

1 Neupro®

2 (Rotigotine Transdermal System)

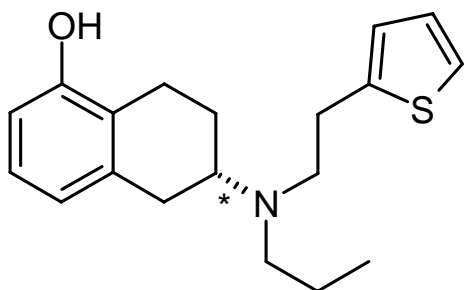
3 CONTINUOUS DELIVERY FOR ONCE-DAILY APPLICATION

4 **Rx Only**

5 DESCRIPTION

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

9 The chemical name of rotigotine is (6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-
10 naphthalenol. The empirical formula is C₁₉H₂₅NOS. The molecular weight is 315.48. The
11 structural formula for rotigotine is:



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13 The asterisk designates the chiral center.

14 Neupro is available in three strengths: 2, 4, and 6 mg/24 hours. Each transdermal system has a
15 release surface area of 10, 20, and 30 cm² and contains 4.5, 9, or 13.5 mg rotigotine,
16 respectively. See Table 1. The composition of the transdermal system per area unit is identical.

17 **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

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19 System Components and Structure

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

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24 Backing film
25 Drug matrix
26 Protective liner

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

36 **CLINICAL PHARMACOLOGY**

37 **Mechanism of Action**

38 Rotigotine is a non-ergoline D₃/D₂/D₁ dopamine agonist for the treatment of Parkinson's disease.
39 The precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown
40 although it is thought to be related to its ability to stimulate dopamine D₂ receptors within the
41 caudate-putamen in the brain. Rotigotine improved motor deficits in animal models of
42 Parkinson's disease (6-OHDA in rat and MPTP model in monkey) including when administered
43 transdermally

44 **Pharmacokinetics**

45 On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2
46 mg/cm²). Rotigotine is primarily eliminated in the urine as inactive conjugates. After removal of
47 the patch, plasma levels decreased with a terminal half-life of 5 to 7 hours. The pharmacokinetic
48 profile showed a biphasic elimination with an initial half-life of 3 hours.

49 **Absorption**

50 When single doses of 40 cm² systems are applied to the trunk, there is an average lag time of
51 approximately 3 hours until drug is detected in plasma, (range 1 to 8 hours). T_{min} occurs most
52 commonly between 0 to 7 hours post dose. T_{max} typically occurs between 15 to 18 hours post
53 dose but can occur from 4 to 27 hours post dose. However, there is no characteristic peak
54 concentration observed. Rotigotine displays dose-proportionality over a daily dose range of
55 2 mg/24 hours to 8 mg/24 hours.

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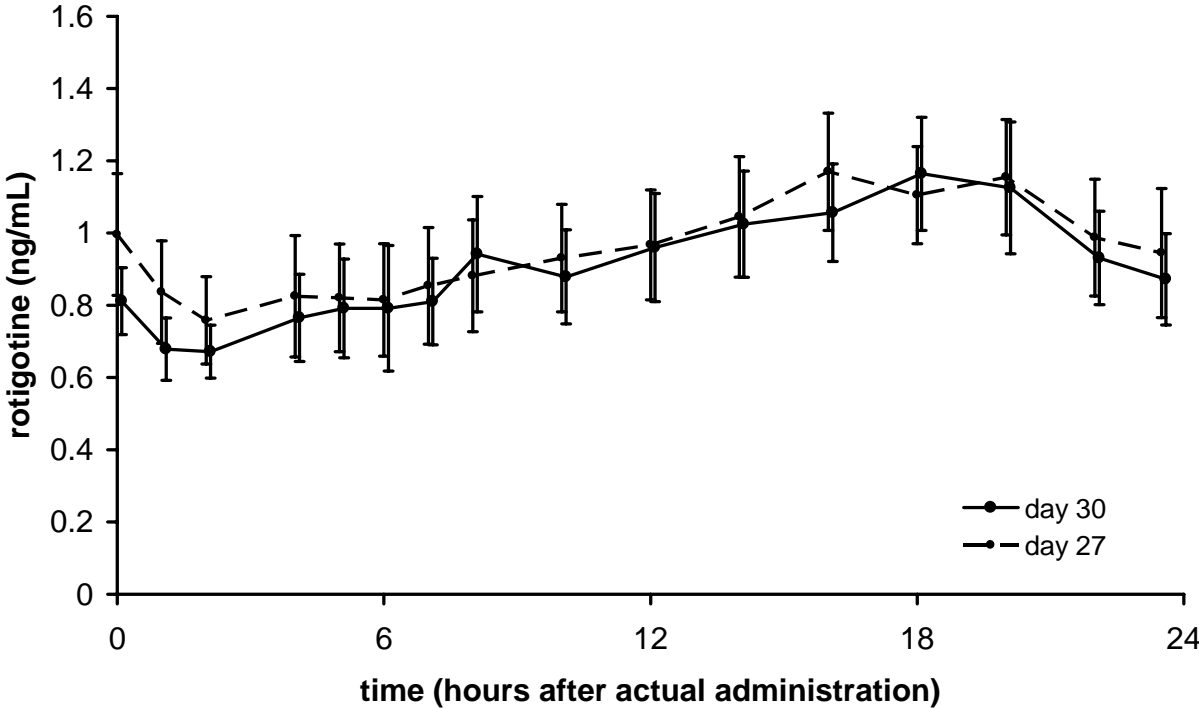
57 On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2
58 mg/cm²), independent of patch size. Similar absorption per cm² was observed in healthy subjects
59 and patients with early stage Parkinson's disease.

