CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21829

LABELING

Neupro®

(Rotigotine Transdermal System)

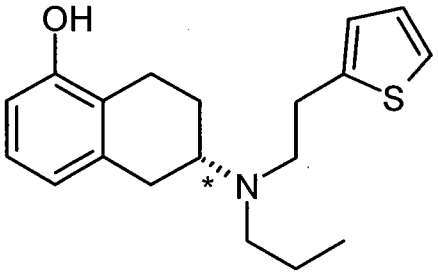
CONTINUOUS DELIVERY FOR ONCE-DAILY APPLICATION

Rx Only

DESCRIPTION

Neupro® (Rotigotine Transdermal System) is a transdermal delivery system that provides rotigotine, a non-ergolinic dopamine agonist. When applied to intact skin, Neupro is designed to continuously deliver rotigotine over a 24-hour period.

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 $C_{19}H_{25}NOS$. The molecular weight is 315.48. The structural formula for rotigotine is:



The asterisk designates the chiral center.

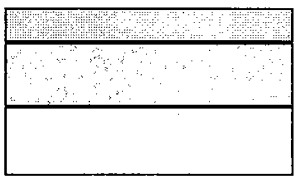
Neupro is available in three strengths: 2, 4, and 6 mg/24 hours. Each transdermal system has a release surface area of 10, 20, and 30 cm^2 and contains 4.5, 9, or 13.5 mg rotigotine, respectively. See Table 1. The composition of the transdermal system per area unit is identical.

Table 1 Transdermal System Size, Drug Content, and Nominal Delivery Rate

Neupro Nominal Dose	Rotigotine Content per System	Neupro System Size
2 mg/24 hours	4.5 mg	10 cm^2
4 mg/24 hours	9 mg	20 cm^2
6 mg/24 hours	13.5 mg	30 cm^2

System Components and Structure

Neupro is a thin, matrix-type transdermal system composed of three layers:



Backing film

Drug matrix

Protective liner

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.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rotigotine is a non-ergoline $D_3/D_2/D_1$ dopamine agonist for the treatment of Parkinson's disease. 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 D2 receptors within the caudate-putamen in the brain. Rotigotine improved motor deficits in animal models of Parkinson's disease (6-OHDA in rat and MPTP model in monkey) including when administered transdermally

Pharmacokinetics

On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2 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

When single doses of 40 cm^2 systems 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). Tmin occurs most commonly between 0 to 7 hours post dose. Tmax 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 2 mg/24 hours to 8 mg/24 hours.

On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2 mg/cm^2), independent of patch size. Similar absorption per cm^2 was observed in healthy subjects and patients with early stage Parkinson's disease.

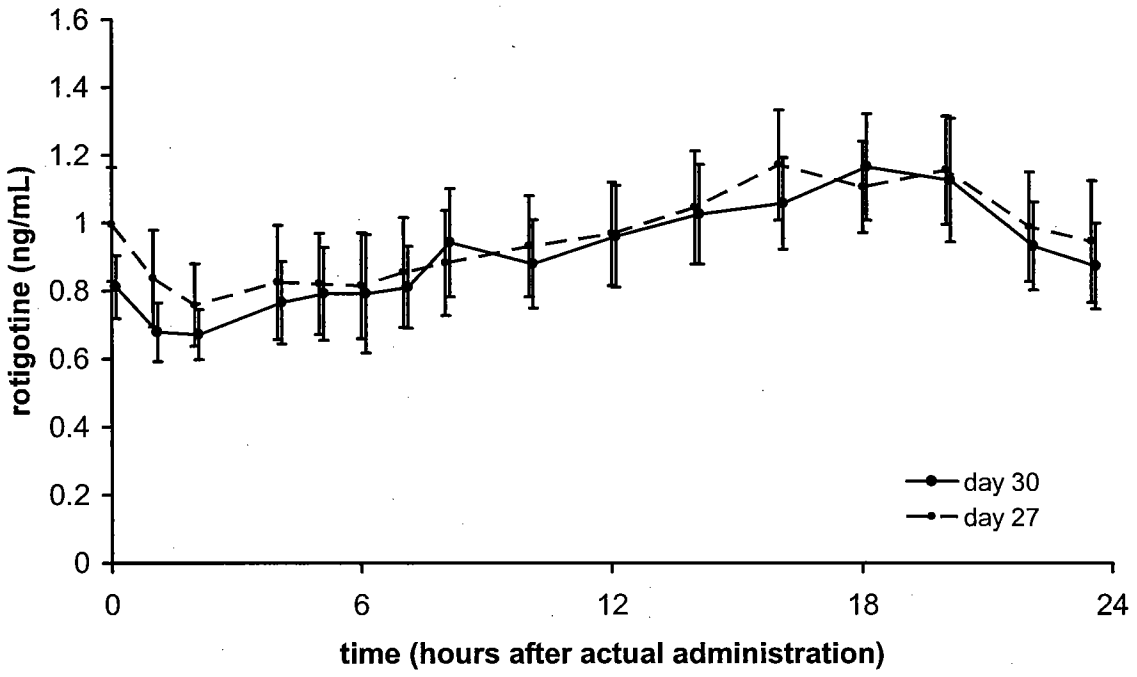
In the clinical studies of rotigotine effectiveness, the transdermal system application site was rotated from day to day (abdomen, thigh, hip, flank, shoulder, or upper arm) and the mean measured plasma concentrations of rotigotine were stable over the six months of maintenance treatment. Relative bioavailability for the different application sites at steady-state was evaluated in subjects with Parkinson's disease. Differences in bioavailability ranged from less

than 1% (abdomen vs hip) to 64% (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 1 Average (±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, (Vd/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-desthienyl -rotigotine. Multiple CYP isoenzymes, sulfotransferases and two UDP-glucuronosyltransferases catalyze the metabolism of rotigotine (See Drug Interactions)

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 (~11%). The major metabolites found in urine were rotigotine sulfate (16% to 22%of the absorbed dose), rotigotine glucuronide (11%-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).

Pharmacokinetics in Special Populations

Hepatic Insufficiency

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. (See **PRECAUTIONS, Hepatic Insufficiency**)

Renal Insufficiency

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.

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.

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^2), 6 mg/24 hours (30 cm^2), and 8 mg/24 hours (40 cm^2) patches. An adherence of ≥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.

CLINICAL STUDIES

The effectiveness of Neupro in the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease was evaluated in three parallel group, randomized, double-blind placebo controlled studies conducted in the U.S. and abroad. These studies were conducted in patients who were not receiving concomitant dopamine agonist therapy and, who were either L-dopa naïve or off L-dopa for at least 28 days prior to baseline and were never on L-dopa for more than 6 months. Patients were excluded from the study 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 for at least 28 days prior to baseline; they were to attempt to maintain that dose for the duration of the study.

The primary outcome assessment was the change from baseline for the combined scores for Part II (activities of daily living component) plus part III (motor component) of the Unified Parkinson's Disease Rating Scale (UPDRS). Part II of the UPDRS contains 13 questions relating to activities of daily living that 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), each scored 0 (normal) to 4 (maximal severity). 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), scored for different body regions, and has a maximum (worst) score of 108.

