

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEUPRO safely and effectively. See full prescribing information for NEUPRO.

### Neupro (Rotigotine Transdermal System)

Initial U.S. Approval: 2007

#### RECENT MAJOR CHANGES

Indications and Usage, Parkinson's Disease (1.1)	04/2012
Indications and Usage, Restless Legs Syndrome (1.2)	04/2012
Dosage and Administration, Advanced-Stage Parkinson's Disease (2.1)	04/2012
Dosage and Administration, Restless Legs Syndrome (2.2)	04/2012
Warnings and Precautions (5)	4/2012

#### INDICATIONS AND USAGE

Neupro is a dopamine agonist indicated for the treatment of:

- Signs and symptoms of Parkinson's disease (1.1)
- Moderate-to-severe primary Restless Legs Syndrome (1.2)

#### DOSAGE AND ADMINISTRATION

Apply once a day to the skin; press firmly in place for 30 seconds, making good contact. Do not place Neupro on oily, irritated, or damaged skin, or where it will be rubbed by tight clothing. Do not use the same site more than once every 14 days. The prescribed dose may be achieved using single or multiple patches. (2)

- **Parkinson's disease:** Initially, 2 mg/24 hours for early-stage disease or 4 mg/24 hours for advanced-stage disease. The dose may be increased as needed by 2 mg/24 hours at weekly intervals, up to 6 mg/24 hours for early-stage disease and up to 8 mg/24 hours for advanced-stage disease. (2.1)
- **Restless Legs Syndrome:** Initially, 1 mg/24 hours, increased as needed by 1 mg/24 hours at weekly intervals, up to 3 mg/24 hours. (2.2)

To discontinue treatment, reduce the dose gradually until complete withdrawal of Neupro. (2.3)

#### DOSAGE FORMS AND STRENGTHS

Transdermal System: 1 mg, 2 mg, 3 mg, 4 mg, 6 mg and 8 mg rotigotine per 24 hours. (3)

#### CONTRAINDICATIONS

History of hypersensitivity to rotigotine or components of the transdermal patch. (4)

#### WARNINGS AND PRECAUTIONS

- Contains sodium metabisulfite that may cause allergic-type reactions in those with sulfite sensitivity. (5.1)
- Falling asleep during activities of daily living, including the operation of motor vehicles and somnolence may occur. (5.2)
- Hallucinations/psychotic-like behavior and dyskinesia may occur. (5.3, 5.9)
- Symptomatic postural hypotension and syncope may occur, especially during dose escalation. (5.4, 5.5)
- Application site reactions can occur, and may be severe. (5.10)
- Elevation of blood pressure and heart rate may occur. (5.7)
- Intense urges may cause impulse control and compulsive behaviors. (5.6)
- Monitor patients for these adverse reactions. If these adverse reactions occur, lowering the dose or discontinuing Neupro may be beneficial. (5)

#### ADVERSE REACTIONS

- Most common adverse reactions ( $\geq 5\%$  greater than placebo) for the highest recommended doses of Neupro for treatment of Parkinson's disease were nausea, vomiting, somnolence, application site reactions, dizziness, anorexia, hyperhidrosis, insomnia, peripheral edema, and dyskinesia. (6.1)
- Most common adverse reactions ( $\geq 5\%$  greater than placebo) for the highest recommended dose of Neupro for Restless Legs Syndrome were application site reactions, nausea, somnolence, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 866-822-0068 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 04/2012

## FULL PRESCRIBING INFORMATION: CONTENTS\*

1	<b>INDICATIONS AND USAGE</b>	8.5 Geriatric Use
	1.1 Parkinson's Disease (PD)	8.6 Renal Impairment
	1.2 Restless Legs Syndrome (RLS)	8.7 Hepatic Impairment
2	<b>DOSAGE AND ADMINISTRATION</b>	9 <b>DRUG ABUSE AND DEPENDENCE</b>
	2.1 Parkinson's Disease	9.1 Controlled Substance
	2.2 Restless Legs Syndrome	9.3 Dependence
	2.3 Discontinuation of Treatment	10 <b>OVERDOSAGE</b>
3	<b>DOSAGE FORMS AND STRENGTHS</b>	10.1 Overdose Symptoms
4	<b>CONTRAINDICATIONS</b>	10.2 Overdose Management
5	<b>WARNINGS AND PRECAUTIONS</b>	11 <b>DESCRIPTION</b>
	5.1 Sulfite Sensitivity	11.1 System Components and Structure
	5.2 Falling Asleep During Activities of Daily Living and Somnolence	12 <b>CLINICAL PHARMACOLOGY</b>
	5.3 Hallucinations / Psychotic-Like Behavior	12.1 Mechanism of Action
	5.4 Symptomatic Hypotension	12.2 Pharmacodynamics
	5.5 Syncope	12.3 Pharmacokinetics
	5.6 Impulse Control / Compulsive Behaviors	12.6 Pharmacokinetics in Special Populations
	5.7 Elevation of Blood Pressure and Heart Rate	12.7 Adhesion
	5.8 Weight Gain and Fluid Retention	13 <b>NONCLINICAL TOXICOLOGY</b>
	5.9 Dyskinesia	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
	5.10 Application Site Reactions	13.2 Animal Toxicology and/or Pharmacology
	5.11 Melanoma	14 <b>CLINICAL STUDIES</b>
	5.12 Augmentation and Rebound in RLS	14.1 Parkinson's Disease
	5.13 Magnetic Resonance Imaging and Cardioversion	14.2 Restless Legs Syndrome
	5.14 Heat Application	16 <b>HOW SUPPLIED/STORAGE AND HANDLING</b>
	5.15 Withdrawal-Emergent-Hyperpyrexia and Confusion	17 <b>PATIENT COUNSELING INFORMATION</b>
	5.16 Fibrotic Complications	17.1 Sulfite Sensitivity
	5.17 Binding to Melanin	17.2 Falling Asleep During Activities of Daily Living and Somnolence
6	<b>ADVERSE REACTIONS</b>	17.3 Hallucinations / Psychotic-Like Behavior
	6.1 Clinical Trials Experience	17.4 Symptomatic Hypotension
	6.2 Laboratory Changes	17.5 Syncope
7	<b>DRUG INTERACTIONS</b>	17.6 Impulse Control / Compulsive Behaviors
	7.1 Dopamine Antagonists	17.7 Elevation of Blood Pressure and Heart Rate
8	<b>USE IN SPECIFIC POPULATIONS</b>	17.8 Weight Gain and Fluid Retention
	8.1 Pregnancy	17.9 Dyskinesias
	8.3 Nursing Mothers	17.10 Application Site Reactions
	8.4 Pediatric Use	17.11 Melanoma
		17.12 Augmentation and Rebound in RLS

17.13 Magnetic Resonance Imaging and Cardioversion  
17.14 Heat Application

17.15 Nausea, Vomiting, and Dyspepsia  
17.16 Instructions for Use

\*Sections or subsections omitted from the Full Prescribing Information are not listed.

---

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Parkinson's Disease (PD)

Neupro (Rotigotine Transdermal System) is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of Neupro was demonstrated in randomized, controlled trials in patients with early-stage Parkinson's disease who were not receiving concomitant levodopa therapy as well as in patients with advanced-stage Parkinson's disease on concomitant levodopa.

#### 1.2 Restless Legs Syndrome (RLS)

Neupro (Rotigotine Transdermal System) is indicated for the treatment of moderate-to-severe primary restless legs syndrome.

### 2 DOSAGE AND ADMINISTRATION

Neupro is applied once a day. The adhesive side of the transdermal system should be applied to clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm. The transdermal system should be applied at approximately the same time every day, at a convenient time for the patient. Because Neupro is administered transdermally, food is not expected to affect absorption and it can be applied irrespective of the timing of meals. No dosage adjustment is necessary for patients who have moderate impairment of hepatic function or mild to severe impairment of renal function. The application site for Neupro should be moved on a daily basis (for example, from the right side to the left side and from the upper body to the lower body). Neupro should not be applied to the same application site more than once every 14 days and should not be placed on skin that is oily, irritated, or damaged, or where it will be rubbed by tight clothing. If it is necessary to apply Neupro to a hairy area, the area should be shaved at least 3 days prior to Neupro application. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place for 30 seconds, making sure there is good contact, especially around the edges. If the patient forgets to replace Neupro, or if the transdermal system becomes dislodged, another transdermal system should be applied for the remainder of the day. The prescribed dose may be achieved using single or multiple patches. [*Refer Patients to Instructions for Use in the Patient Information Section at the end of the Full Prescribing Information.*]

#### 2.1 Parkinson's Disease

##### Early-Stage Parkinson's Disease

Neupro should be started at 2 mg/24 hours for patients with early-stage Parkinson's disease. Based upon individual patient clinical response and tolerability, Neupro dosage may be increased weekly by 2 mg/24 hours if tolerated and if additional therapeutic effect is needed. The lowest effective dose was 4 mg/24 hours. The highest recommended dose for early-stage Parkinson's disease is 6 mg/24 hours.

##### Advanced-Stage Parkinson's Disease

Patients with advanced-stage Parkinson's disease may be initiated at 4 mg/24 hours. Based upon individual patient clinical response and tolerability, Neupro dosage may be increased weekly by 2 mg/24 hours. The recommended dose for advanced-stage Parkinson's disease is 8 mg/24 hours.

#### 2.2 Restless Legs Syndrome

Neupro should be started at 1 mg/24 hours. Based upon individual patient clinical response and tolerability, Neupro dosage may be increased weekly by 1 mg/24 hours if tolerated and if additional therapeutic effect is needed. The lowest effective dose was 1 mg/24 hours. The highest recommended dose is 3 mg/24 hours.

#### 2.3 Discontinuation of Treatment

For patients with Parkinson's disease, the daily dose should be reduced by a maximum of 2 mg/24 hours with a dose reduction preferably every other day, until complete withdrawal of Neupro is achieved.

---

For patients with RLS, the daily dose should be reduced by 1 mg/24 hours preferably every other day, until complete withdrawal of Neupro is achieved.

### **3 DOSAGE FORMS AND STRENGTHS**

Transdermal System: 1 mg, 2 mg, 3 mg, 4 mg, 6 mg and 8 mg rotigotine per 24 hours.

