
Based on the analysis of pooled placebo controlled clinical trials comprising a total of 748 Neupro and 214 placebo treated patients, 65.2% of the patients on Neupro and 33.2% of patients on placebo reported at least one adverse reaction.

In trials where the application sites were rotated as reflected in the instructions provided in the SPC and package leaflet, 34.2% of 748 patients using Neupro, 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 Neupro in 7.2% of subjects.

Table 3 covers adverse drug reactions from all studies in patients with restless legs syndrome. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse Drug Reactions from all Studies in Restless Legs Syndrome

System/organ classes (MedDRA)	Very common ≥ 1/10	Common ≥ 1/100, <1/10	Uncommon ≥ 1/1,000, <1/100	Rare ≥1/10,000, <1/1,000
Gastrointestinal disorders	Nausea	Vomiting, Dyspepsia		
General disorders and administration site conditions	Application and instillation site reactions[a] (incl. erythema, pruritus, irritation, rash, dermatitis, vesicles, pain, eczema, inflammation, swelling, discolouration, papules, exfoliation, urticaria, hypersensitivity), Asthenic conditions[a] (incl. fatigue, asthenia, malaise)	Irritability		
Immune system disorders		Hypersensitivity which may include angioedema, lip oedema and tongue oedema		
Nervous system disorders	Headache	Somnolence		
Psychiatric disorders		Sleep attacks/Sudden onset of sleep, Sexual desire disorders[a] (incl. hypersexuality, libido increased), Insomnia, Sleep disorder, Abnormal dreams, Impulse control disorder[a] (incl. pathological gambling, punding/ stereotypy, compulsive shopping)	Obsessive compulsive disorder, disorientation, agitation	Binge eating[b] /eating disorder, aggressive behaviour /aggression[b], delusions, delirium
Skin and subcutaneous tissue disorders		Pruritus		
Vascular disorders		Hypertension	Orthostatic hypotension	
Investigations		CPK increased		

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

Postmarketing experience (both indications)
In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported in postmarketing experience.

Frequency not known: dopamine dysregulation syndrome, diarrhoea, dropped head syndrome*, rhabdomyolysis.

* Only observed in Parkinson's disease patients

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The most likely adverse reactions of overdose of Neupro 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. 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 since rotigotine is not eliminated by dialysis.

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Rotigotine is a non-ergolinic dopamine receptor agonist for the treatment of idiopathic Parkinson's disease and restless legs syndrome (RLS). *In vitro* binding studies and functional assays indicate a high affinity for the dopaminergic system (D_1, D_2, D_3, D_4, D_5 receptors), particularly D_3 receptors. Rotigotine is thought to elicit its beneficial effect by activation of the D_3, D_2 and D_1 receptors of the caudate-putamen region. Rotigotine improved motor deficits in animal models of Parkinson's disease.

Rotigotine also shows affinities and activities at some nondopaminergic receptors, notably antagonism at $alpha_{2B}$ and agonism at $5HT_{1A}$ receptor subtypes. The significance of these nondopaminergic interactions to its efficacy profile *in vivo* has not been clinically demonstrated. There is no affinity of rotigotine for the $5HT_{2B}$ receptor, which has been implicated in valvular heart disease.

The mechanism of action of rotigotine for RLS is unknown, but could involve a dopaminergic mechanism, as central dopaminergic dysfunction has been implicated in RLS.

A contribution of rotigotine metabolites to the pharmacological effect of rotigotine *in vivo* is unlikely.

Clinical trials

Parkinson's disease

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

Two trials investigating the effectiveness of Neupro for the treatment of idiopathic Parkinson's disease were conducted in patients with early stage Parkinson's disease who were not receiving concomitant dopamine agonist therapy and were either levodopa naive or previous levodopa treatment was ≤ 6 months.

The primary outcome assessment was the score for the Activities of Daily Living (ADL) component (Part II) plus the Motor Examination Component (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS). Efficacy was determined by the subject's response to therapy in terms of responder and absolute points improvement in the scores of ADL and Motor Examination combined (UPDRS part II + III).

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

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

Clinical trials of Neupro in early stage disease

In a double blind study, 177 patients received Neupro and 96 patients received placebo. The patients were titrated to their optimal dose of Neupro or placebo in weekly increments of 2 mg/24 h starting at 2 mg/24 h to a maximum dose of 6 mg/24 h. Onset of treatment benefits began as early as the second week of treatment. Patients were maintained at their optimal dose for 6 months.

