

Neupro (rotigotine) transdermal STEPS

Recommendation

There are presently two oral non-ergot dopamine agonists available (pramipexole-Mirapex® and ropinirole-Requip®). The three studies that are the basis of the FDA approval were funded by Schwarz Pharma and showed efficacy over placebo and a fourth study showed non-inferiority to comparative treatment. Neupro® (rotigotine) is possibly an alternative to patients who are unable to swallow pills although others can be crushed. There is no evidence that safety or efficacy of rotigotine is better than either pramipexole or ropinirole. Both oral agents are administered up to three times a day; rotigotine is applied once daily. Rotigotine is only approved in early-stage Parkinson's disease at this point, thus other dopamine agonists should remain first line when a dopamine agonist is prescribed. Neupro's place in Parkinson's treatment is difficult to evaluate at this point. Head to head studies don't allow comparison of side effect profiles and rotigotine has a high incidence of transdermal related reactions. Due to its limited usage history present therapies should be considered first and rotigotine only after conventional treatments fail to adequately maintain functionality for the patient or when side effects of other therapies require a treatment alternative.

Approved by the FDA May 9, 2007 (Schwarz Pharma)

Neupro is a nonergoline D3/D2/D1 dopamine agonist for the treatment of Parkinson's disease. The exact mechanism of action is unknown, but it is thought to relate to its ability to stimulate dopamine D2 receptors within the caudate-putamen in the brain.

Indications

Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson disease. *The manufacturer is seeking FDA approval for advanced Parkinson's disease and restless legs syndrome.*

Safety — (new medication)

Neupro may be confused with Neupogen.

Neupro does not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 or CYP3A4 in vitro. There are no interactions with warfarin, digoxin, cimetidine or L-dopa in pharmacokinetic studies. There is a possibility that dopamine antagonist, such as antipsychotics or metoclopramide could decrease effectiveness of Neupro.

Contraindication

Neupro is contraindicated in patients with hypersensitivity to rotigotine or the components of the transdermal system.

Warnings/Precautions

Sulfite Sensitivity

Neupro contains sodium metabisulfite, which can cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible patients.

Sleep Attacks

Reports of patients treated with Neupro falling asleep while engaging in activities have been reported. It is significant the some of these events have been reported as late as one year after initiation of therapy. Patients should take precautions and be advised of the potential for "sleep attack" and its risk.

MRI/cardioversion

To avoid skin burns Neupro should be removed prior to a MRI or cardioversion. The backing layer of Neupro contains aluminum.

Hallucinations

In the three studies in patients with early-stage Parkinson's disease (patients 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. One of the Neupro patients and none of the placebo patients discontinued treatment due to the hallucinations.

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Syncope

Patients should be alerted to the possibility of syncope. In studies the incidence in patients receiving Neupro (1%) was no greater than the incidence in those receiving placebo (1%). However, the studies excluded patients with clinically relevant cardiovascular disease. Therefore, patients with severe cardiovascular disease should be treated with caution.

Postural hypotension

This was noted in clinical trials orthostatic hypotension was noted. Patients should be informed of the risk because Parkinson's disease patients, in addition, may have an impaired capacity to respond to the postural challenges. Results depend on method used to evaluate and dosages.

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

Dyskinesia was reported at a similar rate in patients treated with Neupro (0.5%) or placebo (0.3%).

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. It is unknown whether increased incidence is due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear. Therefore, providers are advised to monitor for melanomas.

Renal:

No dosage adjustment is needed in patients with mild to severe renal impairment.

Hepatic:

No dosage adjustment is needed in patients with moderate impairment of hepatic function. The pharmacokinetics of rotigotine has not been studied in patients with severe hepatic impairment.

Children:

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

Pregnancy: Category Risk Factor C

Nursing Mothers: Rotigotine decrease prolactin secretion in humans and could potentially inhibit lactation. Studies in rats show it is excreted in breast milk.

Tolerability =/— (due to application reactions)

The most common adverse reactions ($\geq 5\%$ incidence) in the clinical trials were nausea, application-site reaction, drowsiness or sleepiness, dizziness, headache, vomiting, and trouble sleeping.

The most common adverse effects leading to discontinuation of therapy were application site reactions (5%), nausea (2%), and vomiting (1%). During the titration phase the dopaminergic adverse effects of nausea, vomiting and somnolence were more frequent.

Neupro may potentiate the dopaminergic side effects of L-dopa and may cause and/or exacerbate pre-existing dyskinesia. In the clinical trials, the dyskinesia was similar in patients on Neupro (0.5%) vs. placebo (0.3%).

Heat application has been shown to increase transdermal absorption. Patients should be advised to avoid exposing the patch to external sources of direct heat.

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Efficacy =

The efficacy of rotigotine transdermal in the treatment of the signs and symptoms of early-stage idiopathic Parkinson disease was evaluated in 3 parallel-group, randomized, double-blind, placebo-controlled studies conducted in the United States and abroad. These studies were conducted in patients who were not receiving concomitant dopamine agonist therapy and who were either levodopa naive or off levodopa for at least 28 days prior to baseline and were never on levodopa 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.