<u>Dose-Response Study</u>

This study was a randomized, double-blind, dose-response, multicenter, multinational study in which 316 early stage Parkinson's Disease patients were assigned to treatment with either placebo or one of several fixed doses (2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, or 8 mg/24 hours) of Neupro, given as 1, 2, 3, or 4 2-mg patches for a period up to 11 weeks. 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 ≥ 65 years) and the study enrolled more men (62 %) than women (39 %). Most patients (85 %) were Caucasian and most randomized patients (≥ 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. Patients experienced a mean improvement (i.e. reductions) in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of week 11 or last visit for patients discontinuing early) of -3.5, -4.5, -6.3, and -6.3 for the 2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours Neupro groups respectively and –1.4 for the placebo group. The difference from the placebo group for the mean change for each Neupro dose is shown in Table 2. 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 2 Dose-Response Study: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Neupro Nominal Dose	Rotigotine Content per System	Difference from placebo
2 mg/24 hours	4.5 mg	-2.1
4 mg/24 hours	9 mg	-3.1
6 mg/24 hours	13.5 mg	-4.9
8 mg/24 hours	18 mg	-5.0

North American Study

This study was a randomized, double-blind, multinational, flexible Neupro dose (2, 4, or 6 mg/24 hours), parallel group study in which 277 early stage, idiopathic Parkinson's Disease patients were assigned (2: 1 ratio) to treatment with Neupro or placebo for a period up to about 28 weeks. This study 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, and placebo treated patients showed a mean change from baseline of +1.39 , a difference (see Table 3)that was statistically significant.

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

Neupro Nominal Dose	Rotigotine Content per System	Difference from placebo
Up to 6 mg/24 hours	Up to 13.5 mg	-5.3

Foreign Multinational Study

This study was a randomized, double-blind, multinational, flexible Neupro dose (2 mg/24 hours, 4 mg/2 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 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 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 - 6.83, and placebo treated patients showed a mean change from baseline of – 2.33 (see Table 4), a difference that was statistically significant.

Table 4 Foreign Multinational Study: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Neupro Nominal Dose	Rotigotine Content per System	Difference from placebo
Up to 8 mg/24 hours	Up to 18 mg	-4.5

INDICATIONS AND USAGE

Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease.

The effectiveness of Neupro was demonstrated in randomized, controlled studies in patients with early-stage Parkinson's disease who were not receiving concomitant L-dopa therapy. (See **CLINICAL STUDIES**)

CONTRAINDICATIONS

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

WARNINGS

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 and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Falling Asleep During Activities of Daily Living

Patients treated with Neupro have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on Neupro, some perceived no warning signs, such as excessive drowsiness, and believed that they were alert

immediately prior to the event. Some of these events have been reported as late as one year after initiation of treatment.

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

Before initiating treatment with Neupro, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with Neupro such as concomitant sedating medications and the presence of sleep disorders. If a patient develops meaningful daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), Neupro should ordinarily be discontinued (see DOSAGE AND ADMINISTRATION for guidance on discontinuing Neupro). If a decision is made to continue Neupro, patients should be advised not to drive and to avoid other potentially dangerous activities. There is insufficient information to establish whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Hallucinations

In three double-blind, placebo-controlled studies in patients with early-stage Parkinson's disease who were not treated with L-dopa, 2.0% (13 of 649) of patients treated with Neupro reported hallucinations compared to 0.7% (2 of 289) of patients on placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 0.2% (1 of 649) Neupro treated patients compared to 0% (0 of 289) on placebo.

PRECAUTIONS

General

Symptomatic Hypotension

Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, resulting in postural 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, Parkinson's 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. (See **PRECAUTIONS, Information for Patients**)

The pooled analyses of a variety of adverse event terms suggestive of orthostatic hypotension in the three controlled efficacy studies showed the incidence of these events with Neupro 6 mg/24 hours was 5%vs 4% for placebo. Examination of systolic blood pressure decreases of $\geq$20 mmHg at 3 minutes after arising showed an incidence of 5% for Neupro 6 mg/24 hours vs 4%

for placebo. In a separate analysis, decreases in systolic blood pressure from baseline at anytime of ≥40 mmHg in the supine position were seen in 7% of subjects who received Neupro 6 mg/24 hours and 4% for placebo.

An analysis of the dose response study using a variety of adverse event terms suggestive of orthostatic hypotension, including dizziness and postural dizziness, showed a 2 fold higher incidence of these events with Neupro (22 %) vs placebo (11 %). This increased risk 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 study showed a dose-related increased risk for mild-moderate systolic orthostatic hypotension (decrease of ≥ 20 mm Hg) at the end of the titration period (after 4 weeks treatment) with the highest recommended 6 mg/24 hours Neupro dose (6 %) vs placebo (3 %) or lower Neupro doses (2 mg/24 hours or 4 mg/24 hours 0 %). An increased dose-related risk (3 % for 4 and 6 mg/24 hours Neupro; 2 % for placebo and 2 mg/24 hours Neupro) of systolic orthostatic hypotension was also observed after 7 weeks of treatment.

Syncope

Syncope has been reported in patients using dopamine agonists, and for this reason patients should be alerted to the possibility of syncope. The reported incidence of syncope was no greater among those receiving Neupro (1%) than among those receiving placebo (1%). Because the studies of Neupro excluded patients with clinically relevant cardiovascular disease, it is not known to what extent the estimated incidence figures apply to Parkinson's disease patients as a whole. Therefore, patients with severe cardiovascular disease should be treated with caution.

Elevation of Heart Rate and Blood Pressure

Neupro on average increased heart rate by 2 to 4 bpm in rotigotine treated patients compared to placebo patients. Subjects who received Neupro in clinical studies had a slightly higher incidence of a heart rate exceeding 100 beats per minute (9% vs 7% of placebo subjects).

Neupro treatment was not associated with a consistent mean change in systolic and diastolic blood pressure. Subjects on Neupro had a higher incidence of systolic blood pressures >180 mm Hg and diastolic blood pressures >105 mmHg compared to placebo (SBP: 4% vs 2%; DBP: 9% vs 5%). In the Dose-Response study, there was a dose-related increase in systolic blood pressure increases ≥ 20 mm Hg at the highest recommended Neupro dose (6 mg/24 hours), 12 % vs 9 % for lower doses or placebo when standing at the final visit and 8 % vs 3 % for lower doses or placebo after changing from supine to standing at the final visit. These findings of blood pressure elevations should be considered when treating patients with cardiovascular disease.

Weight Gain and Fluid Retention

Subjects taking Neupro had a higher incidence (3%) of substantial weight gain (more than 10% of baseline weight) than placebo subjects (<1%). This weight gain was frequently associated with the development of peripheral edema, suggesting that Neupro may cause substantial fluid retention in some patients. Although the weight gain was usually well-tolerated in subjects observed in 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.

Dyskinesia

Neupro may potentiate the dopaminergic side effects of L-dopa and may cause and/or exacerbate pre-existing dyskinesia. Dyskinesia was reported at a similar rate in patients treated with Neupro (0.5%) or placebo (0.3%).

Hepatic Insufficiency

No adjustment of the dose is needed in patients with moderate hepatic impairment (Child Pugh classification – Grade B). The pharmacokinetics of rotigotine have not been studied in patients with severe hepatic impairment.

Application Site Reactions

Application site reactions (ASRs) were reported at a greater frequency in the Neupro treated patients (37%, 239/649) than in placebo patients (14%, 40/289) in the three double-blind, placebo-controlled studies with Neupro.