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

65 than 1% (abdomen vs hip) to 64% (shoulder vs thigh) with shoulder application showing higher
66 bioavailability.
67 Because rotigotine is administered transdermally, food should not affect absorption, and the
68 product may be administered without regard to the timing of meals.
69 In a 14-day clinical study with rotigotine administered to healthy subjects, steady-state plasma
70 concentrations were achieved within 2 to 3 days of daily dosing.

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

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78 **Distribution**

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

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

83 **Metabolism and Elimination**

84 Rotigotine is extensively metabolized by conjugation and N-dealkylation. After intravenous
85 dosing the predominant metabolites in human plasma are sulfate conjugates of rotigotine,
86 glucuronide conjugates of rotigotine, sulfate conjugates of the N-despropyl-rotigotine and

87 conjugates of N-desethienyl -rotigotine. Multiple CYP isoenzymes, sulfotransferases and two
88 UDP-glucuronosyltransferases catalyze the metabolism of rotigotine (See Drug Interactions)

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

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92 Rotigotine is primarily excreted in urine (~71%) as inactive conjugates of the parent compound
93 and N-desalkyl metabolites. A smaller proportion is excreted in feces (~11%). The major
94 metabolites found in urine were rotigotine sulfate (16% to 22% of the absorbed dose), rotigotine
95 glucuronide (11%-15%), and N-despropyl-rotigotine sulfate metabolite (14% to 20%) and N-
96 desethienylethyl-rotigotine sulfate metabolite (10% to 21%). Approximately 11% is renally
97 eliminated as other metabolites. A small amount of unconjugated rotigotine is renally eliminated
98 (<1% of the absorbed dose).

99 **Pharmacokinetics in Special Populations**

100 **Hepatic Insufficiency**

101 The effect of impaired hepatic function on the pharmacokinetics of rotigotine has been studied in
102 subjects with moderate impairment of hepatic function (Child Pugh classification – Grade B).
103 There were no relevant changes in rotigotine plasma concentrations. No dose adjustment is
104 necessary in subjects with moderate impairment of hepatic function. No information is available
105 on subjects with severe impairment of hepatic function. (See **PRECAUTIONS, Hepatic**
106 **Insufficiency**)

107 **Renal Insufficiency**

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

114 **Gender**

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

117 **Geriatric Patients**

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

121 **Pediatric Patients**

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

124 **Race**

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

127 **Adhesion**

128 Adhesion was examined in subjects with Parkinson's disease when patches were applied to
129 rotating sites. Similar results were observed for the 4 mg/24 hours (20 cm²), 6 mg/24 hours (30
130 cm²), and 8 mg/24 hours (40 cm²) patches. An adherence of $\geq 90\%$ of the patch surface was
131 observed in 71% to 82% of cases. A partial detachment of $>10\%$ was observed in 15% to 24% of
132 cases. A complete detachment of the patch was observed in 3% to 5% of cases.