Title	Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomized controlled trial. ⁵
Objective	To determine efficacy and safety of transdermal rotigotine in patients with advanced Parkinson disease in comparison with placebo or pramipexole
Design	Multicenter, double-blind, double-dummy placebo-controlled and pramipexole controlled, three arm, parallel group study. Rotigotine was assessed for superiority versus placebo and non-inferiority versus pramipexole.
Methods	Patients were randomly assigned in a 2:2:1 ratio for rotigotine, pramipexole, and placebo in a double-blind, double-dummy fashion. A titration phase of up to 7 weeks was implemented to determine optimum efficacy and tolerability of each patient. Rotigotine 4 mg/24 hour was the initial dose and could be increased in weekly increments of 2 mg/24 hours up to a maximum dose of 16 mg/24 hours. Pramipexole 0.375 mg/day was the initial dose for the first week followed by 0.75 mg/day for the second week. Doses for pramipexole were increased in weekly increments of 0.75 mg up to a maximum dose of 4.5 mg/day (in three divided doses). Medication back titration was permitted in the titration phase. After reaching optimum doses, patients were entered into a 16 week maintenance phase on fixed doses followed by a dose-de-escalation phase and safety follow-up period. Two primary endpoints were chosen based on regulatory requirements of FDA and EMEA. Change from baseline to end of maintenance period in absolute time spent off, and proportion of patients with 30% or more reduction in absolute off time from baseline to end of maintenance period.
Results	Out of 506 randomized patients, approximately 15% of pramipexole-treated subjects, 11% of rotigotine-treated subjects, and 26% of placebo treated subjects discontinued the study before the end of the maintenance period. Adverse events accounted for discontinuation in 7%, 5%, and 5% of pramipexole, rotigotine, and placebo groups respectively. The change from baseline to end of maintenance period in absolute off time was -2.5 h with rotigotine, -2.8 h with pramipexole, and -0.9 h with placebo. The proportion of patients with 30% or more reduction in absolute off time from baseline to end of the maintenance period was 67% with pramipexole, 59.7% with rotigotine, and 35% with placebo.
Conclusion	Rotigotine was non-inferior to pramipexole in change in absolute off time but was unable to demonstrate non-inferiority in terms of proportion of patients with 30% or more reduction
Comments	Schwarz Pharma funded the study and provided statistical analysis and editorial assistance of the manuscript

Neupro (rotigotine) transdermal STEPS

Title	Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease ²
Objective	To compare safety and efficacy of rotigotine transdermal system versus placebo in patients with early-stage, idiopathic Parkinson disease (PD)
Design	Multicenter (50 sites in US and Canada), randomized, double-blind, placebo-controlled, two-arm, parallel-group study. The study period consisted of a 4 week pretreatment period, a titration period up to 3 weeks, a maintenance period of 24 weeks, and a down-titration, 4 week follow-up.
Methods	Patients with early-stage, idiopathic PD were randomized to receive rotigotine (n=181) or placebo (n=96). Demographic characteristics of subjects included a mean age of 63 (range 32 to 86 with 45% ≥ 65, mean years since diagnoses of 1.4, percent men 64%, percent Caucasian 96%, and percent previously on anti-PD drugs in past 28 days 31%. Subjects were allowed to continue anti-PD meds provided they were on a stable dose in the 4 week pretreatment phase with the exception of dopamine agonists. After a 4 week pretreatment/screening phase, dose was titrated to an optimal dose every week in increments of 2 mg/24 hour from a starting dose of 2 mg/24 hours or placebo. A 24 week maintenance phase was begun upon reaching the optimal dose that was tolerable. At the end of the maintenance phase, all patients were down-titrated every 2 days to a dose of 2 mg/24 hours. Patients were offered the option to enroll in an open-label extension after a 28 day follow-up after the end of their maintenance phase. The primary efficacy endpoint was the change in the sum of scores from the Activities of Daily Living (ADL) and the Motor Examination of the United Parkinson Disease Rating Scale (UPDRS). Responders were defined as subjects with a 20% decrease in the sum of scores. Safety assessments were also assessed.
Results	A higher number of drop-outs were noted in the rotigotine arm during the study (22% vs 16%). The optimal rotigotine dose was 6 mg/24 hours in the majority of subjects (n=115). At the end of the maintenance period, subjects in the placebo group had a mean increase in UPDRS part II and III of 1.39 (+/- 0.956), while the rotigotine group had a mean decrease of 3.98 (+/-0.707). A responder analysis was higher for rotigotine versus placebo (48% vs 19%). Rotigotine was discontinued due to adverse effects in 14% of rotigotine subjects versus 6% of placebo. Adverse events in the rotigotine group that were 5% or greater than placebo included application site disorders (44% vs 12%), accident NOS (8% vs 2%), dizziness (19% vs 13%), headache (16% vs 9%), nausea (41% vs 17%), vomiting (9% vs 1%), dyspepsia (7% vs 2%), somnolence (33% vs 20%), insomnia (9% vs 3%). Withdrawal or rebound effects were not noted in the down-titration or follow-up period.
Conclusion	Rotigotine improved UPDRS part II and III scores over a 6 month period versus placebo when given to early-stage, idiopathic PD subjects.
Comments	Schwarz Pharma sponsored the study and participated in the design of the study, collection, management and analysis of data, and review and approval of manuscript. Subjects with renal, hepatic, or cardiac dysfunction were excluded from this study.