In the Dose-Response study, ASRs exhibited a dose-response relationship for the highest recommended Neupro dose (6 mg/24 hours) not only during the whole study period (placebo 19 %, 2 mg/24 hours 24 %, 4 mg/24 hours 21 %, 6 mg/24 hours 34 %) but also in separate analyses of the titration period and of the maintenance period. ASRs as a cause for study discontinuation also showed a dose-response increased risk for the whole study period for 6 mg/24 hours Neupro vs other treatments (placebo 0%, 2 mg/24 hours 2 %, 4 mg/24 hours 0 %, 6 mg/24 hours 3 %).

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. About 5% of patients treated with Neupro in these studies discontinued as a result of an ASR. 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 to investigate the cumulative human 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 in normal volunteers with continuous rotating transdermal system application to a 2.5 cm^2 system, (0.5 mg/24 hours), after induction of maximal irritational stress 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 risks 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.

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).

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.

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 applied Neupro transdermal system 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.

Events Reported with Dopaminergic Therapy

Withdrawal-Emergent-Hyperpyrexia and Confusion

Although not reported with Neupro, 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** for guidance on discontinuing Neupro).

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.

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.

Information for Patients

Patients should be instructed to use Neupro only as prescribed.

Patients should be asked about sensitivity to sulfites. Advise patient that 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.

Patients should be alerted to the potential sedating effects associated with Neupro, including somnolence and particularly to the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event 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. If patients have previously experienced somnolence and/or have fallen asleep without warning prior to use of Neupro, they should be advised not to drive, operate machinery, or work at heights during treatment.

As Neupro is administered transdermally, food intake and delayed gastric emptying will not influence the rate of absorption.

Patients should be instructed 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.

Neupro should be applied once daily to clean, dry, and intact skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. If applied to a hairy area, the area should be shaved at least 3 days prior to applying the patch. Neupro should not be applied to areas that could be rubbed by tight clothing or under a waistband. Neupro should not be applied to skin folds. Neupro should not be applied to skin that is red, irritated, or impaired. Creams, lotions, ointments, oils, and powders should not be applied to the skin area where Neupro will be placed.

Care should be used to avoid dislodging the patch while showering, bathing or during physical activity. After applying Neupro, patients or caregivers should wash their hands to remove any drug and should be careful not to touch their eyes or any objects. 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.

Patients should be informed that application site reactions can occur and that the Neupro transdermal system application site should be rotated on a daily basis (e.g., from the right side to the left side and from the upper body to the lower body). Neupro should not be applied to the same application site more than once every 14 days. 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 that spreads outside the application site, an assessment of the risk/benefit balance for the individual patient should be conducted. If a generalized skin reaction associated with the use of Neupro is observed, Neupro should be discontinued.

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.

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. After removal the application site should be washed 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. Neupro patients or caregivers should wash their hands to remove any drug and should be careful not to touch their eyes or any objects.

Use of Neupro is associated with nausea, vomiting, and general gastrointestinal distress. Nausea and vomiting may occur more frequently during initial therapy and may require dose adjustment.

Patients should be informed that hallucinations can occur during treatment with Neupro.

Although not reported with Neupro at a greater frequency than with placebo, patients using dopamine agonists may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sweating. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to a postural challenge and orthostatic hypotension may occur more frequently during initial therapy or with an increase in dose at any time.

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.

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.

Patients should be instructed not to cut or damage Neupro.

To avoid potential burns, Neupro patients should be instructed to remove Neupro before undergoing magnetic resonance imaging (MRI) or cardioversion.

Because of the possibility rotigotine might be excreted in human breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

Because experience in humans is limited, patients should be advised to notify their physician if they become or plan to become pregnant during therapy. (See **PRECAUTIONS, Pregnancy**)

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges 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.

Drug Interactions

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 t 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.

L-dopa

Co-administration of L-dopa/carbidopa (100/25mg 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-dopa/carbidopa.

Dopamine Antagonists

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year subcutaneous carcinogenicity studies of rotigotine were conducted in CD-1 mice at doses of 0, 3, 10 and 30 mg/kg and in Sprague-Dawley rats at doses of 0, 0.3, 1, and 3 mg/kg; in both studies rotigotine was administered once every 48 hours. No significant increases in tumors occurred in the mouse study at doses up to 12 times the maximum recommended human dose (MRHD) of 6 mg/24 hours.

In rats, there were significant increases in Leydig cell tumors in males and uterine tumors (adenocarcinomas, squamous cell carcinomas) in females. These findings are of questionable significance because the endocrine mechanisms believed to be involved in the production of Leydig cell and uterine tumors in rats are not considered relevant to humans. Therefore, there were no significant tumor findings considered relevant to humans at plasma exposures (AUC) up to 5 to 9 times the plasma AUC in humans at the MRHD.

Mutagenesis

Rotigotine was not mutagenic in the *in vitro* Ames test or the *in vivo* Unscheduled DNA Synthesis test in hepatocytes from male Fisher rats. In the *in vitro* mouse lymphoma assay, rotigotine was mutagenic and clastogenic in the presence and absence of metabolic activation. Rotigotine was not clastogenic in the in vivo mouse micronucleus test.

Infertility

When administered to female Sprague-Dawley rats prior to and during mating and through gestation day 7, rotigotine disrupted implantation at subcutaneous (s.c.) doses of 1.5 mg/kg/day (2 times the maximum recommended human dose (MRHD) on a mg/m^2 basis) or greater. There was no no-effect dose. In male rats treated from 70 days prior to and through mating, there was no effect on fertility; however, a decrease in epididymal sperm motility was observed at 15 mg/kg. The no-effect dose was 5 mg/kg/day (8 times the MRHD on a mg/m^2 basis). Rotigotine was administered to female CD-1 mice at s.c. doses of 10, 30, and 90 mg/kg/day (8 to 73 times the MRHD on a mg/m^2 basis) from 2 weeks until 4 days before mating and then at a dose of 6 mg/kg/day (all groups) (5 times the MRHD on a mg/m^2 basis) from 3 days before mating until gestation day 7; disrupted implantation was observed at all doses. The effects on implantation are thought to be due to the prolactin-lowering effect of rotigotine. In humans, chorionic gonadotropin, not prolactin, is essential for implantation.

Pregnancy

Pregnancy Category C

In subcutaneous studies in Sprague-Dawley rats and CD-1 mice, rotigotine was shown to have adverse effects on embryo-fetal development. Rotigotine given to pregnant rats during organogenesis (0.5, 1.5 or 5 mg/kg/day on gestation days 6 through 17) resulted in increased fetal death at all doses. The lowest effect dose was 0.8 times the MRHD on a mg/m^2 basis. This effect is thought to be due to the prolactin-lowering effect of rotigotine. Rotigotine given to pregnant mice during organogenesis (10, 30 or 90 mg/kg/day on gestation days 6 through 15) resulted in an increased incidence of skeletal retardation at 30 and 90 mg/kg/day, and an increase in fetal death at 90 mg/kg/day. No effects were observed at 10 mg/kg/day (8 times the MRHD on a mg/m^2 basis). Rotigotine given to pregnant Himalayan rabbits during organogenesis (1, 5, or 15 mg/kg/day (3-49 times the MRHD on a mg/m^2 basis) on gestation days 6 through 20) had no effects on embryo-fetal development; however, the study was not conducted at sufficiently high doses. In a pre- and postnatal development study, Sprague-Dawley rats were administered 0.1, 0.3 or 1 mg/kg/day from gestation day 6 through postnatal day 21. Rotigotine impaired growth and development of offspring during lactation and produced neurobehavioral abnormalities in offspring at 1 mg/kg/day. When offspring were mated, growth and survival of their offspring were adversely affected. No adverse effects were observed at 0.3 mg/kg/day (0.5 times the maximum recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies using Neupro in pregnant women.