### **4 CONTRAINDICATIONS**

Neupro is contraindicated in patients who have demonstrated hypersensitivity to rotigotine or the components of the transdermal system.

### **5 WARNINGS AND PRECAUTIONS**

Patients should be monitored for developing adverse reactions described in this section. If any of these adverse reactions develop, lowering or discontinuing the dose of Neupro may be beneficial.

#### **5.1 Sulfite Sensitivity**

Neupro contains 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. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

#### **5.2 Falling Asleep During Activities of Daily Living and Somnolence**

Patients with early and advanced Parkinson's disease and with Restless Legs Syndrome 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 did not perceive 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. In trials of Restless Legs Syndrome, 2 % of patients treated with the highest recommended Neupro dose (3 mg/24 hours) reported sleep attacks vs 0 % of placebo patients.

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.

Somnolence is a common occurrence in patients receiving Neupro. For the highest recommended Neupro dose, the treatment different incidence (Neupro % - Placebo %) for somnolence was 16% for early Parkinson's disease, 4 % for advanced Parkinson's disease, and 6 % for Restless Legs Syndrome. 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 this risk with Neupro such as concomitant sedating medications and the presence of sleep disorders. If a patient develops daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), Neupro should ordinarily be discontinued. [*see Dosage and Administration (2.3)*].

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.

#### **5.3 Hallucinations / Psychotic-Like Behavior**

There was an increased risk for hallucinations in patients with advanced-stage Parkinson's disease treated with Neupro. For the highest recommended Neupro dose, the incidence of the treatment difference (Neupro % - Placebo %) for hallucinations was 4% for patients with advanced-stage Parkinson's disease, and this difference increased with increasing dose. Hallucinations were of sufficient severity to cause discontinuation of treatment (mainly during the dose escalation/titration period) in 3% of advanced-stage Parkinson's disease patients treated with the highest recommended dose of Neupro

compared with 1 % of placebo treated patients. Hallucinations have also been reported in post-marketing reports.

Post-marketing reports indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior during Neupro treatment or after starting or increasing the dose of Neupro. Other drugs prescribed to improve the symptoms of Parkinson's disease can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium. These various manifestations of psychotic-like behavior were also observed during the clinical development of Neupro for early and advanced-stage Parkinson's disease and Restless Legs Syndrome.

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 *Drug Interactions (7.1)*].

#### **5.4 Symptomatic Hypotension**

Dopaminergic agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, resulting in postural/orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to a postural challenge. For these reasons, both Parkinson's and RLS patients being treated with dopaminergic agonists ordinarily (1) require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and (2) should be informed of this risk.

Mild-moderate decreases in systolic blood pressure ( $\geq 20$  mm Hg) and in diastolic blood pressure ( $\geq 10$  mm Hg) occurred more frequently (Neupro %  $\geq 5$  % greater than placebo %) in all patients (i.e., early and advanced-stage Parkinson's disease and Restless Legs Syndrome) with the highest recommended Neupro dose. These decreases in systolic and diastolic blood pressure were observed when supine, standing, and changing from supine to standing position. More severe decreases in systolic blood pressure ( $> 40$  mm Hg) and in diastolic blood pressure ( $\geq 20$  mm Hg) also occurred more frequently (Neupro %  $\geq 2$  % greater than placebo %) in patients with early and advanced-stage Parkinson's disease during measurements when supine, standing and/or changing from supine to standing position. Some threshold decreases in blood pressure described earlier appeared to be dependent on the dose of Neupro and were also observed at the final study visit.

An analysis using a variety of adverse reaction terms suggestive of orthostatic hypotension, including dizziness/postural dizziness and others, showed an increased risk for all patients treated with Neupro. For the highest recommended Neupro dose, the treatment different incidence (Neupro % - Placebo %) for adverse reactions suggestive of hypotension/orthostatic hypotension was 18 % for early Parkinson's disease, 4 % for advanced Parkinson's disease, and 1 % for Restless Legs Syndrome.

This increased risk for symptomatic hypotension and decreases in blood pressure was observed in a setting in which patients were very carefully titrated, and patients with clinically relevant cardiovascular disease or symptomatic orthostatic hypotension at baseline had been excluded from this study. The increased risk for significant decreases in blood pressure or orthostatic hypotension occurred especially in the dose escalation/titration period.

#### **5.5 Syncope**

Syncope has been reported in patients using dopamine agonists, and for this reason patients should be alerted to the possibility of syncope. Because the studies of Neupro excluded patients with clinically relevant cardiovascular disease, patients with severe cardiovascular disease should be treated with caution.

#### **5.6 Impulse Control / Compulsive Behaviors**

Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including Neupro, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. 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 recognize these behaviors as abnormal, it is important for prescribers to specifically ask 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 [see *Patient Counseling Information (17.6)*].

## 5.7 Elevation of Blood Pressure and Heart Rate

Some patients treated with Neupro exhibited moderately severe increases in systolic blood pressure ( $> 180$  mm Hg) and/or in diastolic blood pressure ( $> 105$  mm Hg) while supine and/or standing. In patients with advanced-stage Parkinson's disease, there was an increased risk (treatment difference = highest recommended Neupro dose % - placebo %) of 2 % for systolic blood pressure  $> 180$  mm Hg and of 4 % for diastolic blood pressure  $> 105$  mm Hg. In patients with Restless Legs Syndrome, there was an increased risk (treatment difference = highest recommended Neupro dose % - placebo %) of 4 % for diastolic blood pressure  $> 105$  mm Hg.

Mild-moderate increases in systolic blood pressure ( $\geq 20$  mm Hg) and in diastolic blood pressure ( $\geq 10$  mm Hg) occurred more frequently (Neupro %  $\geq 5$  % greater than placebo %) in all patients (i.e., early and advanced-stage Parkinson's disease and Restless Legs Syndrome) with the highest recommended Neupro dose. These increases in systolic and diastolic blood pressure were observed when supine, standing, and changing from supine to standing position. More severe increases in systolic blood pressure ( $> 40$  mm Hg) and in diastolic blood pressure ( $\geq 20$  mm Hg) also occurred more frequently (Neupro %  $\geq 2$  % greater than placebo %) in patients with early and advanced-stage Parkinson's disease and with Restless Legs Syndrome during measurements when supine, standing and/or changing from supine to standing position. Some threshold increases in blood pressure described earlier appeared to be dependent on the dose of Neupro and were also observed at the final study visit.

In the placebo-controlled trials, there was an increased risk for hypertension as an adverse reaction with the highest recommended dose for advanced-stage Parkinson's disease (Neupro 3 % vs placebo 0 %) and for Restless Legs Syndrome (Neupro 4 % vs placebo 0 %).

Some patients treated with Neupro exhibited moderately increased pulse ( $> 100$  beats per minute) while supine and/or standing. In patients with advanced-stage Parkinson's disease, there was an increased risk (treatment difference = highest recommended Neupro dose % - placebo %) of 2 % for increased pulse. In patients with Restless Legs Syndrome, there was an increased risk (treatment difference = highest recommended Neupro dose % - placebo %) of 5 % for increased pulse.

These findings of blood pressure and heart rate elevations should be considered when treating patients with cardiovascular disease.

## 5.8 Weight Gain and Fluid Retention

Patients taking the highest recommended Neupro dose for early-stage Parkinson's disease had a higher incidence (2 %) of substantial weight gain (more than 10% of baseline weight) than subjects taking placebo (0 %). In advanced-stage Parkinson's disease, the incidence of weight gain more than 10 % of baseline weight was 9 % Neupro (for highest recommended dose) and 1 % placebo. This weight gain was frequently associated with the development of peripheral edema in patients with Parkinson's disease, suggesting that Neupro may cause substantial fluid retention in some Parkinson's patients. Although the weight gain was usually well-tolerated in subjects observed in the Parkinson's clinical studies, it could cause greater difficulty in patients who may be especially vulnerable to negative clinical consequences from fluid retention such as those with significant congestive heart failure or renal insufficiency.

For the highest recommended Neupro dose, the treatment different incidence (Neupro % - Placebo %) for peripheral edema was 1% for early Parkinson's disease, and 8% for advanced Parkinson's disease. These treatment differences increased further with treatment at Neupro dosing above the highest recommended doses.

## 5.9 Dyskinesia

Neupro may potentiate the dopaminergic side effects of levodopa and may cause and/or exacerbate pre-existing dyskinesia. For the highest recommended Neupro dose, the treatment different incidence (Neupro % - Placebo %) for dyskinesia was 7 % for patients with advanced-stage Parkinson's disease, and this incidence increased with increasing dose. There was also an increased risk (Neupro 3 % vs placebo 0 %) for discontinuation from the study because of dyskinesia for the highest recommended Neupro dose in these same patients.

## 5.10 Application Site Reactions

Application site reactions (ASRs) were reported at a greater frequency in the Neupro-treated patients than in placebo patients in the double-blind, placebo-controlled dose-response studies with Neupro. For the highest recommended Neupro dose, the treatment different incidence (Neupro % - Placebo %) for various ASRs was 15 % for early-stage Parkinson's disease, 23% for advanced-stage Parkinson's disease, and 39 % for Restless Legs Syndrome. ASRs exhibited a dose-dependent relationship for all doses for patients with early and advanced-stage Parkinson's disease and Restless Legs Syndrome ASRs

were also of sufficient severity to cause study discontinuation for patients with early-stage Parkinson's disease (Neupro 3 % vs placebo 0 %), advanced-stage Parkinson's disease (Neupro 2 % vs placebo 0 %, and Restless Legs Syndrome (Neupro 12 % vs placebo 0 %) who were treated with the highest recommended Neupro dose.

Of ASRs in Neupro-treated patients, most were mild or moderate in intensity. The signs and symptoms of these reactions generally were localized erythema, edema, or pruritus limited to the patch area and usually did not lead to dose reduction. Generalized skin reactions (e.g., allergic rash, including erythematous, macular-papular rash, or pruritus), have been reported at lower rates than ASRs during the development of Neupro.