133 **CLINICAL STUDIES**

134 The effectiveness of Neupro in the treatment of the signs and symptoms of early-stage idiopathic
135 Parkinson's disease was evaluated in three parallel group, randomized, double-blind placebo
136 controlled studies conducted in the U.S. and abroad. These studies were conducted in patients
137 who were not receiving concomitant dopamine agonist therapy and, who were either L-dopa
138 naïve or off L-dopa for at least 28 days prior to baseline and were never on L-dopa for more than
139 6 months. Patients were excluded from the study if they had a history of pallidotomy,
140 thalamotomy, deep brain stimulation, or fetal tissue transplant. Patients receiving selegiline,
141 anticholinergic agents, or amantadine must have been on a stable dose for at least 28 days prior
142 to baseline; they were to attempt to maintain that dose for the duration of the study.

143 The primary outcome assessment was the change from baseline for the combined scores for Part
144 II (activities of daily living component) plus part III (motor component) of the Unified
145 Parkinson's Disease Rating Scale (UPDRS). Part II of the UPDRS contains 13 questions relating
146 to activities of daily living that are scored from 0 (normal) to 4 (maximal severity) for a
147 maximum (worst) score of 52. Part III of the UPDRS contains 27 questions (for 14 items), each
148 scored 0 (normal) to 4 (maximal severity). Part III is designed to assess the severity of the
149 cardinal motor findings in patients with Parkinson's disease (e.g., tremor, rigidity, bradykinesia,
150 postural instability), scored for different body regions, and has a maximum (worst) score of 108.

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152 Dose-Response Study

153 This study was a randomized, double-blind, dose-response, multicenter, multinational study in
154 which 316 early stage Parkinson's Disease patients were assigned to treatment with either
155 placebo or one of several fixed doses (2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, or 8 mg/24
156 hours) of Neupro, given as 1, 2, 3, or 4 2-mg patches for a period up to 11 weeks. The patches
157 were applied to the upper abdomen and the sites of application were rotated on a daily basis.
158 Patients underwent a weekly titration (increasing the number of 2 mg/24 hours patches or
159 placebo patches at weekly intervals) over 4 weeks such that the target doses of Neupro were
160 achieved for all groups by the end of 3 weeks and were administered over the fourth week of the
161 titration phase. Patients then continued on treatment for a 7 week maintenance phase followed
162 by a down titration during the last week. Two back titrations by a single patch (i.e. 2 mg/24
163 hours decrement of Neupro or placebo) at a time were permitted for intolerable adverse events.

164 The mean age of patients was approximately 60 years (range 33 to 83 years; approximately 36 %
165 were ≥ 65 years) and the study enrolled more men (62 %) than women (39 %). Most patients (85
166 %) were Caucasian and most randomized patients (≥ 88 %) completed the full treatment period.

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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.

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178 **Table 2 Dose-Response Study: Mean Change in UPDRS (Parts II + III) from Baseline at**
179 **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

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182 North American Study

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

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

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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.

210 **Table 3 North American Study: Mean Change in UPDRS (Parts II + III) from Baseline at**
211 **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

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Foreign Multinational Study

217 This study was a randomized, double-blind, multinational, flexible Neupro dose (2 mg/24 hours,
218 4 mg/2 hours, 6 mg/24 hours, or 8 mg/24 hours), three arm, parallel group, study using a double-
219 dummy treatment in which 561 early stage, Parkinson's Disease patients were assigned to
220 treatment with either placebo or Neupro or active oral comparator in a ratio of 1: 2: 2 for a period
221 up to about 39 weeks. This study was conducted in up to 81 sites in many countries outside of
222 North America. Patches were applied to different body parts including upper or lower abdomen,
223 thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were to be rotated on a
224 daily basis. Treatment with a patch and placebo was given to all patients in a double-blinded
225 manner such that no one would know the actual treatment (i.e. Neupro, comparator, or placebo).
226 Patients underwent a weekly dose escalation of patch (consisting of 2 mg/24 hours increments of
227 Neupro or placebo) and a dose escalation of capsules of comparator or placebo over 13 weeks up
228 to a maximal dose of 8 mg/24 hours of Neupro depending on achieving optimal efficacy or
229 intolerability at a lower dose. Patients randomized to Neupro achieved the maximal dose of 8
230 mg/24 hours after a 4 week titration if maximal efficacy and intolerability had not occurred over
231 a 4 week titration period. Patients then received treatment over a 24 week maintenance phase
232 followed by a de-escalation over a period up to 12 days. A single back titration by a single patch
233 (i.e. 2 mg/24 hours decrement of Neupro or placebo) or capsule was permitted during the
234 titration phase for intolerable adverse events but was not permitted during the maintenance phase
235 (i.e. patients with intolerable adverse events had to discontinue from this study). Primary efficacy
236 data were collected after a treatment period of up to approximately 37 weeks of randomized
237 treatment.