Therefore, the use of Neupro cannot be recommended during pregnancy unless the potential benefits of therapy justify the potential risk to the fetus.

Nursing Mothers

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

Studies in rats have shown that rotigotine and/or its metabolite(s) is excreted in breast milk. It is not known whether rotigotine is excreted in human breast milk. Because of the possibility that rotigotine may be excreted in human milk, and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

Safety and effectiveness in pediatric patients have not been established.

Geriatric use

Of the subjects treated with Neupro in clinical studies for treatment of early-stage Parkinson's disease, 42% were 65 years old and over, and 9% were 75 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. (See **CLINICAL PHARMACOLOGY, Geriatric Patients**)

ADVERSE REACTIONS

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

In the 3 double-blind, placebo-controlled studies in patients with early-stage Parkinson's disease, the most commonly observed AEs (incidence ≥5%) that appeared substantially more frequently in the rotigotine groups than in the placebo groups were nausea, application site reaction, somnolence, dizziness, headache, vomiting, and insomnia.

Approximately 13% of 649 rotigotine-treated patients who participated in the 3 longest controlled studies discontinued treatment because of AEs, compared with 6% of 289 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were: application site reaction (5% vs 0% on placebo), nausea (2% vs 0% on placebo), and vomiting (1% vs 0% on placebo).

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

Table 5 lists treatment-emergent adverse events that occurred in the three placebo-controlled studies in early-stage Parkinson's disease in ≥2% of the patients treated with Neupro and were more frequent than in the placebo group. In these studies, patients did not receive concomitant L-dopa.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse reactions in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies

cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and no-drug factors to the adverse-events incidence rate in the population studied.

Table 5 Treatment-Emergent Adverse Event (Regardless of Causal Relationship) Incidence in Double-Blind, Placebo-Controlled Early-Stage Parkinson's Disease Studies (Events ≥2% of Subjects Treated with Neupro and Numerically More Frequent Than in the Placebo Group)

Body system/preferred term	Placebo N=289 (%)	Neupro N=649 (%)
Application site reactions	14	37
Autonomic nervous system		
Sweating increased	2	4
Mouth dry	1	3
Body as a Whole		
Fatigue	7	8
Accident NOS	4	5
Cardiovascular		
Extremity edema	6	7
Hypertension	2	3
Central and peripheral nervous system		
Dizziness	11	18
Headache	10	14
Vertigo	2	3
Gastrointestinal system		
Nausea	15	38
Vomiting	2	13
Constipation	4	5
Dyspepsia	1	4
Anorexia	1	3
Musculoskeletal system		
Back pain	5	6
Arthralgia	3	4
Psychiatric		
Somnolence	16	25
Insomnia	5	10

Body system/preferred term	Placebo N=289 (%)	Neupro N=649 (%)
Dreaming abnormal	<1	3
Hallucination	1	2
Respiratory system - Sinusitis	2	3
Skin and appendage – erythematous rash	1	2
Urinary tract infection	1	3
Vision abnormal	1	3

NOS=not otherwise specified

Other AEs reported by more than 2% of patients with early-stage Parkinson's disease treated with rotigotine (as displayed), but that were equally or more frequent in the placebo group (after rounding) were: asthenia, influenza-like symptoms, diarrhea, depression, rhinitis, micturition frequency, upper respiratory tract infection, fall, tremor, coughing, anxiety, abdominal pain, and chest pain.

The incidence of AEs was not materially different between men and women in the pooled studies presented in Table 5.

Dose-Related Adverse Events

Many AEs appeared to be dose-related . Table 6 illustrates AEs that were dose-related based upon the highest frequency of AEs occurring with the 6 mg/24 hours dose or with the 4 and 6 mg/24 hours doses compared to the frequency for placebo and the 2 mg/24 hours dose. Rates for the non-recommended 8 mg/24 hr. dose are also shown. Some AEs (anorexia; constipation; vision abnormal) were found to be dose-related only when their onset was in the titration period. Dizziness was only dose-related when it had its onset in the maintenance period.

Table 6 Incidence (%) of Neupro Dose-Related Treatment-Emergent Adverse Events During the Whole Study Period in the Dose-Response Study

Preferred Term Adverse Event	Placebo N = 64	Daily Neupro Dose 2 mg/24 hours N = 67	4 mg/24 hours N = 63	6 mg/24 hours N = 65	8 mg/24 hours N = 70
Application site reaction	19	24	21	34	46
Nausea	11	34	38	48	41
Vomiting	3	10	16	20	11
Weight decrease	0	0	0	2	3
Myalgia	0	0	2	2	3
Somnolence	3	13	16	19	21
Insomnia	8	6	13	14	14

Dreaming abnormal	0	2	5	3	7
Hallucination	2	0	2	3	3
Rash erythematous	2	2	6	3	3

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691

692 Laboratory changes

693 Subjects who received Neupro experienced an average decline in blood hemoglobin levels of
694 about 2% or 0.3 g/dL relative to subjects who received placebo. A decline in blood hemoglobin
695 from baseline of 2 g/dL or more was seen in 4% with Neupro and 1% with placebo. Among
696 subjects with normal baseline hemoglobin levels, about 8% of those who received Neupro
697 developed low hemoglobin levels compared to 5% with placebo. Subjects receiving Neupro who
698 experienced declines in blood hemoglobin were also noted to have declines in serum albumin. It
699 is not known whether these changes are readily reversible with discontinuation of Neupro.

700 Subjects who received Neupro also experienced an average increase in blood urea nitrogen
701 (BUN) levels of about 3.7% or 0.21 mg/dL relative to subjects who received placebo. There was
702 also a higher incidence of abnormally elevated levels of BUN associated with treatment. There
703 were no significant differences between Neupro and placebo in levels of serum creatinine. It is
704 not known whether these changes are readily reversible with discontinuation of Neupro or
705 whether they represent changes in renal function.

706 Treatment with Neupro was associated with a greater likelihood of low levels of blood glucose
707 (less than 50 mg/dL). Among subjects with normal baseline glucose levels, about 7% of subjects
708 who received Neupro developed at least one low blood glucose level compared to 4% with
709 placebo.

710 **Other Adverse Reactions Observed in Subjects with Early-Stage Parkinson's**
711 **Disease during Phase 2 and 3 Studies**

712 Rotigotine was administered to 1220 subjects with early-stage Parkinson's disease in Phase 2
713 and 3 clinical studies, including 6 double-blind, placebo-controlled studies; 319 were in an open-
714 label study in patients with early-stage Parkinson's disease. Adverse events occurring in
715 rotigotine treated patients at least twice, or if the AE was serious, at least once, and events not
716 described elsewhere in labeling, are provided in the following listing. Events too poorly
717 described or not plausibly related to treatment were also omitted. Events are further classified
718 within body system categories and enumerated in order of decreasing frequency using the
719 following definitions: frequent AEs are defined as those occurring in at least 1/100 patients;
720 infrequent AEs are those occurring in 1/100 to 1/1000 patients; and rare events are those
721 occurring in fewer than 1/1000 patients.