In a clinical study designed to investigate the cumulative skin irritation of Neupro, daily rotation of Neupro application sites has been shown to reduce the incidence of ASRs in comparison to repetitive application to the same site. In a clinical study investigating the skin sensitizing potential of Neupro in 221 healthy subjects, no case of contact sensitization was observed. Localized sensitization reactions were observed in a study with healthy subjects by continuously rotating a 0.5 mg/24 hours transdermal system, after induction of maximal irritational stress was achieved by repetitive transdermal system application to the same site. If a patient reports a persistent application site reaction (of more than a few days), reports an increase in severity, or reports a skin reaction spreading outside the application site, an assessment of the risk and benefits for the individual patient should be conducted. If a generalized skin reaction associated with the use of Neupro is observed, Neupro should be discontinued.

### **5.11 Melanoma**

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using Neupro for *any* indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

### **5.12 Augmentation and Rebound in RLS**

Augmentation is a worsening of RLS symptoms during treatment, leading to an increase in overall symptom severity or earlier time of symptom onset each day compared to before initiation of treatment. Dopaminergic medicinal products, including rotigotine, may result in augmentation.

Rebound, an exacerbation of RLS symptoms, is considered to be an end of dose effect, related to the half-life of the therapeutic agent. Reports in the published literature indicate discontinuation or wearing off of dopaminergic medications can result in rebound.

### **5.13 Magnetic Resonance Imaging and Cardioversion**

The backing layer of Neupro contains aluminum. To avoid skin burns, Neupro should be removed prior to magnetic resonance imaging or cardioversion.

### **5.14 Heat Application**

The effect of application of heat to the transdermal system has not been studied. However, heat application has been shown to increase absorption several fold with other transdermal products. Patients should be advised to avoid exposing the Neupro application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

### **5.15 Withdrawal-Emergent-Hyperpyrexia and Confusion**

A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, rhabdomyolysis, and/or autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy. Therefore it is recommended that the dose be tapered at the end of Neupro treatment as a prophylactic measure [*see Dosage and Administration (2.3)*]

### 5.16 Fibrotic Complications

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

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

### 5.17 Binding to Melanin

As has been reported with other dopamine agonists, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident after a single dose of rotigotine, but was slowly cleared over the 14-day observation period.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in the Warnings and Precautions section of labeling.

- Sulfite Sensitivity [see Warnings and Precautions (5.1)]
- Falling Asleep During Activities of Daily Living and Somnolence [see Warnings and Precautions (5.2)]
- Hallucinations / Other Psychiatric Disorders [see Warnings and Precautions (5.3)]
- Symptomatic Hypotension [see Warnings and Precautions (5.4)]
- Syncope [see Warnings and Precautions (5.5)]
- Impulse Control / Compulsive Behaviors [see Warnings and Precautions (5.6)]
- Elevation of Blood Pressure and Heart Rate [see Warnings and Precautions (5.7)]
- Weight Gain and Fluid Retention [see Warnings and Precautions (5.8)]
- Dyskinesia [see Warnings and Precautions (5.9)]
- Application Site Reactions [see Warnings and Precautions (5.10)]
- Melanoma [see Warnings and Precautions (5.11)]
- Augmentation and Rebound in RLS [see Warnings and Precautions (5.12)]
- Heat Application [see Warnings and Precautions (5.14)]
- Withdrawal-Emergent-Hyperpyrexia and Confusion [see Warnings and Precautions (5.15)]
- Fibrotic Complications [see Warnings and Precautions (5.16)]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions (number of unique patients experiencing an adverse reaction associated with treatment / total number of patients treated) observed in the clinical trials of a drug cannot be directly compared to incidence of adverse reactions in the clinical trials of another drug and may not reflect the incidence of adverse reactions observed in practice.

#### Adverse Reactions Incidence in Controlled Clinical Studies in Early-Stage Parkinson's Disease

The safety of Neupro was evaluated in a total of 649 early-stage Parkinson's disease patients who participated in three double-blind, placebo-controlled studies with durations of 3 to 9 months. Additional safety information was collected in short term studies, and two open-label extension studies in patients with early-stage Parkinson's disease.

The incidence of adverse reactions in a randomized, double-blinded, placebo-controlled, fixed-dose trial is shown in Table 1. Incidences for the non-recommended 8 mg/24 hour dose are also shown.

In the double-blind, placebo-controlled, Dose-Response study in patients with early-stage Parkinson's disease, the most commonly observed adverse reactions ( $\geq 5\%$  greater than placebo) for the highest recommended dose of Neupro (6 mg/24 hours) were nausea, vomiting, somnolence, application site reactions, dizziness, anorexia, hyperhidrosis, and insomnia.

In this trial, 12% of patients treated with the highest, recommended Neupro dose (6 mg/24 hours) discontinued treatment because of adverse reactions, compared with 6% of patients who received placebo.

**Table 1 Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Trial of Patients with Early-Stage Parkinson's Disease (Dose-Response Study) Where Incidence Was  $\geq 2\%$  in 6 mg/24 hours Neupro Group and Greater Than the Incidence in Placebo-Treated Patients**

Adverse Reactions	Placebo N=64 %	Neupro dose			
		2 mg/24h N=67 %	4 mg/24h N=64 %	6 mg/24h N=65 %	8 mg/24h N=70 %
<b>Ear and labyrinth disorders</b>					
Tinnitus	0	0	2	3	0
<b>Gastrointestinal disorders</b>					
Nausea*	13	34	38	48	41
Vomiting*	3	10	16	20	11
Anorexia	0	0	2	8	4
Dyspepsia	0	2	2	3	0
<b>General disorders and administration site conditions</b>					
Application and instillation site reactions	19	24	21	34	46
Fatigue	3	8	18	6	13
Oedema peripheral*	2	2	3	3	4
<b>Infections and infestations</b>					
Upper respiratory tract infection	0	3	5	2	0
Sinusitis	0	2	0	2	1
<b>Injury, poisoning and procedural complications</b>					
Contusion*	0	2	0	2	4
<b>Investigations</b>					
White blood cells urine positive	2	3	3	3	1
Electrocardiogram T wave abnormal	0	0	2	3	0
Weight decreased*	0	0	0	2	3
<b>Metabolism and nutrition disorders</b>					
Anorexia	0	2	2	6	1
Decreased appetite*	0	0	0	3	3
<b>Musculoskeletal and connective tissue disorders</b>					
Muscle spasms*	2	3	2	3	4
<b>Nervous system disorders</b>					
Dizziness	11	21	14	22	20
Dizziness postural	0	2	2	2	1
Somnolence*	3	12	14	19	20
Lethargy	0	2	2	2	1
Balance disorder	0	0	2	3	0
<b>Psychiatric disorders</b>					
Insomnia	6	5	10	11	7
Early morning awakening*	0	0	0	2	3
Abnormal dreams*	0	2	5	3	7
Depression	0	5	3	2	0
<b>Reproductive system and breast disorders</b>					
Erectile dysfunction*	0	0	0	2	3
<b>Respiratory, thoracic and mediastinal disorders</b>					

Pharyngolaryngeal pain	0	2	2	2	0
Hiccups*	0	2	2	2	3
<b>Skin and subcutaneous tissue disorders</b>					
Hyperhidrosis	3	3	3	11	3
Erythema*	3	3	6	5	6
Rash pruritic*	0	0	0	2	3

\*Dose-related

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAEs=treatment-emergent adverse events

The incidence of certain adverse reactions with Neupro treatment was notably increased compared to placebo treatment (i.e., Neupro % - placebo % =  $\geq 5$  %) in either the titration or maintenance phases of the Dose-Response trial. During the titration phase, an increased incidence (in descending order of % treatment difference) was observed for nausea, somnolence, vomiting, application site reactions (ASRs), dizziness, sweating increased, anorexia and vision abnormal. During the maintenance phase, an increased incidence was observed for nausea, and ASRs. Some adverse reactions developing in the titration phase persisted ( $\geq 7$  days) into the maintenance phase. These “persistent” adverse reactions included ASRs, anorexia, somnolence, nausea, and vision abnormal.

### Adverse Reactions Incidence in Controlled Clinical Studies in Advanced-Stage Parkinson’s Disease

The safety evaluation of Neupro was based on a total of 672 Neupro-treated subjects with advanced-stage Parkinson’s disease who participated in 3 double-blind, placebo-controlled studies (2 fixed-dose trials and one flexible dose trial) with durations of 3 to 7 months. Patients received concomitant levodopa in these studies. Additional safety information was collected in earlier short-term studies, and 2 open-label extension studies in subjects with advanced-stage Parkinson’s disease.

The incidence of adverse reactions in a randomized, double-blinded, placebo-controlled, fixed-dose trial is shown in Table 2. Incidences for the non-recommended 12 mg/24 hour dose are also shown.

In the Dose-Response, placebo controlled trial for advanced-stage Parkinson's disease, the most common adverse reactions ( $\geq 5$  % greater than placebo) for the highest recommended dose of Neupro (8 mg) were application site reactions, nausea, somnolence, and headache.

In this trial, approximately 15 % of patients treated with the highest, recommended Neupro dose (8 mg/24 hours) discontinued treatment because of adverse reactions, compared with 9 % of patients who received placebo.