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

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

At the end of the maintenance treatment in 92% of the subjects in the Neupro arm the optimal dose was the maximal dose allowed, i.e. 8 mg/24 h at the end of the maintenance treatment. An

improvement over baseline of 20% was seen in 52% of the subjects receiving Neupro, 68% of the subjects receiving ropinirole and 30% of the subjects receiving placebo (difference Neupro versus placebo 21.7%; $CI_{95\%}$ 11.1%; 32.4%, difference ropinirole versus placebo 38.4% $CI_{95\%}$ 28.1%; 48.6%, difference ropinirole versus rotigotine 16.6%; $CI_{95\%}$ 7.6%; 25.7%). The mean improvement in the UPDRS score (Parts II + III) was -6.83 points (baseline 33.2 points) in the Neupro arm, -10.78 points in the ropinirole arm (baseline 32.2 points) and -2.33 points in the placebo arm (baseline 31.3 points). All differences between the active treatments and placebo were statistically significant.

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

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

In a second double blind study, 201 patients received Neupro, 200 received pramipexole and 100 patients received placebo. All patients were also receiving levodopa. The patients were titrated to their optimal dose of Neupro in weekly increments of 2 mg/24 h starting at 4 mg/24 h to a maximum dose of 16 mg/24 h. In the pramipexole group, patients received 0.375 mg in the first week, 0.75 mg in the second week and were titrated further in weekly increments of 0.75 mg to their optimal dose up to a maximum of 4.5 mg/day. Patients in each treatment group were maintained for 4 months.

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

Clinical trial on effect of Neupro in early morning motor function and sleep
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. Patients in both treatment groups were maintained at their optimal dose for 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 coprimary outcome measures. At the end of maintenance, the mean UPDRS part III score had improved by 7.0 points in rotigotine treated patients (baseline 29.7), and by 3.9 points in the placebo group (baseline 31.8). Improvements in the mean PDSS-2 total score

were 5.9 (rotigotine, baseline 19.3) and 1.9 points (placebo, baseline 20.3). Treatment differences for the coprimary variables were statistically significant ($p = 0.0002$ and $p < 0.0001$).

In the secondary outcome measures, numerical improvement from baseline to end of maintenance was seen with rotigotine compared to placebo in the Nocturnal Akinesia, Dystonia and Cramps Score (NACDS), and little change in either group was observed for the number of nocturias.

Restless legs syndrome

The effectiveness of Neupro in the treatment of moderate to severe idiopathic RLS was evaluated in a multinational drug development program consisting of two pivotal, parallel, randomized, double blind, placebo controlled studies and a placebo controlled, optimal dose sleep lab trial.

The primary outcome assessment in the two pivotal trials was the absolute change from baseline at the end of the maintenance period in the International RLS Study Group Rating Scale (IRLS) sum score and the Clinical Global Impression (CGI) Item 1 score (Severity of Illness).

The primary objective of the first double blind trial (SP790) was to demonstrate efficacy of 3 different transdermal doses of Neupro (1, 2 and 3 mg/24 h) versus placebo in subjects with moderate to severe idiopathic RLS over a 6 month maintenance period. A total of 333 patients received rotigotine in the three active treatment arms and 114 patients received placebo. At the end of maintenance both efficacy variables showed clinically relevant efficacy for all 3 rotigotine doses tested. (See Table 4.)

The primary objective of the second double blind trial (SP792) was to demonstrate efficacy of 4 different transdermal doses of Neupro (0.5, 1, 2 and 3 mg/24 h) versus placebo in subjects with moderate to severe idiopathic RLS over a 6 month maintenance period. A total of 395 patients received rotigotine in the 4 active treatment arms and 99 patients received placebo. At the end of maintenance both efficacy variables showed clinically relevant efficacy of rotigotine 2 mg/24 h and 3 mg/24 h. (See Table 4.)

Table 4: Change from Baseline to End of Maintenance Period

	Study SP790			
	Neupro 1 mg/24 h	**Neupro 2 mg/24 h**	**Neupro 3 mg/24 h**	**Placebo**
IRLS Sum Score				
Number of patients	112	109	112	114
LS Mean	-13.7	-16.2	-16.8	-8.6
Difference to placebo	-5.1	-7.5	-8.2	
(95% CI)	(-7.6, -2.7)	(-10.0, -5.1)	(-10.6, -5.7)	
p-value	<0.0001	<0.0001	<0.0001	
CGI Item 1				
Number of patients	112	109	112	114
LS Mean	-2.09	-2.41	-2.55	-1.34
Difference to placebo	-0.76	-1.07	-1.21	
(95% CI)	(-1.13, -0.38)	(-1.44, -0.69)	(-1.58, -0.83)	
p-value	<0.0001	<0.0001	<0.0001	

	Study SP792				
	Neupro 0.5 mg/24 h	**Neupro 1 mg/24 h**	**Neupro 2 mg/24 h**	**Neupro 3 mg/24 h**	**Placebo**
IRLS Sum Score					
Number of patients	98	99	95	103	99
LS Mean	-11.1	-11.2	-13.5	-14.2	-9.0
Difference to placebo	-2.2	-2.3	-4.5	-5.2	
(95% CI)	(-4.5, 0.2)	(-4.6, 0.0)	(-6.9, -2.2)	(-7.5, -2.9)	
p-value	0.0682	0.0535	0.0002	<0.0001	
CGI Item 1					
Number of patients	98	99	95	103	99
LS Mean	-1.75	-1.72,	-2.05	-2.31	-1.40
Difference to placebo	-0.35	-0.32	-0.65	-0.90	
(95% CI)	(-0.72, 0.02)	(-0.69, 0.05)	(-1.02, -0.28)	(-1.27, -0.54)	
p-value	0.0603	0.0857	0.0007	<0.0001	