722 **Application site disorders:** *frequent* –contact dermatitis

723 **Autonomic nervous system:** *infrequent* – saliva increased, appetite increased, impotence,
724 flushing

725 **Body as a whole:** *frequent* –leg pain, malaise, fever; *infrequent* – allergic reaction, rigors, hot
726 flushes, hyperesthesia

727 **Cardiovascular disorders, general:** *frequent* –syncope; *infrequent* –cardiac failure

Central and peripheral nervous system disorders: *frequent* – paresthesia, confusion, ataxia, gait abnormal, neuralgia, hypoesthesia, hypertonia; *rare*-convulsions

Hearing and vestibular disorders: *infrequent* – tinnitus

Heart rate and rhythm disorders: *infrequent* –, AV (atrioventricular) block, bundle branch block, fibrillation atrial; *rare* – arrhythmia ventricular, tachycardia ventricular

Hematologic disorders: *infrequent* – thrombocytopenia

Liver and biliary disorders: *frequent* – GGT (gamma-glutamyl transferase) increased

Metabolic and nutritional disorders: *frequent* – weight increase

Psychiatric disorders: *infrequent* –paranoid reaction, psychosis

Skin and appendage disorders: *frequent* –pruritus

Urinary system disorders: *frequent* – urinary incontinence

Vascular disorders: *frequent* – purpura

Vision disorders: *infrequent* – photopsia

OVERDOSAGE

There were no reports of overdose of Neupro in the clinical studies.

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 warned against this possibility.

Overdose Management

There is no known antidote for overdosage of dopamine agonists. In case of suspected overdose, the 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. If it is necessary to discontinue use of rotigotine after overdose, it should be discontinued gradually to prevent neuroleptic malignant syndrome. (See **PRECAUTIONS**) The daily dose should be reduced by 2 mg/24 hours 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, please consult the **DOSAGE AND ADMINISTRATION** section.

The predominant symptoms of overdose with Neupro are expected to be nausea, vomiting, hypotension, involuntary movements, hallucinations, confusion, convulsions, and other signs of excessive dopaminergic stimulation.

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.

DOSAGE AND ADMINISTRATION

Initiation of Therapy

Neupro should be started at 2 mg/24 hours. 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 is 6 mg/24 hours. Doses above 6 mg/24 hours have not shown any additional therapeutic benefit (See **CLINICAL STUDIES**, Dose-Response Study) and are associated with an increased incidence of adverse reactions (see Adverse Reactions) If it is necessary to discontinue use of Neupro, it should be discontinued gradually. The daily dose should be reduced by 2 mg/24 hours with a dose reduction preferably every other day, until complete withdrawal of Neupro. (see Precautions; Withdrawal-Emergent-Hyperpyrexia and Confusion)

Administration of transdermal system

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 20 to 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.

Complete instructions to facilitate patient counseling on proper usage may be found in the **PRECAUTIONS, Information for Patients** section and in the **PATIENT INFORMATION LEAFLET.**

Animal Toxicology

Retinal Pathology: Albino rats: Retinal degeneration was observed in albino rats in the 6-month toxicity study at the highest dose tested. Retinal degeneration was not observed in the 2-year carcinogenicity studies in albino rat (at plasma exposures (AUC) up to 5 to 9 times the plasma AUC in humans at the MRHD of 6 mg/24 hours) and 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.

HOW SUPPLIED

Neupro® is available in 3 strengths, as described in Table 7:

Table 7 Transdermal System Size, Drug Content, and Nominal Delivery Rate

Neupro Nominal Dose	Rotigotine Content per System	Neupro System Size
2 mg/24 hours	4.5 mg	10 cm^2
4 mg/24 hours	9 mg	20 cm^2
6 mg/24 hours	13.5 mg	30 cm^2

Each transdermal system is packaged in a separate pouch.

Each strength is available in cartons of 7 and 30 transdermal systems.

2 mg/24 hours 7 transdermal systems	NDC # 0091-6486-21
2 mg/24 hours 30 transdermal systems	NDC # 0091-6486-01
4 mg/24 hours 7 transdermal systems	NDC # 0091-6487-21
4 mg/24 hours 30 transdermal systems	NDC # 0091-6487-01
6 mg/24 hours 7 transdermal systems	NDC # 0091-6488-21
6 mg/24 hours 30 transdermal systems	NDC # 0091-6488-01

Storage

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.

Manufactured for:
SCHWARZ PHARMA, LLC
Mequon, WI 53092, USA

By:
LTS Lohmann Therapie System AG
Lohmannstrasse 2
D-56626 Andernach, Germany

PC4862
Rev. 07/04

PATIENT INFORMATION
NEUPRO® [NU pro]
(rotigotine transdermal system)

Rx Only

IMPORTANT: NEUPRO is for use on the skin only.

Read the Patient Information that comes with NEUPRO before you start using it and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. If you have any questions about NEUPRO, ask your doctor or pharmacist.

What is the most important information I should know about NEUPRO?

NEUPRO may make you very sleepy or cause you to fall asleep suddenly, and without warning while doing normal activities such as driving, talking with other people, watching TV, or eating. This can happen any time during treatment with NEUPRO.

- Do not drive, work on ladders, or do other dangerous activities while using NEUPRO until you know how NEUPRO affects you.
- If NEUPRO does make you very sleepy, or you fall asleep suddenly while doing normal activities, do not drive or do other dangerous activities until you talk with your doctor.

Tell your doctor if you fall asleep suddenly while doing normal activities or feel sleepier than normal.

Heat may cause too much medicine from a Neupro patch to pass through your skin. While you are wearing a NEUPRO patch, do not:

- **apply a heating pad to the application site area**
- **take a hot bath**
- **use a sauna**
- **expose the application site to direct sunlight**

What is NEUPRO?

NEUPRO is a type of medicine called a dopamine agonist. NEUPRO is a patch (transdermal delivery system) worn on the skin. It is used to treat the signs and symptoms of early-stage Parkinson's disease in adults.
NEUPRO has not been studied in children.

Who should not use NEUPRO?

Do not use NEUPRO if you are allergic to anything in it. See the end of this leaflet for a complete list of ingredients in NEUPRO.

NEUPRO contains a sulfite called sodium metabisulfate. Sulfites can cause life-threatening allergic reactions in people that are sensitive to sulfites. People with asthma are more likely to be sensitive to sulfites. If you have trouble breathing or swallowing while using NEUPRO, remove NEUPRO right away and call your doctor or get emergency care.

NEUPRO may not be right for you. Before starting NEUPRO tell your doctor about all of your health conditions including if you:

- are allergic to sulfites
- have asthma
- have blood pressure problems
- have heart problems
- are pregnant or breastfeeding or planning on becoming pregnant

Tell your doctor if you drink alcohol
Alcohol should be avoided while using NEUPRO. ALCOHOL and NEUPRO can interact and increase your chance of being sleepy or falling asleep suddenly while doing normal activities.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Some medicines may affect how NEUPRO works. NEUPRO may also affect how your other medicines work. **Especially tell your doctor if you take other medicines that can make you sleepy such as sleep medicines, antidepressants, or antipsychotics.**

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I use NEUPRO?

See the end of this leaflet for complete instructions "How to use and apply a NEUPRO patch."