**Table 2 Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Trial of Patients with Advanced-Stage Parkinson's Disease (Dose-Response Study) Where Incidence Was  $\geq 2$  % in 8 mg/24 hours Neupro Group and Greater Than the Incidence in Placebo-Treated Patients**

Adverse Reaction	Placebo N=120 %	Neupro dose	
		8 mg/24h N=118 %	12 mg/24h N=111 %
<b>Gastrointestinal disorders</b>			
Nausea	19	28	22
Vomiting	6	10	8
Constipation	6	9	5
Diarrhea	5	7	5
<b>General disorders and administration site conditions</b>			
Application and instillation site reactions <sup>a*</sup>	13	36	46
Edema peripheral*	1	9	14
Asthenia	3	4	3
<b>Musculoskeletal and connective tissue disorders</b>			
Musculoskeletal pain	1	2	2
Arthralgia	7	11	8

<b>Nervous system disorders</b>			
Somnolence	28	32	32
Dizziness	15	23	14
Dyskinesia*	7	14	17
Headache	8	10	8
Paraesthesias/Dysesthesias*	3	5	6
Tremor	3	4	3
<b>Psychiatric disorders</b>			
Disturbances in initiating and maintaining sleep <sup>a</sup> *	6	9	14
Hallucinations *	3	7	14
Nightmare*	2	3	5
<b>Respiratory, thoracic and mediastinal disorders</b>			
Cough	1	3	3
Nasal congestion	0	3	3
Sinus congestion	0	3	2
<b>Skin and subcutaneous tissue disorders</b>			
Hyperhidrosis	0	3	1
Erythema	1	3	2
<b>Vascular disorders</b>			
Hypertension*	0	3	5

\*Dose-related

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAEs=treatment-emergent adverse events

<sup>a</sup> The following selected HLTs were considered and included, if applicable: application and instillation site reactions, asthenic conditions, and disturbances in initiating and maintaining sleep

The incidence of certain adverse reactions with Neupro treatment was notably increased compared to placebo treatment (i.e., Neupro % - placebo % =  $\geq 5$  %) in either the titration or maintenance phases of the Dose-Response trial. During the titration phase, an increased incidence (in descending order of % treatment difference) was observed for nausea, hallucinations, constipation, dyskinesia, dizziness. During the maintenance phase, an increased incidence was observed for ASRs, peripheral edema, and dyskinesia. Some adverse reactions developing in the titration phase persisted ( $\geq 7$  days) into the maintenance phase. A notably “persistent” adverse reaction was ASRs.

### Adverse Reactions Incidence in Controlled Clinical Studies in Restless Legs Syndrome

The safety evaluation of rotigotine was based on a total of 745 Neupro-treated subjects with RLS who participated in 2 double-blind, placebo-controlled studies with maintenance durations of 6 months. Additional safety information was collected in earlier short term studies, and 3 open-label extension studies in subjects with RLS.

The incidence of adverse reactions in two randomized, double-blinded, placebo-controlled, fixed-dose trials are shown in Table 3.

In the two randomized, double-blinded, placebo-controlled, fixed-dose trials for RLS, the most common adverse reactions ( $\geq 5$  % greater than placebo) for the highest recommended dose of Neupro (3 mg) were application site reactions, nausea, somnolence, and headache.

In the two Dose-Response, placebo controlled trials, 24 % of Neupro-treated patients treated with the highest recommended dose (3 mg) discontinued treatment because of adverse reactions, compared with 3 % of patients who received placebo.

**Table 3 Incidence of Treatment-Emergent Adverse Reactions in Placebo-Controlled, Trial of Patients with Restless Legs Syndrome (North American and Foreign Multinational Studies) Where Incidence Was  $\geq 2$  % in 2 mg or 3 mg/24 hours Neupro Groups and Greater Than the Incidence in Placebo-Treated Patients**

Adverse Reaction	Placebo	Neupro Dose
------------------	---------	-------------

	N=217 %	0.5 mg/24h N=99 %	1 mg/24h N=215 %	2 mg/24h N=211 %	3 mg/24h N=220 %
<b>Ear and labyrinth disorders</b>					
Vertigo	1	0	4	3	1
<b>Gastrointestinal disorders</b>					
Nausea	10	18	15	23	21
Dry mouth*	4	3	3	3	7
Constipation	3	6	3	2	5
Vomiting*	1	2	2	4	4
Dyspepsia*	1	2	1	2	3
<b>General disorders and administration site conditions</b>					
Application and instillation site reactions <sup>a *</sup>	4	23	27	38	43
Asthenic conditions <sup>a *</sup>	8	11	7	14	12
<b>Infections and infestations</b>					
Nasopharyngitis	7	5	10	7	8
Sinusitis*	1	2	1	2	3
<b>Investigations</b>					
Serum ferritin decreased*	1	2	1	1	2
<b>Musculoskeletal and connective tissue disorders</b>					
Muscle spasms	1	3	1	4	1
<b>Nervous system disorders</b>					
Headache	11	21	15	18	16
Somnolence*	4	8	5	8	10
Dizziness	6	7	5	9	6
<b>Psychiatric disorders</b>					
Disturbances in initiating and/or maintaining sleep <sup>a *</sup>	3	2	4	3	10
Sleep disorder*	1	0	2	3	3
Abnormal dreams*	0	2	1	2	3
Sleep attacks*	0	0	1	0	2
<b>Skin and subcutaneous tissue disorders</b>					
Pruritus	3	9	4	3	7
Hyperhidrosis*	2	1	3	5	3
Erythema*	1	1	1	0	2
<b>Vascular disorders</b>					
Hypertension*	0	3	1	1	4
Hot flush	1	4	1	3	0

\*Dose-related

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class

<sup>a</sup> The following selected HLTs were considered and included, if applicable: application and instillation site reactions, asthenic conditions (i.e., asthenia, malaise, fatigue), and disturbances in initiating and maintaining sleep.

The incidence of certain adverse reactions with Neupo treatment was notably increased compared to placebo treatment (i.e., Neupo % - placebo % =  $\geq 5$  %) in either the titration or maintenance phases of the Dose-Response trial. During the titration phase, an increased incidence (in descending order of % treatment difference) was observed for ASRs, and disturbances in initiating and/or maintaining sleep. During the maintenance phase, an increased incidence was observed for ASRs. Some

adverse reactions developing in the titration phase persisted ( $\geq 7$  days) into the maintenance phase. These “persistent” adverse reactions were ASRs, nausea, and disturbances in initiating and/or maintaining sleep.

## 6.2 Laboratory Changes

Some clinical laboratory analytes were abnormal for patients treated with the highest recommended Neupro dose in the dose-response trials for patients with early-stage and advanced-stage Parkinson's disease and with RLS.

There was a treatment difference (Neupro % - placebo %) of 6 % for decreased hemoglobin (below the normal reference range) and of 3 % for decreased hematocrit (below the normal reference range) in patients with early-stage Parkinson's disease. There was a treatment difference of 4 % for a decreased hemoglobin (below the normal reference range) and of 3 % for decreased hematocrit (below the normal reference range) in patients with advanced-stage Parkinson's disease. There was a treatment difference of 3 % for a decreased hemoglobin (below the normal reference range) in patients with RLS. There was also a treatment difference of 2 % for markedly decreased hemoglobin and hematocrit in patients with advanced Parkinson's disease and of 1 % for markedly decreased hematocrit in patients with RLS.

There was a treatment difference of 9 % for increased serum BUN (above the normal reference range) in patients with early-stage Parkinson's disease. There was a treatment difference of 1 % for markedly increased serum BUN in patients with advanced-stage Parkinson's disease.

There was a treatment difference of 9 % for decreased serum glucose (below the normal reference range) in patients with early-stage Parkinson's disease and of 3 % in patients with advanced-stage Parkinson's disease. There was a treatment difference of 1 % for markedly decreased serum glucose in patients with advanced-stage Parkinson's disease.

## 7 DRUG INTERACTIONS

### 7.1 Dopamine Antagonists

It is possible that dopamine antagonists, such as antipsychotics or metoclopramide, could diminish the effectiveness of rotigotine.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In studies conducted in mice, rats, and rabbits, rotigotine was shown to have adverse effects on embryo-fetal development when administered during pregnancy at doses similar to or lower than those used clinically. Neupro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Rotigotine administered subcutaneously (10, 30, or 90 mg/kg/day) to pregnant mice during organogenesis (gestation days 6 through 15) resulted in increased incidences of delayed skeletal ossification and decreased fetal body weights at the two highest doses and an increase in embryo-fetal death at the high dose. The no-effect dose for embryo-fetal developmental toxicity in mice is approximately 6 times the maximum recommended human dose (MRHD) for Parkinson's disease (8 mg/24 hours) on a body surface area ( $\text{mg}/\text{m}^2$ ) basis. Rotigotine administered subcutaneously (0.5, 1.5, or 5 mg/kg/day) to pregnant rats during organogenesis (gestation days 6 through 17) resulted in increased embryo-fetal death at all doses. The lowest effect dose is less than the MRHD on a  $\text{mg}/\text{m}^2$  basis. This effect in rats is thought to be due to the prolactin-lowering effect of rotigotine. When rotigotine was administered subcutaneously (5, 10, or 30 mg/kg/day) to pregnant rabbits during organogenesis (gestation days 7 through 19), an increase in embryo-fetal death occurred at the two highest doses tested. The no-effect dose is 12 times the MRHD on a  $\text{mg}/\text{m}^2$  basis.

In a study in which rotigotine was administered subcutaneously (0.1, 0.3, or 1 mg/kg/day) to rats throughout pregnancy and lactation (gestation day 6 through postnatal day 21), impaired growth and development during lactation and long-term neurobehavioral abnormalities were observed in the offspring at the highest dose tested; when those offspring were mated, growth and survival of the next generation were adversely affected. The no-effect dose for pre- and postnatal developmental toxicity (0.3 mg/kg/day) is less than the MRHD on a  $\text{mg}/\text{m}^2$  basis.

### **8.3 Nursing Mothers**

Rotigotine decreases prolactin secretion in humans and could potentially inhibit lactation.

Studies have shown that rotigotine and/or its metabolite(s) are excreted in rat milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NEUPRO is administered to a nursing woman.

### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients for any indication have not been established.

### **8.5 Geriatric Use**

Of subjects treated with Neupro in clinical studies for the treatment of Parkinson's disease, approximately 50% were 65 years old and over, and approximately 11% were 75 and over. Among subjects treated with Neupro in clinical studies for the treatment of RLS, 26% were 65 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

No overall differences in plasma levels of rotigotine were observed between patients who were 65 to 80 years old compared with younger patients receiving the same rotigotine doses.

### **8.6 Renal Impairment**

The effect of renal function on rotigotine pharmacokinetics has been studied in subjects with mild to severe impairment of renal function including subjects requiring dialysis compared to healthy subjects. There were no relevant changes in rotigotine plasma concentrations. In subjects with severe renal impairment not on dialysis, (i.e., creatinine clearance 15 to <30 ml/min), exposure to rotigotine conjugates was doubled. No dosage adjustment is recommended.