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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.

244 Mean baseline combined UPDRS (Parts II + III) was similar across all groups (33.2 Neupro,
245 31.3 placebo, 32.2 comparator). Neupro treated patients experienced a mean change in the
246 combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 37 or
247 last visit for patients discontinuing early) of - 6.83, and placebo treated patients showed a mean
248 change from baseline of - 2.33 (see Table 4), a difference that was statistically significant.

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253 **Table 4 Foreign Multinational Study: Mean Change in UPDRS (Parts II + III) from**
254 **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

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256 **INDICATIONS AND USAGE**

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

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

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263 **CONTRAINDICATIONS**

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

266 **WARNINGS**

267 **Sulfite Sensitivity**

268 Neupro contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including
269 anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain
270 susceptible people. The overall prevalence of sulfite sensitivity in the general population is
271 unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in
272 nonasthmatic people.

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274 **Falling Asleep During Activities of Daily Living**

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

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

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

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

302 **Hallucinations**

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

308 **PRECAUTIONS**

309 **General**

310 Symptomatic Hypotension

311 Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic
312 regulation of blood pressure, resulting in postural hypotension, especially during dose escalation.
313 Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to a
314 postural challenge. For these reasons, Parkinson's patients being treated with dopaminergic
315 agonists ordinarily (1) require careful monitoring for signs and symptoms of postural
316 hypotension, especially during dose escalation, and (2) should be informed of this risk. (See
317 **PRECAUTIONS, Information for Patients**)

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

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

325 An analysis of the dose response study using a variety of adverse event terms suggestive of
326 orthostatic hypotension, including dizziness and postural dizziness, showed a 2 fold higher
327 incidence of these events with Neupro (22 %) vs placebo (11 %). This increased risk was
328 observed in a setting in which patients were very carefully titrated, and patients with clinically
329 relevant cardiovascular disease or symptomatic orthostatic hypotension at baseline had been
330 excluded from this study. The study showed a dose-related increased risk for mild-moderate
331 systolic orthostatic hypotension (decrease of ≥ 20 mm Hg) at the end of the titration period (after
332 4 weeks treatment) with the highest recommended 6 mg/24 hours Neupro dose (6 %) vs placebo
333 (3 %) or lower Neupro doses (2 mg/24 hours or 4 mg/24 hours 0 %). An increased dose-related
334 risk (3 % for 4 and 6 mg/24 hours Neupro; 2 % for placebo and 2 mg/24 hours Neupro) of
335 systolic orthostatic hypotension was also observed after 7 weeks of treatment.

336

337 Syncope

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

344

345 Elevation of Heart Rate and Blood Pressure

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

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

357 Weight Gain and Fluid Retention

358 Subjects taking Neupro had a higher incidence (3%) of substantial weight gain (more than 10%
359 of baseline weight) than placebo subjects (<1%). This weight gain was frequently associated
360 with the development of peripheral edema, suggesting that Neupro may cause substantial fluid
361 retention in some patients. Although the weight gain was usually well-tolerated in subjects
362 observed in clinical studies, it could cause greater difficulty in patients who may be especially
363 vulnerable to negative clinical consequences from fluid retention such as those with significant
364 congestive heart failure or renal insufficiency.

365 Dyskinesia

366 Neupro may potentiate the dopaminergic side effects of L-dopa and may cause and/or exacerbate
367 pre-existing dyskinesia. Dyskinesia was reported at a similar rate in patients treated with Neupro
368 (0.5%) or placebo (0.3%).