- Use NEUPRO exactly as prescribed by your doctor.
- NEUPRO comes in 4 different size (dose) patches. Your doctor will probably start you on a low dose of NEUPRO. Your doctor will change the dose weekly until you are taking the right amount of medicine to control your symptoms. It may take several weeks before you reach the dose that controls your symptoms best. Do not stop or change your dose of NEUPRO without first talking with your doctor.
- Talk to your doctor often about your condition. **Do not stop or change your treatment with Neupro without talking to your doctor.**
- **Patients with Parkinson's disease may have an increased chance of getting a skin cancer called melanoma. People with Parkinson's disease should have a doctor check their skin for skin cancer regularly.**

What are the possible side effects of NEUPRO?

Possible serious side effects with NEUPRO include:

- **falling asleep while do normal activities.** See "What is the most important information I should know about NEUPRO?"
- **low blood pressure** that makes you feel dizzy, faint, sweaty, or have nausea. Stand up slowly when getting up from a sitting or lying position. Tell you doctor if you if you have symptoms of low blood pressure with NEUPRO.
- **fainting**
- **hallucinations** (seeing, hearing, or sensing things that are not real). The chance for hallucinations is higher in elderly patients with Parkinson's disease.
- **compulsive** behavior and trouble controlling strong urges such as:
  - gambling too much
  - increased sexual desire
  - repeating meaningless actions

Talk to your doctor if you or family members notice that you are having unusual urges

-

The most common side effects with NEUPRO are:

- nausea
- application site reaction
- drowsiness or sleepiness
- dizziness
- headache
- vomiting
- trouble sleeping (insomnia)

These are not all the side effects of NEUPRO. For more information, ask your doctor or pharmacist. Talk to your doctor about any side effects or problems you may have.

How do I store NEUPRO?

- Store NEUPRO at 68° to 77°F (20° to 25°C).
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- **Keep NEUPRO and all medicines out of reach of children and away from pets.**

General information about NEUPRO

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use NEUPRO for a condition for which it was not prescribed. Do not give NEUPRO to other people even if they have the same condition you have. It may harm them.

This leaflet summarizes important information about NEUPRO. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about NEUPRO that was written for healthcare professionals.

For more information, visit www.website.com or call 1-800-xxx-xxxx.

What are the ingredients in NEUPRO?

Active ingredient: rotigotine

Inactive ingredients: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol.

How to use and apply a NEUPRO patch

Read these instructions carefully before you apply NEUPRO. Ask your doctor or pharmacist about anything you do not understand.

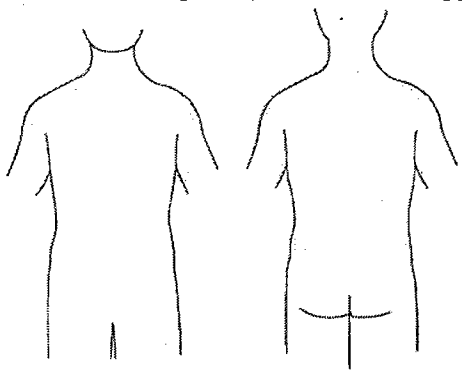
When to Apply NEUPRO:

Each patch is sealed in a pouch that protects it until you are ready to apply it.

- NEUPRO should be applied right away after removing it from the protective pouch.
- Wear NEUPRO for 24 hours. After 24 hours, remove the patch and apply a new one right away to a different area of skin.
- Choose the time of day or night that works best for you to apply NEUPRO. Apply the patch at the same time each day.

Where to Apply NEUPRO:

- Choose an area of clean, dry, and healthy skin on the stomach, thigh, hip, flank (side of the body between the ribs and the pelvis), shoulder, or upper arm.



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- Each patch should be applied to a different place on the skin each day, for example, from the right side to the left side and from the upper body to the lower body.

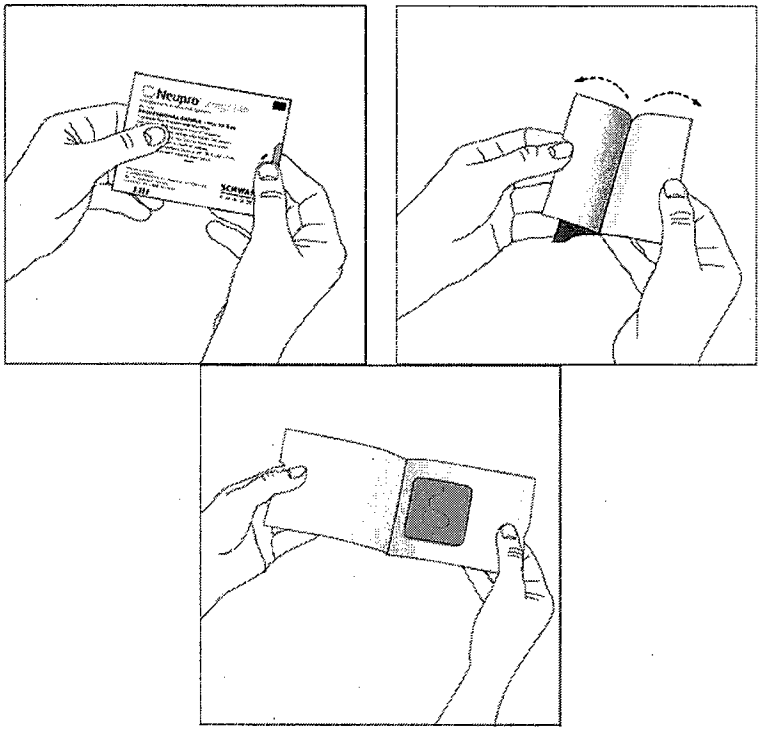
NEUPRO should not be applied to the same area of skin more than once every 14 days.

- Creams, lotions, ointments, oils, and powders should not be applied to the skin area where the patch will be placed.

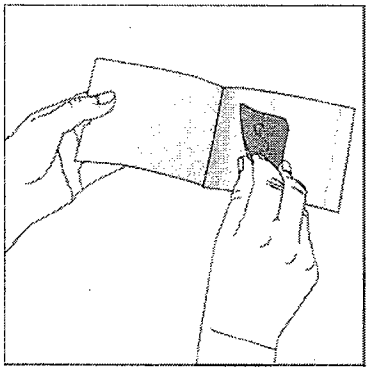
How to Apply NEUPRO:

Each patch is individually packaged. Just before you apply the patch, remove it from its sealed pouch, remove the protective liner and apply to the skin right away. Do not store the patch outside the sealed pouch. Do not cut a NEUPRO patch into smaller pieces.

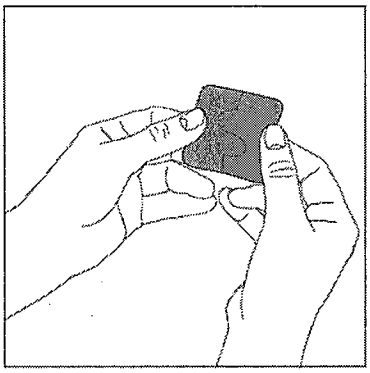
1. Grasp the two sides of the pouch and pull apart.



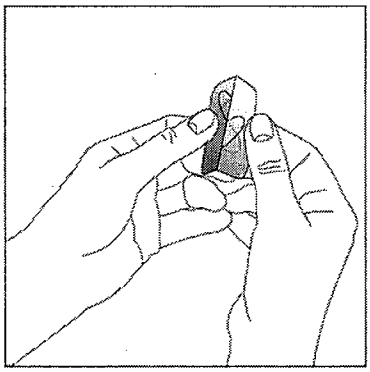
2. Remove the patch from the pouch.