### **8.7 Hepatic Impairment**

The effect of impaired hepatic function on the pharmacokinetics of rotigotine has been studied in subjects with moderate impairment of hepatic function (Child Pugh classification – Grade B). There were no relevant changes in rotigotine plasma concentrations. No dose adjustment is necessary in subjects with moderate impairment of hepatic function. No information is available on subjects with severe impairment of hepatic function.

## **9 DRUG ABUSE AND DEPENDENCE**

### **9.1 Controlled Substance**

Rotigotine is not a controlled substance

### **9.3 Dependence**

Animal studies and human clinical trials with rotigotine did not reveal potential for drug-seeking behavior or physical dependence.

## **10 OVERDOSAGE**

Since Neupro is a transdermal system, overdosing is not likely to occur in clinical practice unless patients forget to remove the previous day's transdermal system; patients should be advised regarding this possibility.

### **10.1 Overdose Symptoms**

The most likely symptoms of overdose 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 excessive dopaminergic stimulation.

### **10.2 Overdose Management**

There is no known antidote for overdosage of dopamine agonists. In case of suspected overdose, the excess transdermal system(s) should immediately be removed from the patient. Concentrations of rotigotine decrease after patch removal. The terminal half-life of rotigotine is 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-

life of 3 hours. If it is necessary to discontinue use of rotigotine after overdose, it should be discontinued gradually to prevent neuroleptic malignant syndrome [see *Warnings and Precautions (5.14)*]. The daily dose should be reduced by 2 mg/24 hours for Parkinson's disease patients and 1 mg/24 hours for RLS patients with a dose reduction preferably every other day, until complete withdrawal of rotigotine is achieved. Before completely stopping use of Neupro in the event of an overdose [see *Dosage and Administration (2.3)*].

The patient should be monitored closely, including heart rate, heart rhythm, and blood pressure. As shown in a study of renally impaired patients, dialysis is not expected to be beneficial. Treatment of overdose may require general supportive measures to maintain vital signs.

## 11 DESCRIPTION

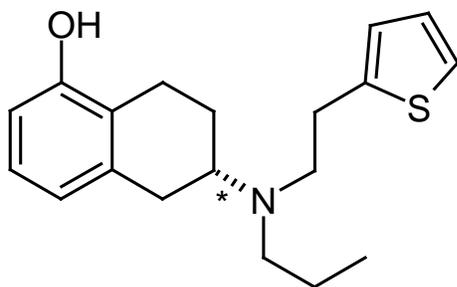
Neupro is a transdermal system that provides continuous delivery of rotigotine, a non-ergoline dopamine agonist, for 24 hours following application to intact skin.

Neupro is available in six strengths as shown in Table 4.

**Table 4 Nominal Dose, Drug Content, and Transdermal System Size**

Neupro Nominal Dose	Rotigotine Content per System	Neupro System Size
1 mg/24 hours	2.25 mg	5 cm <sup>2</sup>
2 mg/24 hours	4.5 mg	10 cm <sup>2</sup>
3 mg/24 hours	6.75 mg	15 cm <sup>2</sup>
4 mg/24 hours	9 mg	20 cm <sup>2</sup>
6 mg/24 hours	13.5 mg	30 cm <sup>2</sup>
8 mg/24 hours	18 mg	40 cm <sup>2</sup>

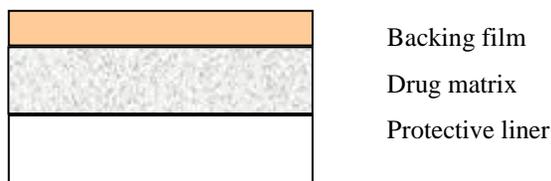
The chemical name of rotigotine is (6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol. The empirical formula is C<sub>19</sub>H<sub>25</sub>NOS. The molecular weight is 315.48. The structural formula for rotigotine is:



The asterisk designates the chiral center.

### 11.1 System Components and Structure

Neupro is a thin, matrix-type transdermal system composed of three layers as shown in Figure 1:



## Figure 1: System Schematic

1. A flexible, tan-colored backing film, consisting of an aluminized polyester film coated with a pigment-layer on the outer side. The backing provides structural support and protection of the drug-loaded adhesive layer from the environment.
2. A self-adhesive drug matrix layer, consisting of the active component rotigotine and the following inactive components: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol.
3. A protective liner, consisting of a transparent fluoropolymer-coated polyester film. This liner protects the adhesive layer during storage and is removed just prior to application.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Rotigotine is a non-ergoline dopamine agonist. The precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown, although it is thought to be related to its ability to stimulate dopamine receptors within the caudate-putamen in the brain. The precise mechanism of action of rotigotine as a treatment for Restless Legs Syndrome is unknown but is thought to be related to its ability to stimulate dopamine receptors.

### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

There is no indication of a QT/QTc prolonging effect of Neupro in doses up to 24 mg/24 hours. The effects of Neupro at doses up to 24 mg/24 hours (supratherapeutic doses) on the QT/QTc interval was evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg IV, single dose) parallel-group trial with an overall treatment period of 52 days in male and female patients with advanced-stage Parkinson's disease. Assay sensitivity was confirmed by significant QTc prolongation by moxifloxacin.

### 12.3 Pharmacokinetics

On average, approximately 45% of the rotigotine from the patch is released within 24 hours ( $0.2 \text{ mg/cm}^2$ ). Rotigotine is primarily eliminated in the urine as inactive conjugates. After removal of the patch, plasma levels decreased with a terminal half-life of 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-life of 3 hours.

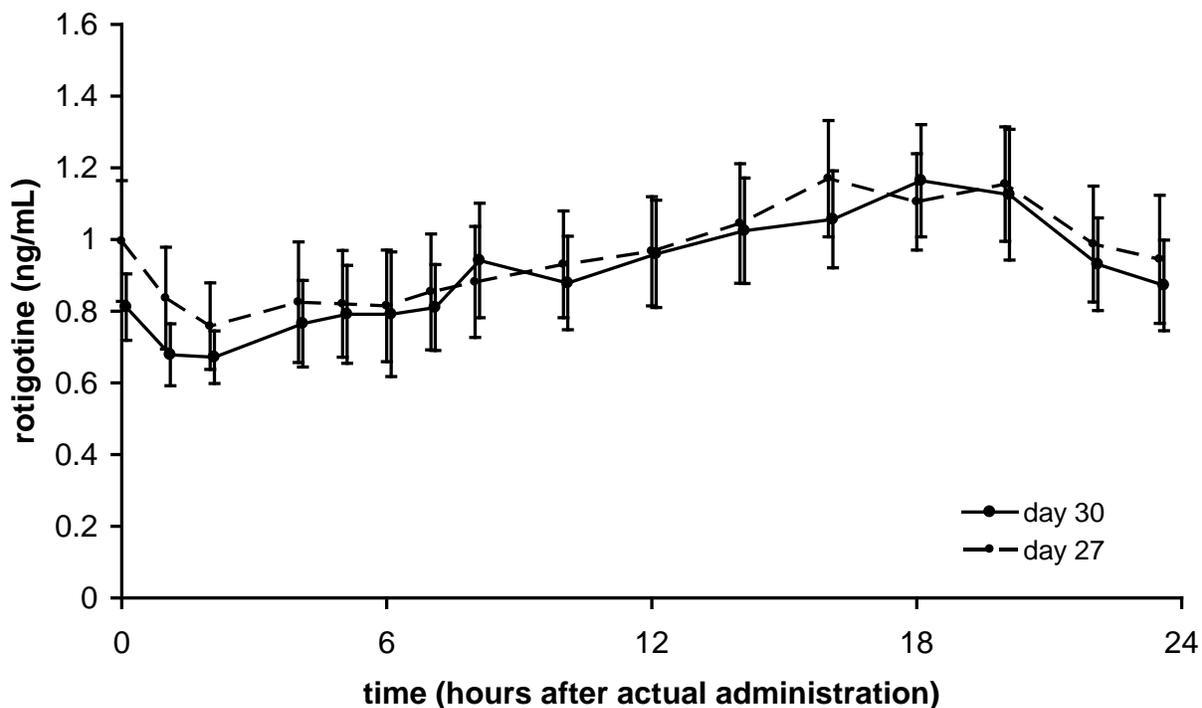
#### Absorption and Bioavailability

When single doses of 8 mg/24 hours are applied to the trunk, there is an average lag time of approximately 3 hours until drug is detected in plasma (range 1 to 8 hours).  $T_{\text{max}}$  typically occurs between 15 to 18 hours post dose but can occur from 4 to 27 hours post dose. However, there is no characteristic peak concentration observed. Rotigotine displays dose-proportionality over a daily dose range of 1 mg/24 hours to 24 mg/24 hours. In the clinical studies of rotigotine effectiveness, the transdermal system application site was rotated from day to day (abdomen, thigh, hip, flank, shoulder, or upper arm) and the mean measured plasma concentrations of rotigotine were stable over the six months of maintenance treatment. Relative bioavailability for the different application sites at steady-state was evaluated in subjects with Parkinson's disease. In a single trial conducted in patients with early-stage Parkinson's disease differences in bioavailability ranged from less than 1% (abdomen vs hip) to 46% (shoulder vs thigh) with shoulder application showing higher bioavailability.

Because rotigotine is administered transdermally, food should not affect absorption, and the product may be administered without regard to the timing of meals.

In a 14-day clinical study with rotigotine administered to healthy subjects, steady-state plasma concentrations were achieved within 2 to 3 days of daily dosing.

**Figure 2 Average ( $\pm 95\%$  CI) Neupro Plasma Concentrations in Patients with Early-stage Parkinson's Disease After Application of 8 mg/24 hours to 1 of 6 Application Sites (shoulder, upper arm, flank, hip, abdomen, or thigh) on 2 Different Days During the Maintenance Phase**



### Distribution

The weight normalized apparent volume of distribution, ( $V_d/F$ ), in humans is approximately 84 L/kg after repeated dose administration.

The binding of rotigotine to human plasma proteins is approximately 92% *in vitro* and 89.5% *in vivo*.