369 Hepatic Insufficiency

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

373 Application Site Reactions

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

377 In the Dose-Response study, ASRs exhibited a dose-response relationship for the highest
378 recommended Neupro dose (6 mg/24 hours) not only during the whole study period (placebo 19
379 %, 2 mg/24 hours 24 %, 4 mg/24 hours 21 %, 6 mg/24 hours 34 %) but also in separate analyses
380 of the titration period and of the maintenance period. ASRs as a cause for study discontinuation
381 also showed a dose-response increased risk for the whole study period for 6 mg/24 hours Neupro
382 vs other treatments (placebo 0%, 2 mg/24 hours 2 %, 4 mg/24 hours 0 %, 6 mg/24 hours 3 %).

383 Of ASRs in Neupro treated patients, most were mild or moderate in intensity. The signs and
384 symptoms of these reactions generally were localized erythema, edema, or pruritus limited to the
385 patch area and usually did not lead to dose reduction. About 5% of patients treated with Neupro
386 in these studies discontinued as a result of an ASR. Generalized skin reactions (e.g., allergic rash,
387 including erythematous, macular-papular rash, or pruritus), have been reported at lower rates
388 than ASRs during the development of Neupro.

389 In a clinical study to investigate the cumulative human skin irritation of Neupro, daily rotation of
390 Neupro application sites has been shown to reduce the incidence of ASRs in comparison to
391 repetitive application to the same site. In a clinical study investigating the skin sensitizing
392 potential of Neupro in 221 healthy subjects, no case of contact sensitization was observed.
393 Localized sensitization reactions were observed in a study in normal volunteers with continuous
394 rotating transdermal system application to a 2.5 cm² system, (0.5 mg/24 hours), after induction of
395 maximal irritational stress by repetitive transdermal system application to the same site. If a
396 patient reports a persistent application site reaction (of more than a few days), reports an increase
397 in severity, or reports a skin reaction spreading outside the application site, an assessment of the
398 risks and benefits for the individual patient should be conducted. If a generalized skin reaction
399 associated with the use of Neupro is observed, Neupro should be discontinued.

400

401 Melanoma

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

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

409

410 **Magnetic Resonance Imaging and Cardioversion**

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

413 **Heat Application**

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

419 **Events Reported with Dopaminergic Therapy**

420 **Withdrawal-Emergent-Hyperpyrexia and Confusion**

421 Although not reported with Neupro, a symptom complex resembling the neuroleptic malignant
422 syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness,
423 rhabdomyolysis, and/or autonomic instability), with no other obvious etiology, has been reported
424 in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy.
425 Therefore it is recommended that the dose be tapered at the end of Neupro treatment as a
426 prophylactic measure (See **DOSAGE AND ADMINISTRATION** for guidance on
427 discontinuing Neupro).

428 **Fibrotic complications**

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

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

435 **Binding to Melanin**

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

439 **Information for Patients**

440 Patients should be instructed to use Neupro only as prescribed.

441 Patients should be asked about sensitivity to sulfites. Advise patient that Neupro contains sodium
442 metabisulfite, which may cause allergic-type reactions including anaphylactic symptoms and life
443 threatening or less severe asthmatic episodes in certain susceptible people.

444 Patients should be alerted to the potential sedating effects associated with Neupro, including
445 somnolence and particularly to the possibility of falling asleep while engaged in activities of
446 daily living. Since somnolence is a frequent adverse event with potentially serious consequences,
447 patients should neither drive a car nor engage in other potentially dangerous activities until they

448 have gained sufficient experience with Neupro to gauge whether or not it affects their mental
449 and/or motor performance adversely. Patients should be advised that if increased somnolence or
450 new episodes of falling asleep during activities of daily living (e.g., watching television,
451 passenger in a car, etc.) are experienced at any time during treatment, they should not drive or
452 participate in potentially dangerous activities until they have contacted their physician. If
453 patients have previously experienced somnolence and/or have fallen asleep without warning
454 prior to use of Neupro, they should be advised not to drive, operate machinery, or work at
455 heights during treatment.