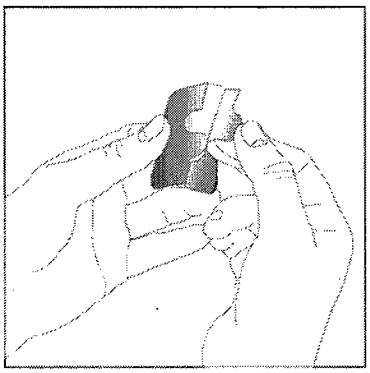
3. Hold the patch with both hands, with the protective liner on top.



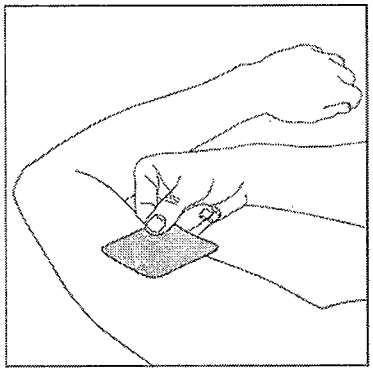
4. Bend the edges of the patch away from you so that the S-shaped cut in the liner opens up.

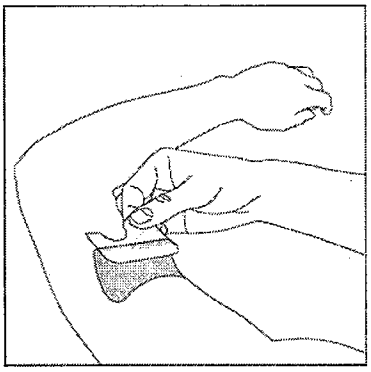


5. Peel off one half of the protective liner. **Do not touch the sticky surface because the medicine could come off on your fingers.**

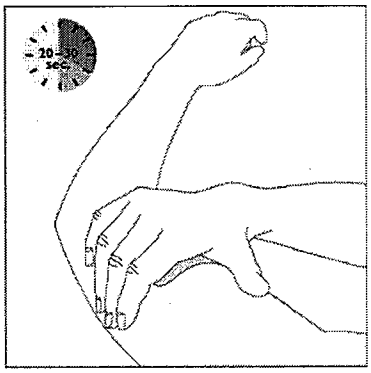


6. Apply the sticky half of the patch to a clean area of skin and remove the remaining liner.





7. Press the patch firmly with the palm of your hand for **20 to 30** seconds to make sure there is good contact with the skin, especially around the edges. Make sure that the patch is flat against the skin (there should be no bumps or fold in the patch).



8. Be sure to wash your hands with soap and water right after handling the patch to remove any medicine that may have gotten on them. Do not touch your eyes until after you have washed your hands.

How to Remove NEUPRO:

1. Slowly and carefully peel off the used patch. Carefully fold it in half (sticky sides together) and throw away the folded patch so that children and pets cannot reach it. This patch still contains some medicine and could harm a child or pet.
2. Gently wash the area with warm water and mild soap to remove any sticky material (adhesive) that stays on your skin. Baby or mineral oil may also be used to remove any adhesive. Alcohol or other solvents, such as nail polish remover, may cause skin irritation and should not be used.
3. Wash your hands with soap and water.
4. You may see mild redness at the site when a patch is removed. This redness should go away over time. If irritation or itchiness continues, tell your doctor.

Other Information:

- Heat may cause too much medicine from a Neupro patch to pass through your skin. While you are wearing a NEUPRO patch, do not:
  - apply a heating pad to the application site area
  - take a hot bath

  - use a sauna
  - expose the application site to direct sunlight
- You may bathe, shower, or swim while wearing a NEUPRO patch. Water may loosen your NEUPRO patch. If a NEUPRO patch falls off, apply a new NEUPRO patch for the rest of the day. The following day, apply a new patch at your regular time.
- If you forget to apply a NEUPRO patch at the usual time, remove the used NEUPRO patch you are currently wearing and put on a new NEUPRO patch on a different area of skin. Then apply a new NEUPRO patch the next day at your regular time.
- If you develop a skin rash or irritation from the patch, avoid direct sunlight on the area until the skin heals because sun exposure could lead to changes of skin color.
- Do not cut or damage a NEUPRO patch.
- To avoid a possible burn on your skin, remove your NEUPRO patch before you have procedures called magnetic resonance imaging (MRI) or a cardioversion.

Distributed by:

SCHWARZ PHARMA, LLC
Mequon, WI 53092

PC4803
Rev. 06/06

PATIENT INFORMATION
NEUPRO® [NU pro]
(rotigotine transdermal system)

Rx Only

IMPORTANT: NEUPRO is for use on the skin only.

Read the Patient Information that comes with NEUPRO before you start using it and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. If you have any questions about NEUPRO, ask your doctor or pharmacist.

What is the most important information I should know about NEUPRO?

NEUPRO may make you very sleepy or cause you to fall asleep suddenly, and without warning while doing normal activities such as driving, talking with other people, watching TV, or eating. This can happen any time during treatment with NEUPRO.

- Do not drive, work on ladders, or do other dangerous activities while using NEUPRO until you know how NEUPRO affects you.
- If NEUPRO does make you very sleepy, or you fall asleep suddenly while doing normal activities, do not drive or do other dangerous activities until you talk with your doctor.

Tell your doctor if you fall asleep suddenly while doing normal activities or feel sleepier than normal.

Heat may cause too much medicine from a Neupro patch to pass through your skin. While you are wearing a NEUPRO patch, do not:

- **apply a heating pad to the application site area**
- **take a hot bath**
- **use a sauna**
- **expose the application site to direct sunlight**

What is NEUPRO?

NEUPRO is a type of medicine called a dopamine agonist. NEUPRO is a patch (transdermal delivery system) worn on the skin. It is used to treat the signs and symptoms of early-stage Parkinson's disease in adults.
NEUPRO has not been studied in children.

Who should not use NEUPRO?

Do not use NEUPRO if you are allergic to anything in it. See the end of this leaflet for a complete list of ingredients in NEUPRO.

NEUPRO contains a sulfite called sodium metabisulfate. Sulfites can cause life-threatening allergic reactions in people that are sensitive to sulfites. People with asthma are more likely to be sensitive to sulfites. If you have trouble breathing or swallowing while using NEUPRO, remove NEUPRO right away and call your doctor or get emergency care.

NEUPRO may not be right for you. Before starting NEUPRO tell your doctor about all of your health conditions including if you:

- are allergic to sulfites
- have asthma
- have blood pressure problems
- have heart problems
- are pregnant or breastfeeding or planning on becoming pregnant

Tell your doctor if you drink alcohol
Alcohol should be avoided while using NEUPRO. ALCOHOL and NEUPRO can interact and increase your chance of being sleepy or falling asleep suddenly while doing normal activities.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Some medicines may affect how NEUPRO works. NEUPRO may also affect how your other medicines work. **Especially tell your doctor if you take other medicines that can make you sleepy such as sleep medicines, antidepressants, or antipsychotics.**

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I use NEUPRO?

See the end of this leaflet for complete instructions "How to use and apply a NEUPRO patch."