### Metabolism and Elimination

Rotigotine is extensively metabolized by conjugation and N-dealkylation. After intravenous dosing the predominant metabolites in human plasma are sulfate conjugates of rotigotine, glucuronide conjugates of rotigotine, sulfate conjugates of the N-despropyl-rotigotine and conjugates of N-desthienylethyl-rotigotine. Multiple CYP isoenzymes, sulfotransferases and two UDP-glucuronosyltransferases catalyze the metabolism of rotigotine.

After removal of the patch, plasma levels decreased with a terminal half-life of 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-life of 3 hours.

Rotigotine is primarily excreted in urine (~71%) as inactive conjugates of the parent compound and N-desalkyl metabolites. A smaller proportion is excreted in feces (~23%). The major metabolites found in urine were rotigotine sulfate (16% to 22% of the absorbed dose), rotigotine glucuronide (11% to 15%), and N-despropyl-rotigotine sulfate metabolite (14% to 20%) and N-desthienylethyl-rotigotine sulfate metabolite (10% to 21%). Approximately 11% is renally eliminated as other metabolites. A small amount of unconjugated rotigotine is renally eliminated (<1% of the absorbed dose).

### Drug Interaction Studies

#### CYP Interactions

In vitro studies indicate that multiple CYP-isoforms are capable of catalyzing the metabolism of rotigotine. In human liver microsomes, no extensive inhibition of the metabolism of rotigotine was observed when co-incubated with CYP isoform specific inhibitors. If an individual CYP isoform is inhibited, other isoforms can catalyze rotigotine metabolism.

Rotigotine, the 5-O-glucuronide and its desalkyl and monohydroxy metabolites were analyzed for interactions with the human CYP isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in vitro. Based on these results, no risk for inhibition of CYP1A2, CYP2C9 and CYP3A4 catalyzed metabolism of other drugs is predicted at therapeutic rotigotine concentrations. There is a low risk of inhibition of CYP2C19 and CYP2D6 catalyzed metabolism of other drugs at therapeutic concentrations.

In human hepatocytes in vitro, there was no indication for induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4.

Rotigotine is metabolized by multiple sulfotransferases and two UDP-glucuronosyltransferases (UGT1A9 and UGT2B15). These multiple pathways make it unlikely that inhibition of any one pathway would alter rotigotine concentrations significantly.

#### Protein Displacement, Warfarin

In vitro, no potential for displacement of warfarin by rotigotine (and vice versa) from their respective human serum albumin binding sites was detected.

#### Digoxin

The effect of rotigotine on the pharmacokinetics of digoxin has been investigated in vitro in Caco-2 cells. Rotigotine did not influence the P-glycoprotein-mediated transport of digoxin. Therefore, rotigotine would not be expected to affect the pharmacokinetics of digoxin.

#### Cimetidine

Co-administration of rotigotine (up to 4 mg/24 hours) with cimetidine (400 mg b.i.d.), an inhibitor of CYP1A2, CYP2C19, CYP2D6, and CYP3A4, did not alter the steady-state pharmacokinetics of rotigotine in healthy subjects.

#### Levodopa/Carbidopa

Co-administration of levodopa/carbidopa (100/25 mg b.i.d.) with rotigotine (4 mg/24 hours) had no effect on the steady-state pharmacokinetics of rotigotine; rotigotine had no effect on the pharmacokinetics of L-levodopa/carbidopa.

#### Oral Contraception

Co-administration of rotigotine (3 mg/24 hours) did not affect the pharmacodynamics and pharmacokinetics of oral contraceptives (0.03 mg ethinylestradiol, 0.15 mg levonorgestrel).

#### Omeprazole

Co-administration of the CYP2C19 selective inhibitor omeprazole (40 mg/day) had no effect on the steady-state pharmacokinetics of rotigotine (4 mg/24 hours).

## **12.6 Pharmacokinetics in Special Populations**

### **Hepatic Insufficiency**

There were no relevant changes in rotigotine plasma concentrations in subjects with moderate hepatic impairment (Child Pugh classification – Grade B). No information is available on subjects with severe impairment of hepatic function.

### **Renal Insufficiency**

There were no relevant changes in rotigotine plasma concentrations (up to end stage renal disease requiring hemodialysis). In subjects with severe renal impairment not on dialysis, (i.e., creatinine clearance 15 to <30 ml/min), exposure to conjugated rotigotine metabolites was doubled .

## Gender

Female and male subjects and patients had similar plasma concentrations (body weight normalized).

## Geriatric Patients

Plasma concentrations of rotigotine in patients 65 to 80 years of age were similar to those in younger patients, approximately 40 to 64 years of age. Although not studied, exposures in older subjects (>80 years) may be higher due to skin changes with aging.

## Pediatric Patients

The pharmacokinetics of rotigotine in subjects below the age of 18 years has not been established.

## Race

The pharmacokinetic profile was similar in Caucasians, Blacks, and Japanese. No dose adjustment is necessary based on ethnicity.

## 12.7 Adhesion

Adhesion was examined in subjects with Parkinson's disease when patches were applied to rotating sites. Similar results were observed for the 4 mg/24 hours (20 cm<sup>2</sup>), 6 mg/24 hours (30 cm<sup>2</sup>), and 8 mg/24 hours (40 cm<sup>2</sup>) patches. An adherence of  $\geq 90\%$  of the patch surface was observed in 71% to 82% of cases. A partial detachment of >10% was observed in 15% to 24% of cases. A complete detachment of the patch was observed in 3% to 5% of cases.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

Two-year carcinogenicity studies of rotigotine were conducted in mice at doses of 0, 3, 10, and 30 mg/kg and in rats at doses of 0, 0.3, 1, and 3 mg/kg; in both studies rotigotine was administered subcutaneously once every 48 hours. No significant increases in tumors occurred in mice at doses up to 9 times the maximum recommended human dose (MRHD) in Parkinson's disease (8 mg/24 hours).

In rats, there were increases in Leydig cell tumors and in uterine tumors (adenocarcinomas, squamous cell carcinomas) at all doses. The endocrine mechanisms believed to be involved in the production of these tumors in rats are not considered relevant to humans. Therefore, there were no tumor findings considered relevant to humans at plasma exposures (AUC) up to 4-6 times that in humans at the MRHD.

#### Mutagenesis

Rotigotine was negative in the *in vitro* bacterial reverse mutation (Ames) and in the *in vivo* micronucleus assays. Rotigotine was mutagenic and clastogenic in the *in vivo* mouse lymphoma *tk* assay.

#### Infertility

When rotigotine was administered subcutaneously (1.5, 5, or 15 mg/kg/day) to female rats prior to and during mating and continuing through gestation day 7, an absence of implantation was observed at all doses. The lowest dose tested is 2 times the MRHD on a mg/m<sup>2</sup> basis. In male rats treated from 70 days prior to and during mating, there was no effect on fertility; however, a decrease in epididymal sperm motility was observed at the highest dose tested. The no-effect dose (5 mg/kg/day) is 6 times the MRHD on a mg/m<sup>2</sup> basis. When rotigotine was administered subcutaneously to female mice at doses of 10, 30, and 90 mg/kg/day from 2 weeks until 4 days before mating and then at a dose of 6 mg/kg/day (all groups) (approximately 4 times the MRHD on a mg/m<sup>2</sup> basis) from 3 days before mating until gestation day 7, a markedly reduced (low dose) or complete absence of implantation (mid and high doses) was observed. The effects on implantation in rodents are thought to be due to the prolactin-lowering effect of rotigotine. In humans, chorionic gonadotropin, not prolactin, is essential for implantation.

## 13.2 Animal Toxicology and/or Pharmacology

*Retinal Pathology: Albino rats:* Retinal degeneration was observed in albino rats in a 6-month toxicity study at the highest dose of rotigotine (plasma exposure [AUC] at least 15 times that in humans at the MRHD. Retinal degeneration was not observed in the 2-year carcinogenicity studies in albino rat (plasma AUCs up to 4-6 times that in humans at the MRHD) or albino mouse, or in monkeys treated for 1 year. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

## 14 CLINICAL STUDIES

### 14.1 Parkinson's Disease

The effectiveness of Neupro in the treatment of the signs and symptoms of idiopathic Parkinson's disease was established in five parallel group, randomized, double-blind placebo-controlled trials conducted in the U.S. and abroad. Three of these five trials enrolled patients with early-stage Parkinson's disease (not receiving levodopa), and two enrolled patients with advanced-stage Parkinson's disease who were receiving levodopa. Depending on trial design, patients underwent a weekly titration of Neupro in 2 mg/24 hours increments to either the randomized dose or optimal dose. Back titrations by 2 mg/24 hours decrement of Neupro were permitted for intolerable adverse events. Patch application sites were changed on a daily basis.

Change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS), parts II + III, served as the primary outcome assessment measure in the early-stage studies. The UPDRS is a four-part multi-item rating scale intended to evaluate mentation (part I), Activities of Daily Living (ADL) (part II), motor performance (part III), and complications of therapy (part IV). Part II of the UPDRS contains 13 questions relating to ADL, which are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 27 questions (for 14 items) and is scored as described for part II. Part III is designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (e.g., tremor, rigidity, bradykinesia, postural instability, etc.), scored for different body regions, and has a maximum (worst) score of 108.

Change from baseline in time spent "off" (hours) based on daily diaries was the primary outcome assessment in the two trials of advanced-stage Parkinson's disease (with levodopa).

#### Studies in Patients with Early-Stage Parkinson's Disease

Patients (N=649) in the three trials of early-stage Parkinson's disease had limited or no prior exposure to levodopa (off levodopa for at least 28 days prior to baseline or levodopa use for no more than 6 months). Patients were excluded from the studies if they had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant. Patients receiving selegiline, anticholinergic agents, or amantadine must have been on a stable dose and able to maintain that dose for the duration of the study.

#### PD-1

This trial was a multicenter, multinational dose-response study in which 316 early-stage Parkinson's disease patients were titrated over 4 weeks to their randomized treatment with either placebo or one of four fixed doses of Neupro (2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, or 8 mg/24 hours). The patches were applied to the upper abdomen and the sites of application were rotated on a daily basis.