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

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

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

469 Care should be used to avoid dislodging the patch while showering, bathing or during physical
470 activity. After applying Neupro, patients or caregivers should wash their hands to remove any
471 drug and should be careful not to touch their eyes or any objects. If the edges of the patch lift,
472 Neupro may be taped down with bandage tape. If the patch detaches, a new one may be applied
473 immediately to a different site. The patient should then change the patch according to their
474 regular schedule.

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

483 If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should
484 be avoided until the skin heals. Exposure could lead to changes in the skin color.

485 Neupro should always be removed slowly and carefully to avoid irritation. After removal the
486 patch should be folded over so that it sticks to itself and should be discarded. After removal the
487 application site should be washed with soap and water to remove any drug or adhesive. Baby or
488 mineral oil may be used to remove any excess residue. Alcohol and other solvents (such as nail
489 polish remover) may cause skin irritation and should not be used. Neupro patients or caregivers
490 should wash their hands to remove any drug and should be careful not to touch their eyes or any
491 objects.

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

494 Patients should be informed that hallucinations can occur during treatment with Neupro.
495 Although not reported with Neupro at a greater frequency than with placebo, patients using
496 dopamine agonists may develop postural (orthostatic) hypotension with or without symptoms
497 such as dizziness, nausea, syncope, and sweating. Parkinson's disease patients, in addition,
498 appear to have an impaired capacity to respond to a postural challenge and orthostatic
499 hypotension may occur more frequently during initial therapy or with an increase in dose at any
500 time.

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

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

508 Patients should be instructed not to cut or damage Neupro.

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

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

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

515 There have been reports of patients experiencing intense urges to gamble, increased sexual urges,
516 and other intense urges while taking one or more of the medications generally used for the
517 treatment of Parkinson's disease, including Neupro. Although it is not proven that the
518 medications caused these events, these urges were reported to have stopped in some cases when
519 the dose was reduced or the medication was stopped. Prescribers should ask patients about the
520 development of new or increased gambling urges, sexual urges or other urges while being treated
521 with Neupro. Patients should inform their physician if they experience new or increased
522 gambling urges, increased sexual urges or other intense urges while taking Neupro. Physicians
523 should consider dose reduction or stopping the medication if a patient develops such urges while
524 taking Neupro.

525

526 **Drug Interactions**

527 **CYP Interactions**

528
529 *In vitro* studies indicate that multiple CYP-isoforms are capable of catalyzing the metabolism of
530 rotigotine. In human liver microsomes, no extensive inhibition of the metabolism of rotigotine
531 was observed when co-incubated with CYP isoform specific inhibitors. If an individual CYP
532 isoform is inhibited, other isoforms can catalyze rotigotine metabolism.

533

534 Rotigotine, the 5-O-glucuronide and its desalkyl and monohydroxy metabolites were analyzed
535 for interactions with the human CYP isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and
536 CYP3A4 *in vitro*. Based on these results, no risk for inhibition of CYP1A2, CYP2C9 and

537 CYP3A4 catalyzed metabolism of other drugs is predicted at therapeutic rotigotine
538 concentrations. There is a low risk of inhibition of CYP2C19 and CYP2D6 catalyzed metabolism
539 of other drugs at therapeutic concentrations.

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

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

545 **Protein Displacement, Warfarin**

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

548 **Digoxin**

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

552 **Cimetidine**

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

556 **L-dopa**

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

560 **Dopamine Antagonists**

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

563 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

564 *Carcinogenesis*

565 Two-year subcutaneous carcinogenicity studies of rotigotine were conducted in CD-1 mice at
566 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
567 both studies rotigotine was administered once every 48 hours. No significant increases in tumors
568 occurred in the mouse study at doses up to 12 times the maximum recommended human dose
569 (MRHD) of 6 mg/24 hours.

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

576

577 *Mutagenesis*

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

582

583 *Infertility*

584 When administered to female Sprague-Dawley rats prior to and during mating and through
585 gestation day 7, rotigotine disrupted implantation at subcutaneous (s.c.) doses of 1.5 mg/kg/day
586 (2 times the maximum recommended human dose (MRHD) on a mg/m² basis) or greater. There
587 was no no-effect dose. In male rats treated from 70 days prior to and through mating, there was
588 no effect on fertility; however, a decrease in epididymal sperm motility was observed at 15
589 mg/kg. The no-effect dose was 5 mg/kg/day (8 times the MRHD on a mg/m² basis). Rotigotine
590 was administered to female CD-1 mice at s.c. doses of 10, 30, and 90 mg/kg/day (8 to 73 times
591 the MRHD on a mg/m² basis) from 2 weeks until 4 days before mating and then at a dose of 6
592 mg/kg/day (all groups) (5 times the MRHD on a mg/m² basis) from 3 days before mating until
593 gestation day 7; disrupted implantation was observed at all doses. The effects on implantation are
594 thought to be due to the prolactin-lowering effect of rotigotine. In humans, chorionic
595 gonadotropin, not prolactin, is essential for implantation.