- Use NEUPRO exactly as prescribed by your doctor.
- NEUPRO comes in 4 different size (dose) patches. Your doctor will probably start you on a low dose of NEUPRO. Your doctor will change the dose weekly until you are taking the right amount of medicine to control your symptoms. It may take several weeks before you reach the dose that controls your symptoms best. Do not stop or change your dose of NEUPRO without first talking with your doctor.
- Talk to your doctor often about your condition. **Do not stop or change your treatment with Neupro without talking to your doctor.**
- **Patients with Parkinson's disease may have an increased chance of getting a skin cancer called melanoma. People with Parkinson's disease should have a doctor check their skin for skin cancer regularly.**

What are the possible side effects of NEUPRO?

Possible serious side effects with NEUPRO include:

- **falling asleep while do normal activities.** See "What is the most important information I should know about NEUPRO?"
- **low blood pressure** that makes you feel dizzy, faint, sweaty, or have nausea. Stand up slowly when getting up from a sitting or lying position. Tell you doctor if you if you have symptoms of low blood pressure with NEUPRO.
- **fainting**
- **hallucinations** (seeing, hearing, or sensing things that are not real). The chance for hallucinations is higher in elderly patients with Parkinson's disease.
- **compulsive** behavior and trouble controlling strong urges such as:
  - gambling too much
  - increased sexual desire
  - repeating meaningless actions

Talk to your doctor if you or family members notice that you are having unusual urges

-

The most common side effects with NEUPRO are:

- nausea
- application site reaction
- drowsiness or sleepiness
- dizziness
- headache
- vomiting
- trouble sleeping (insomnia)

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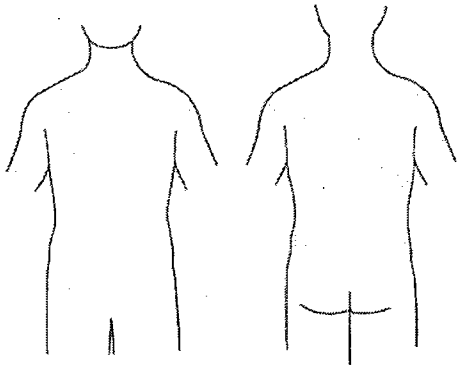

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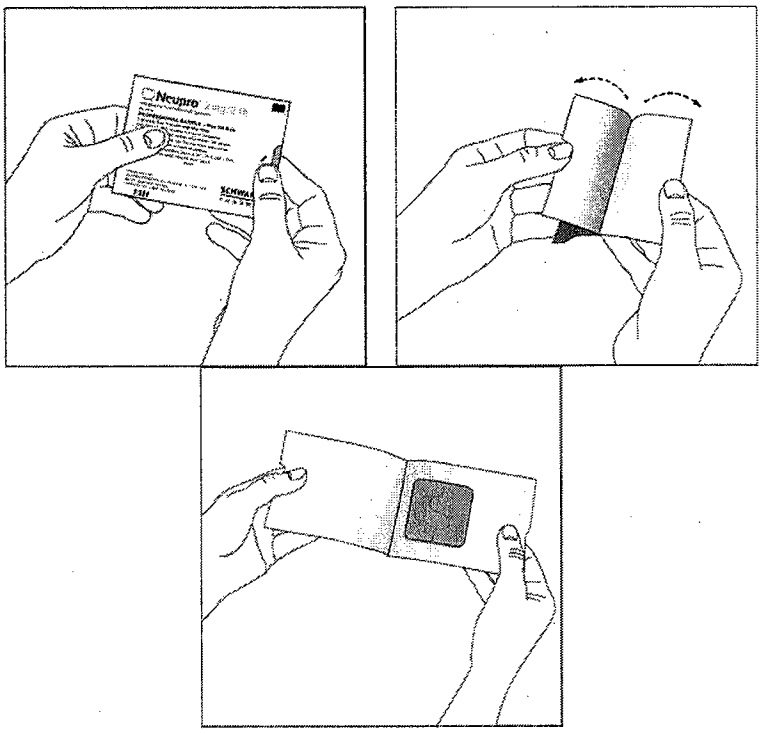

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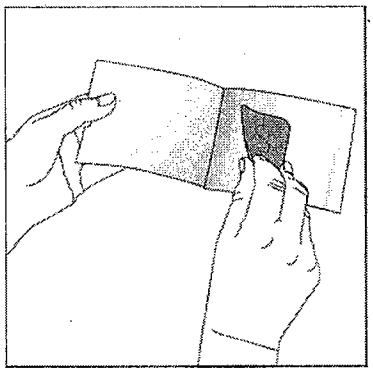
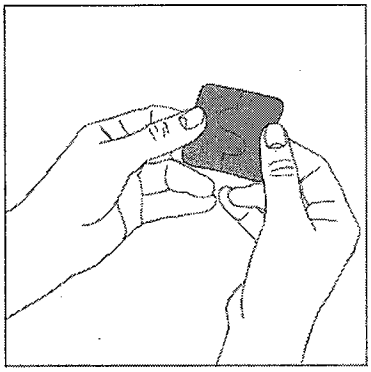


3. Hold the patch with both hands, with the protective liner on top.



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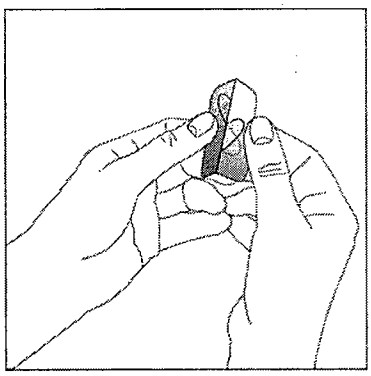

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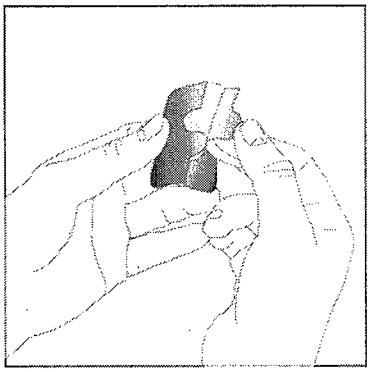

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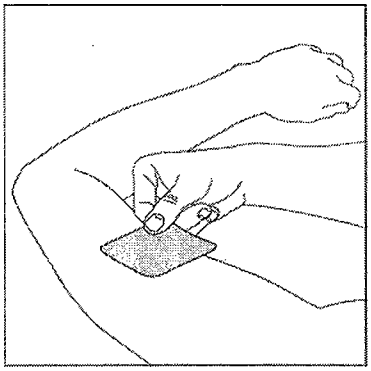

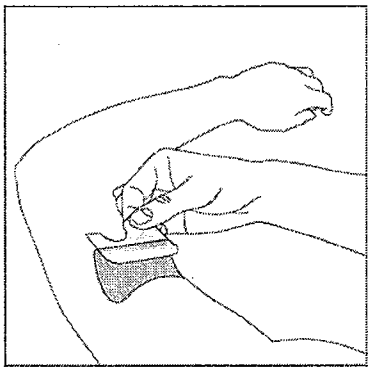

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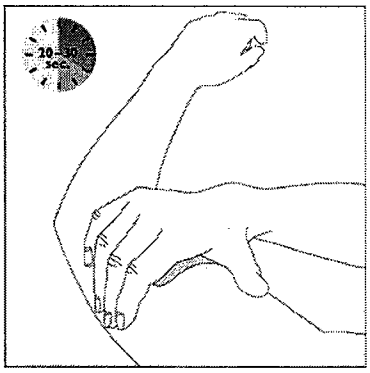

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