Patients underwent a weekly titration (increasing the number of 2 mg/24 hours patches or placebo patches at weekly intervals) over 4 weeks such that the target doses of Neupro were achieved for all groups by the end of 3 weeks and were administered over the fourth week of the titration phase. Patients then continued on treatment for a 7 week maintenance phase followed by a down titration during the last week. Two back titrations by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) at a time were permitted for intolerable adverse events. The mean age of patients was approximately 60 years (range 33 to 83 years; approximately 36% were  $\geq$  65 years) and the study enrolled more men (62%) than women (39%). Most patients (85%) were Caucasian and most randomized patients ( $\geq$  88%) completed the full treatment period.

Mean baseline combined UPDRS (Parts II + III) scores were similar among all treatment groups, between 27.1 and 28.5 for all groups. The mean change from baseline and difference from placebo for each treatment group is shown in Table 5. Statistically significant mean changes reflecting dose-related improvement were observed at the three highest doses, and the 6 mg/24 hours and 8 mg/24 hours doses had a similar effect.

**Table 5 PD-1: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population**

Treatment	Mean Change from Baseline	Difference from placebo
Placebo	-1.4	NA
2 mg/24 hours	-3.5	-2.1
4 mg/24 hours	-4.5	-3.1
6 mg/24 hours	-6.3	-4.9
8 mg/24 hours	-6.3	-5.0

**PD-2**

This trial was a randomized, double-blind, multinational, flexible Neupro dose (2 mg/24 hours, 4 mg/24 hours, or 6 mg/24 hours), parallel group study in which 277 early-stage Parkinson's disease patients were assigned (2: 1 ratio) to treatment with Neupro or placebo for a period up to about 28 weeks. This trial was conducted in 47 sites in North America (U.S. and Canada). Patches were applied to different body parts including upper or lower abdomen, thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were to be rotated on a daily basis. Patients underwent a weekly titration (consisting of 2 mg/24 hours increments at weekly intervals) over 3 weeks to a maximal dose of 6 mg/24 hours depending on efficacy and tolerability, and then received treatment over a 24 week maintenance phase followed by a de-escalation over a period up to 4 days. Back/down titration by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) was permitted during the titration phase for intolerable adverse events but was not permitted during the maintenance phase (i.e., patients with intolerable adverse events had to leave the study). Primary efficacy data were collected after a treatment period of up to approximately 27 weeks.

The mean age of patients was approximately 63 years (range 32 to 86 years; approximately 45% were  $\geq 65$  years), approximately two-thirds of all patients were men, and nearly all patients were Caucasian. Approximately 90% of patients randomized to Neupro achieved a maximal daily dose of 6 mg/24 hours; 70% maintained this dose for most (>20 weeks) of the maintenance phase. Most enrolled patients ( $\geq 81$  %) completed the full treatment period.

Mean baseline combined UPDRS (Parts II + III) was similar in both groups (29.9 Neupro group, 30.0 placebo). Neupro-treated patients experienced a mean change in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 27 or last visit for patients discontinuing early) of -4.0 (Table 6), and the difference from placebo was statistically significant.

**Table 6 PD-2: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population**

Treatment	Mean Change from Baseline	Difference from placebo
Placebo	+1.3	NA
Neupro up to 6 mg/24 hours	-4.0	-5.3

**PD-3**

This study was a randomized, double-blind multinational, flexible Neupro dose (2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, or 8 mg/24 hours), three-arm, parallel-group study using a double-dummy treatment in which 561 early-stage Parkinson's disease patients were assigned to treatment with either placebo or Neupro or active oral comparator in a ratio of 1: 2: 2 for a period up to about 39 weeks. This study was conducted in up to 81 sites in many countries outside of North America. Patches were applied to different body parts including upper or lower abdomen, thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were to be rotated on a daily basis. Treatment with a patch and placebo was given to all patients in a double-blinded manner such that no one would know the actual treatment (i.e. Neupro, comparator, or placebo).

Patients underwent a weekly dose escalation/titration of patch (consisting of 2 mg/24 hours increments of Neupro or placebo) and a dose escalation of capsules of comparator or placebo over 13 weeks (13 week titration was planned for the comparator treatment) up to a maximal dose of 8 mg/24 hours of Neupro depending on achieving optimal efficacy or intolerability at a lower dose. Patients randomized to Neupro achieved the maximal dose of 8 mg/24 hours after a 4 week titration if maximal efficacy and intolerability had not occurred over a 4 week titration period. Patients then received treatment over a 24 week maintenance phase followed by a de-escalation over a period up to 12 days. A single back titration by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) or capsule was permitted during the titration phase for intolerable adverse events but was not permitted during the maintenance phase (i.e. patients with intolerable adverse events had to discontinue from this study). Primary efficacy data were collected after a treatment period of up to approximately 37 weeks of randomized treatment.

The mean age of patients was approximately 61 years (range 30 -86 years; approximately 41% were  $\geq 65$  years), nearly 60% of all patients were men, and nearly all patients were Caucasian. About 73% of patients completed the full treatment period. The mean daily dose of Neupro was just less than 8 mg/24 hours and approximately 90% of patients achieved the maximal daily dose of 8 mg/24 hours.

Mean baseline combined UPDRS (Parts II + III) was similar across all groups (33.2 Neupro, 31.3 placebo, 32.2 comparator). Neupro-treated patients experienced a mean change in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 37 or last visit for patients discontinuing early) of -6.8 (Table 11), and the difference from placebo treated patients showed a mean change from baseline of -2.3 (see Table 7), a difference that was statistically significant.

**Table 7 PD-3: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population**

Treatment	Mean change from baseline	Difference from placebo
Placebo	-2.3	NA
Neupro up to 8 mg/24 hours	-6.8	-4.5

### Advanced-Stage Parkinson’s Disease

Patients (N=658) in the three trials of Neupro in advanced-stage Parkinson’s disease had to be experiencing “on-off” periods at baseline, despite treatment with optimal doses of levodopa. Patients continued concomitant levodopa during the trial; however, reductions in the dosage of levodopa were allowed if patients experienced adverse events that the investigator considered related to dopaminergic therapy. Patients were excluded from the studies if they had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant. Patients receiving selegiline, anticholinergic agents, or amantadine must have been on a stable dose and able to maintain that dose for the duration of the study. In the North American trial, COMT-inhibitors were not permitted.

*PD-4* This trial was a multinational, three-arm, parallel group study in which 351 advanced-stage Parkinson’s disease patients were titrated over 5 weeks to treatment with either placebo or Neupro (8 mg/24 hours or 12 mg/24 hours) and maintained treatment for 24 weeks followed by a down titration over the last week. This study was conducted in 55 sites in North America (U.S. and Canada).

Mean baseline “off” times were similar among all treatment groups (6.4, 6.8, and 6.3 hours for the placebo, Neupro 8 mg/24 hours and 12 mg/24 hours treatment groups, respectively). Neupro-treated patients experienced a mean change in “off” time from baseline to end of treatment of -2.7 hours for the 8 mg/24 hours treatment arm and -2.1 hours for the 12 mg/24 hours treatment arm (Table 8), and the difference from placebo was statistically significant for both Neupro doses (8 mg/24 hours, 12 mg/24 hours). Onset of treatment benefit began as early as the first week of treatment.

**Table 8 PD-4: Mean Change in “off” time (hours) from Baseline at End of Treatment for Intent-to-Treat Population**

Treatment	Mean Change From Baseline	Difference from placebo
Placebo	-0.9	NA
8 mg/24 hours	-2.7	-1.8
12 mg/24 hours	-2.1	-1.2

## PD-5

This trial was a multinational, flexible dose, three-arm, parallel-group study using a double-dummy treatment in which 506 advanced-stage Parkinson's disease patients were titrated over 7 weeks to treatment with either Neupro from a minimum dose of 4 mg/24 hours up to an optimal dose not exceeding 16 mg/24 hours, active oral comparator, or placebo and maintained treatment for 16 weeks followed by a down titration over 6 days. This study was conducted in 77 sites in many countries outside of North America.

Mean baseline "off" times were similar among all treatment groups (6.6, 6.2, and 6.0 hours for the placebo, Neupro, and comparator treatment groups, respectively). Neupro-treated patients experienced a mean 2.5 hour decrease change in "off" time from baseline to end of treatment (Table 9), and the difference from placebo was statistically significant. Onset of treatment benefit began as early as the first week of treatment. The optimal Neupro dose was established as 4 mg/24 hours for 2% of patients, 6 mg/24 hours for 6%, 8mg/24 hours for 8%, 10 mg/24 hours for 9%, 12 mg/24 hours for 16%, 14mg/24 hours for 11% and 16mg/24 hours for 44%.

**Table 9 PD-5: Mean Change in "off" time (hours) from Baseline at End of Treatment for Intent-to-Treat Population**

Treatment	Mean Change From Baseline	Difference from placebo
Placebo	-0.9	NA
Up to 16 mg/24 hours	-2.5	-1.6

## 14.2 Restless Legs Syndrome

The clinical program included 1309 patients with moderate to severe RLS. The efficacy of Neupro in the treatment of Restless Legs Syndrome (RLS) was primarily evaluated in 2 fixed-dose, randomized, double-blind, placebo-controlled trials with maintenance periods of 6 months duration. Patients received Neupro doses ranging from 0.5 mg/24 hours to 3 mg/24 hours or placebo once daily. In these 2 trials, the mean duration of RLS was 2.1 to 3.1 years, mean age was approximately 55 years (range of 19 to 78 years), approximately 68 % were women, and 97% were Caucasian. In both trials, patches were applied to different application sites including the abdomen, thigh, hip, flank, shoulder, and/or upper arm and patch application sites were rotated on a daily basis.

The two outcome measures used to assess the effect of treatment as co-primary efficacy endpoints were the International RLS Rating Scale (IRLS Scale) and a Clinical Global Impression - Improvement (CGI-I) assessment. The IRLS Scale contains 10 items designed to assess the severity of sensory and motor symptoms, sleep disturbance, daytime somnolence, and impact on activities of daily living and mood associated with RLS. The range of scores is 0 to 40, with 0 being absence of RLS symptoms and 40 the most severe symptoms. The CGI-I is designed to assess clinical progress (global improvement) on a 7-point scale.