596

597 **Pregnancy**

598 **Pregnancy Category C**

599 In subcutaneous studies in Sprague-Dawley rats and CD-1 mice, rotigotine was shown to have
600 adverse effects on embryo-fetal development. Rotigotine given to pregnant rats during
601 organogenesis (0.5, 1.5 or 5 mg/kg/day on gestation days 6 through 17) resulted in increased
602 fetal death at all doses. The lowest effect dose was 0.8 times the MRHD on a mg/m² basis. This
603 effect is thought to be due to the prolactin-lowering effect of rotigotine. Rotigotine given to
604 pregnant mice during organogenesis (10, 30 or 90 mg/kg/day on gestation days 6 through 15)
605 resulted in an increased incidence of skeletal retardation at 30 and 90 mg/kg/day, and an increase
606 in fetal death at 90 mg/kg/day. No effects were observed at 10 mg/kg/day (8 times the MRHD
607 on a mg/m² basis). Rotigotine given to pregnant Himalayan rabbits during organogenesis (1, 5, or
608 15 mg/kg/day (3-49 times the MRHD on a mg/m² basis) on gestation days 6 through 20) had no
609 effects on embryo-fetal development; however, the study was not conducted at sufficiently high
610 doses. In a pre- and postnatal development study, Sprague-Dawley rats were administered 0.1,
611 0.3 or 1 mg/kg/day from gestation day 6 through postnatal day 21. Rotigotine impaired growth
612 and development of offspring during lactation and produced neurobehavioral abnormalities in
613 offspring at 1 mg/kg/day. When offspring were mated, growth and survival of their offspring
614 were adversely affected. No adverse effects were observed at 0.3 mg/kg/day (0.5 times the
615 maximum recommended human dose on a mg/m² basis).

616

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

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

620 **Nursing Mothers**

621 Rotigotine decreases prolactin secretion in humans and could potentially inhibit lactation.
622 Studies in rats have shown that rotigotine and/or its metabolite(s) is excreted in breast milk. It is
623 not known whether rotigotine is excreted in human breast milk. Because of the possibility that
624 rotigotine may be excreted in human milk, and because of the potential for adverse reactions in
625 nursing infants, a decision should be made whether to discontinue nursing or to discontinue the
626 drug, taking into account the importance of the drug to the mother.

627 **Pediatric use**

628 Safety and effectiveness in pediatric patients have not been established.

629 **Geriatric use**

630 Of the subjects treated with Neupro in clinical studies for treatment of early-stage Parkinson's
631 disease, 42% were 65 years old and over, and 9% were 75 and over. No overall differences in
632 safety or effectiveness were observed between these subjects and younger subjects, and other
633 reported clinical experience has not identified differences in responses between the elderly and
634 younger patients, but greater sensitivity of some older individuals cannot be ruled out.

635 No overall differences in plasma levels of rotigotine were observed between patients who were
636 65 to 80 years old compared with younger patients receiving the same rotigotine doses. (See
637 **CLINICAL PHARMACOLOGY, Geriatric Patients**)

638 **ADVERSE REACTIONS**

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

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

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

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

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

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

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

665

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

670

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

671 NOS=not otherwise specified

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

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

679 Dose-Related Adverse Events

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

686

687

688 **Table 6 Incidence (%) of Neupro Dose-Related Treatment-Emergent Adverse Events**
689 **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