LS Mean = least squares mean

In a third study (SP794) patients were investigated in a sleep lab setting. The objective of the double blind phase 3 sleep lab trial was to demonstrate that rotigotine is effective in subjects with moderate to severe idiopathic RLS based on the Periodic Limb Movement Index (PLMI; PLMs/total time in bed) as measured by polysomnography (PSG). The patients were titrated to their optimal dose of rotigotine or placebo in weekly increments of 1 mg/24 h starting at 1 mg/24 h to a maximum dose of 3 mg/24 h. Patients were maintained at their optimal dose for 4 weeks. Efficacy was assessed by the PLMI at the end of the maintenance period compared to baseline. A total of 46 patients received rotigotine treatment and 20 patients received placebo. The efficacy of Neupro over placebo was demonstrated for the primary efficacy variable. The PLMI decreased from 50.9 at baseline to 7.7 with rotigotine treatment and from 37.4 to 32.7 with placebo ($p < 0.001$). Rotigotine was 4.25 times more effective than placebo in the reduction of the PLMI at the end of the maintenance period.

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 concentration increases 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 1% (hip versus abdomen) to 46% (shoulder versus thigh). However, there is no indication of a relevant impact on the clinical outcome.

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

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

Metabolism
Rotigotine is extensively metabolised by N-dealkylation as well as direct and secondary conjugation. *In vitro* results indicate that different CYP isoforms are able to catalyse the N-desalkylation of rotigotine. Main metabolites are sulfates and glucuronide conjugates of the parent compound as well as N-desalkyl metabolites.

The information on metabolites is incomplete.

Excretion
Approximately 71% of the rotigotine dose is excreted in urine and a smaller part of about 23% is excreted in faeces. The clearance of rotigotine after transdermal administration is approximately 10 L/min and its overall elimination half-life is 5 to 7 hours. The pharmacokinetic profile shows a biphasic elimination with an initial half-life of about 2.4 to 3 hours.

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

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

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
There was no evidence of genotoxicity in assays for bacterial gene mutation and unscheduled DNA synthesis in rat hepatocytes. A positive result was obtained in the *in vitro* mouse lymphoma assay, but there was no evidence of clastogenicity in *in vivo* mouse micronucleus assays, with plasma exposure up to about 50 times the clinical plasma C_{max} value. On the weight of evidence, the genotoxic potential of rotigotine is considered to be low.

Carcinogenicity
Two year subcutaneous carcinogenicity studies with rotigotine were conducted in mice and rats, achieving respective systemic exposures (plasma AUC) up to 5 and 2-fold the clinical plasma AUC at the maximal recommended dose. There was no evidence of carcinogenicity in mice. Rats developed Leydig cell adenomas and uterine tumours (adenocarcinomas, squamous cell carcinomas), but the findings are of questionable significance because the endocrine mechanisms are not considered relevant to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

30 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in the following presentations:

Neupro 1 mg: Pack sizes: 7s, 28s, 100s.
Neupro 2 mg: Pack sizes: 7s, 28s, 100s.
Neupro 3 mg: Pack sizes: 7s, 28s, 100s.
Neupro 4 mg: Pack sizes 7s, 28s, 100s.
Neupro 6 mg: Pack sizes 7s, 28s, 100s.
Neupro 8 mg: Pack sizes 7s, 28s, 100s.

Please note Neupro 1 mg and 3 mg patches are not supplied. Pack sizes 7s and 100s are not supplied.

Each patch is individually sealed in a sachet.

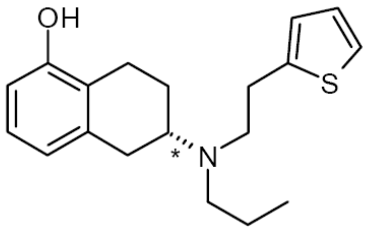
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: (6S)-6-{propyl-[2-(2-thienyl)ethyl]amino}- 5,6,7,8-tetrahydro-1-naphthalenol
Molecular formula: $C_{19}H_{25}NOS$
MW: 315.48

Chemical structure



CAS number
99755-59-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

UCB Pharma
A division of UCB Australia Pty Ltd
Level 1, 1155 Malvern Road
Malvern VIC 3144, Australia

9 DATE OF FIRST APPROVAL

22 November 2007

10 DATE OF REVISION

30 October 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of dopamine dysregulation syndrome and dopamine agonist withdrawal syndrome