### RLS-1

This trial was a multicenter, 5-arm, parallel-group, fixed-dose trial of Neupro in subjects with moderate-to-severe RLS. A total of 505 subjects were randomized in this trial, participating at approximately 50 sites in the US. Subjects received placebo or Neupro (0.5 mg/24 hours, 1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours). Subjects began treatment at a daily dosage of 0.5 mg/24 hours Neupro and were titrated over a 4 week period to their assigned daily dose followed by a 6 month maintenance period and 7 day down titration period.

Mean baseline IRLS sum score were similar among all treatment groups (23.5, 23.1, 23.2, 23.3, and 23.6 for the placebo, Neupro 0.5 mg/24 hours, 1 mg/24 hours, 2 mg/24 hours, and 3 mg/24 hours groups, respectively). Patients experienced a mean change in the IRLS sum score from baseline to the end of treatment for each of the 4 Neupro dose groups. The mean changes from baseline and differences from placebo in IRLS sum score and CGI Item 1 are shown for each treatment group in Table 10. The difference between the 2 highest treatment groups (2 mg/24 hours and 3 mg/24 hours) and placebo were statistically significant. Of the Neupro-treated patients, 23% had an IRLS score of 0 compared to 9.1% of placebo patients at the end of the maintenance period. Onset of treatment benefit was seen with the 1 mg/24 hours dose.

**Table 10 RLS-1: ANCOVA Results for Co-primary Endpoints: Change from Baseline to End of Maintenance Period for Intent-to-Treat Population**

Variable	Treatment	Mean Change From Baseline	Difference from placebo
IRLS sum score	Placebo	-9.0	NA
	0.5 mg/24 hours	-11.1	-2.2
	1 mg/24 hours	-11.2	-2.3
	2 mg/24 hours	-13.5	-4.5
	3 mg/24 hours	-14.2	-5.2
CGI Item 1	Placebo	-1.4	NA
	0.5 mg/24 hours	-1.8	-0.35
	1 mg/24 hours	-1.7	-0.32
	2 mg/24 hours	-2.1	-0.65
	3 mg/24 hours	-2.3	-0.90

### **RLS-2**

This trial was a multicenter, 4-arm, parallel-group trial of Neupro in subjects with moderate-to-severe RLS. A total of 458 subjects were randomized in this trial, participating at approximately 50 sites in 8 European countries. Patients received placebo or Neupro (1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours). Patients began treatment at a daily dosage of 1 mg/24 hours Neupro and were titrated over a 3 week period to their assigned daily dose followed by a 6 month maintenance period and 7 day down-titration period.

Mean baseline IRLS sum score were similar among all treatment groups (28.1, 28.1, 28.2, and 28.0 for the placebo, Neupro 1 mg/24 hours, 2 mg/24 hours, and 3 mg/24 hours groups, respectively). Patients experienced a mean change in the IRLS sum score from baseline to the end of treatment for each of the 3 Neupro dose groups. The mean changes from baseline and differences from placebo in IRLS sum score and CGI Item 1 are shown for each treatment group in Table 11. The difference between all 3 treatment groups (1 mg/24 hours, 2 mg/24 hours, and 3 mg/24 hours) and placebo were statistically significant. Of the Neupro-treated patients, 24% had an IRLS score of 0 compared to 12% of placebo patients at the end of the maintenance period. Onset of treatment benefit was seen with the 1 mg/24 hours dose.

**Table 11 RLS-2: ANCOVA Results for Co-primary Endpoints: Change from Baseline to End of Maintenance Period for Intent-to-Treat Population**

Variable	Treatment	Mean Change From Baseline	Difference from placebo
IRLS sum score	Placebo	-8.6	NA
	1 mg/24 hours	-13.7	-5.1
	2 mg/24 hours	-16.2	-7.5
	3 mg/24 hours	-16.8	-8.2
CGI Item 1	Placebo	-1.3	NA
	1 mg/24 hours	-2.0	-0.76
	2 mg/24 hours	-2.4	-1.07
	3 mg/24 hours	-2.5	-1.21

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Each transdermal system is packaged in a separate pouch.

Each strength is available in cartons of 30 transdermal systems.

1 mg/24 hours	30 transdermal systems	NDC #50474-801-03
2 mg/24 hours	30 transdermal systems	NDC #50474-802-03
3 mg/24 hours	30 transdermal systems	NDC #50474-803-03
4 mg/24 hours	30 transdermal systems	NDC #50474-804-03
6 mg/24 hours	30 transdermal systems	NDC #50474-805-03
8 mg/24 hours	30 transdermal systems	NDC #50474-806-03

Store at 20° - 25°C (68° - 77°F); excursions permitted between 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature]

Neupro should be stored in the original pouch. Do not store outside of pouch.

Apply the transdermal system immediately upon removal from the pouch. Discard used systems in household trash in a manner that prevents accidental application or ingestion by children, pets or others.

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

### 17.1 Sulfite Sensitivity

Advise patients about potential for sulfite sensitivity. Neupro contains sodium metabisulfite, which may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people. An allergy to sulfites is not the same as an allergy to sulfa.

### 17.2 Falling Asleep During Activities of Daily Living and Somnolence

Advise and alert patients about the potential for sedating effects associated with Neupro, including somnolence and particularly to the possibility of falling asleep while engaged in activities of daily living. Because somnolence can be a frequent adverse reaction with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with Neupro to gauge whether or not it affects

their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Patients should not drive, operate machinery, or work at heights during treatment if they have previously experienced somnolence and/or have fallen asleep without warning prior to use of Neupro.

Because of the possible additive effects, caution should also be used when patients are taking alcohol, sedating medications, or other CNS depressants (e.g., benzodiazepines, antipsychotics, antidepressants, etc.) in combination with Neupro.

### **17.3 Hallucinations / Psychotic-Like Behavior**

Inform patients that hallucinations and other psychotic-like behavior can occur while taking Neupro and that the elderly are at a higher risk than younger patients with Parkinson's disease.

### **17.4 Symptomatic Hypotension**

Advise patients that they may develop symptomatic (or asymptomatic) hypotension while taking Neupro. Hypotension may occur more frequently during initial therapy. Accordingly, caution patients against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with Neupro.

### **17.5 Syncope**

Advise patients about the potential for syncope in patients using dopamine agonists. For this reason, patients should be alerted to the possibility of syncope while taking Neupro.

### **17.6 Impulse Control / Compulsive Behaviors**

Advise patients that they may experience impulse control and/or compulsive behaviors while taking one or more of the medications generally used for the treatment of Parkinson's disease, including Neupro. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with Neupro. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking Neupro. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Neupro.

### **17.7 Elevation of Blood Pressure and Heart Rate**

Advise patients that Neupro can increase blood pressure and heart rate,

### **17.8 Weight Gain and Fluid Retention**

Advise patients that Neupro can cause increased weight and fluid retention manifesting itself as peripheral edema.

### **17.9 Dyskinesias**

Inform patients that Neupro may cause and/or exacerbate pre-existing dyskinesias.

### **17.10 Application Site Reactions**

Inform patients that application site reactions can occur and that the Neupro transdermal system application site should be rotated on a daily basis. Neupro should not be applied to the same application site more than once every 14 days. Patients should report persistent application site reaction (of more than a few days), increases in severity, or skin reactions that spread outside the application site

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.

### **17.11 Melanoma**

Advise patients with Parkinson's disease that they have a higher risk of developing melanoma. Advise patients to monitor for melanomas frequently and on a regular basis when using Neupro for any indication.

### **17.12 Augmentation and Rebound in RLS**

Inform patients that Neupro may cause RLS symptoms to have an earlier onset during the day or become worse.

### **17.13 Magnetic Resonance Imaging and Cardioversion**

Inform patients to remove Neupro before undergoing magnetic resonance imaging (MRI) or cardioversion. These procedures could cause a burn to the site where Neupro is applied.

### **17.14 Heat Application**

Advise patients about the potential for heat application to increase drug absorption. Because applying external heat (e.g., a heating pad, sauna, or hot bath) to the transdermal system may increase the amount of drug absorbed, patients should be instructed not to apply heating pads or other sources of heat to the area of the transdermal system. Direct sun exposure of the transdermal system should be avoided.

### **17.15 Nausea, Vomiting, and Dyspepsia**

Inform patients that Neupro causes nausea, vomiting, and general gastrointestinal distress (i.e., dyspepsia/abdominal discomfort). Nausea and vomiting may occur more frequently during initial therapy and may require dose adjustment.

### **17.16 Instructions for Use**

Instruct patients to wear Neupro continuously for 24 hours. After 24 hours, the patch should be removed and a new one applied immediately. Patients can choose the most convenient time of day or night to apply Neupro but should be advised to apply the patch at approximately the same time each day. If a patient forgets to change a patch, a new patch should be applied as soon as possible and replaced at the usual time the following day.

The application site for Neupro should be moved on a daily basis (for example, from the right side to the left side and from the upper body to the lower body). Neupro should not be applied to the same application site more than once every 14 days.

Neupro should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place for 30 seconds, making sure there is good contact, especially around the edges.

Neupro should be applied once daily to clean, dry, and intact skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. Shave hairy areas at least 3 days prior to applying the patch. Do not apply to areas that could be rubbed by tight clothing, or under a waistband, to skin folds, or to skin that is red or irritated. Creams, lotions, ointments, oils, and powders should not be applied to the skin area where Neupro will be placed. Patients should wash their hands to remove any drug and should be careful not to touch their eyes or any objects.

Instruct patients not to cut or damage Neupro.

Care should be used to avoid dislodging the patch while showering, bathing or during physical activity. If the edges of the patch lift, Neupro may be taped down with bandage tape. If the patch detaches, a new one may be applied immediately to a different site. The patient should then change the patch according to their regular schedule.

*Removal of the patch:* Neupro should always be removed slowly and carefully to avoid irritation. After removal the patch should be folded over so that it sticks to itself and should be discarded so that children and pets cannot reach it. Wash the site with soap and water to remove any drug or adhesive. Baby or mineral oil may be used to remove any excess residue. Alcohol and other solvents (such as nail polish remover) may cause skin irritation and should not be used.

Manufactured for:  
UCB, Inc.  
Smyrna, GA 30080  
Made in Germany  
1E