690

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

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

730 **Hearing and vestibular disorders:** *infrequent* – tinnitus

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

733 **Hematologic disorders:** *infrequent* – thrombocytopenia

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

735 **Metabolic and nutritional disorders:** *frequent* – weight increase

736 **Psychiatric disorders:** *infrequent* –paranoid reaction, psychosis

737 **Skin and appendage disorders:** *frequent* –pruritus

738 **Urinary system disorders:** *frequent* – urinary incontinence

739 **Vascular disorders:** *frequent* – purpura

740 **Vision disorders:** *infrequent* – photopsia

741

742 OVERDOSAGE

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

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

747 Overdose Management

748 There is no known antidote for overdosage of dopamine agonists. In case of suspected overdose,
749 the transdermal system(s) should immediately be removed from the patient. Concentrations of
750 rotigotine decrease after patch removal. The terminal half-life of rotigotine is 5 to 7 hours. If it is
751 necessary to discontinue use of rotigotine after overdose, it should be discontinued gradually to
752 prevent neuroleptic malignant syndrome. (See **PRECAUTIONS**) The daily dose should be
753 reduced by 2 mg/24 hours with a dose reduction preferably every other day, until complete
754 withdrawal of rotigotine is achieved. Before completely stopping use of Neupro in the event of
755 an overdose, please consult the **DOSAGE AND ADMINISTRATION** section.

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

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

762 DOSAGE AND ADMINISTRATION

763 Initiation of Therapy

764 Neupro should be started at 2 mg/24 hours. Based upon individual patient clinical response and
765 tolerability, Neupro dosage may be increased weekly by 2 mg/24 hours if tolerated and if
766 additional therapeutic effect is needed. The lowest effective dose was 4 mg/24 hours. The

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

774 **Administration of transdermal system**

775 Neupro is applied once-a-day. The adhesive side of the transdermal system should be applied to
776 clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper
777 arm. The transdermal system should be applied at approximately the same time every day, at a
778 convenient time for the patient. Because Neupro is administered transdermally, food is not
779 expected to affect absorption and it can be applied irrespective of the timing of meals. No dosage
780 adjustment is necessary for patients who have moderate impairment of hepatic function or mild
781 to severe impairment of renal function.

782 The application site for Neupro should be moved on a daily basis (for example, from the right
783 side to the left side and from the upper body to the lower body). Neupro should not be applied to
784 the same application site more than once every 14 days and should not be placed on skin that is
785 oily, irritated, or damaged, or where it will be rubbed by tight clothing. If it is necessary to apply
786 Neupro to a hairy area, the area should be shaved at least 3 days prior to Neupro application. The
787 system should be applied immediately after opening the pouch and removing the protective liner.
788 The system should be pressed firmly in place for 20 to 30 seconds, making sure there is good
789 contact, especially around the edges. If the patient forgets to replace Neupro, or if the
790 transdermal system becomes dislodged, another transdermal system should be applied for the
791 remainder of the day.

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

795

796 ***Animal Toxicology***

797 *Retinal Pathology: Albino rats:* Retinal degeneration was observed in albino rats in the 6-month
798 toxicity study at the highest dose tested. Retinal degeneration was not observed in the 2-year
799 carcinogenicity studies in albino rat (at plasma exposures (AUC) up to 5 to 9 times the plasma
800 AUC in humans at the MRHD of 6 mg/24 hours) and albino mouse, or in monkeys treated for 1
801 year. The potential significance of this effect in humans has not been established, but cannot be
802 disregarded because disruption of a mechanism that is universally present in vertebrates (i.e.,
803 disk shedding) may be involved.

804

805 **HOW SUPPLIED**

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

807

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

808

809 Each transdermal system is packaged in a separate pouch.

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

811 2 mg/24 hours 7 transdermal systems NDC # 0091-6486-21

812 2 mg/24 hours 30 transdermal systems NDC # 0091-6486-01

813 4 mg/24 hours 7 transdermal systems NDC # 0091-6487-21

814 4 mg/24 hours 30 transdermal systems NDC # 0091-6487-01

815 6 mg/24 hours 7 transdermal systems NDC # 0091-6488-21

816 6 mg/24 hours 30 transdermal systems NDC # 0091-6488-01

817 **Storage**

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

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

821 Apply the transdermal system immediately upon removal from the pouch.

822 Manufactured for:

823 SCHWARZ PHARMA, LLC

824 Mequon, WI 53092, USA

825 By:

826 LTS Lohmann Therapie System AG

827 Lohmannstrasse 2

828 D-56626 Andernach, Germany

829 PC4862

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