Neupro (rotigotine) transdermal STEPS

Title	A controlled trial of rotigotine monotherapy in early Parkinson's disease ³
Objective	To determine the efficacy, safety, and tolerability of rotigotine in patients with early-stage, idiopathic PD who had not previously received dopamine therapy
Design	Multicenter (36 sites), randomized, double-blind, placebo-controlled, five-arm, parallel-group study.
Methods	Two hundred forty two subjects were randomized 1:1:1:1:1 to receive placebo, rotigotine 4.5 mg, 9 mg, 13 mg, or 18 mg. A rotigotine patch containing 4.5mg is the commercial product that delivers 2mg/24 hours. All subjects received 4 patches for blinding purposes. The mean age of subjects was 60.5-62.3 with the mean years since diagnosis ranging from 1.1-1.5 years. The majority of subjects were Caucasian (>90%) males (>50%). Selegiline, amantadine, or anticholinergic agents were allowed to be continued if at a stable dose within the 4 week screening period. The study period included a 4 week screening period, a 4 week double-blind titration period, a 7 week maintenance period, a 1 week dose de-escalation period, and a 2 week safety follow up period without study drug. The primary efficacy endpoint was the change in the sum of the UPDRS part II and III (ADL and motor examination) between baseline and the end of the maintenance period (11 weeks). Safety assessments were conducted throughout the study.
Results	<p><u>Safety and tolerability</u></p> <p>Thirty six subjects withdrew from the study due to adverse effects although no differences were seen between groups. The main reason for discontinuation was skin reaction (n=8) although there were two cases of sudden onset of sleep in individuals while driving. Adverse events that were noted to be 5% greater in the active treatment groups included nausea (47% vs 15%), application site reactions (39% vs 21%), dizziness (24% vs 13%), somnolence (22% vs 4), insomnia (19% vs 11%), vomiting (16% vs 2%), fatigue (15% vs 2%) and peripheral edema (5% vs 0%). These effects were not dose related and with the exception of skin reactions, were not causes of withdrawal from the study.</p> <p><u>Efficacy</u></p> <p>The mean dosage of subjects in the active treatment arms was not available for the trial data but 60-75% of subjects completed the study at the target dose. The mean change in the sum of the UPDRS part II and III between baseline and end of maintenance period was -0.29 for placebo, -1.20 for 4.5 mg, -3.13 for 9.0 mg, -5.09 for 13.5 mg, and -5.30 for 18.0 mg. Treatment effects were statistically significant versus placebo at 11 weeks for 13.5 mg and 18.0 mg.</p>
Conclusion	Rotigotine administered transdermally at doses ranging from 4.5 mg up to 18.0 mg over a period of 11 weeks in early-stage, idiopathic PD is safe and tolerable. A statistical difference was noted for both 13.5 mg and 18.0 mg versus placebo when given over 11 weeks.
Comments	Schwarz Pharma sponsored the study but the role outside of funding was not stated. Subjects with cardiac abnormalities were excluded from this study. The 9.0 mg dose was statistically significant at week 7 however, the effects decreased from weeks 7 to 11 and statistical significance was not found at week 11. A plateau in therapeutic efficacy appears to be present between 13.5 mg and 18.0 mg. This is likely the basis for the absence of a commercial product delivering 18.0 mg.

Neupro (rotigotine) transdermal STEPS

Title	Advanced Parkinson disease treated with rotigotine transdermal system: PREFER study ⁴
Objective	To determine efficacy and safety of rotigotine in subjects with advanced PD with greater than 2.5 hours of daily off time.
Design	Multicenter (54 sites in US and Canada), randomized, double-blind, placebo-controlled, three-arm, parallel-group study.
Methods	Three hundred fifty one subjects were randomized 1:1:1 to receive placebo, rotigotine 8 mg/24 hour, or rotigotine 12 mg/24 hour. The mean age of subjects was 64.5-66.5 years with mean years since diagnosis of PD of 7.7-7.8 years. At baseline, subjects experienced an average of 6.7 hours of daily off time and had a mean MMSE of 28.5-28.9. The mean daily dose of levodopa in subjects was 740-760 mg/day. Anticholinergic medications, CNS medications, selegiline, and amantadine were permitted in the trial provided subjects were stable for at least 28 days prior to study entry. Dopamine agonists, COMT inhibitors, CNS stimulants, centrally acting anti-hypertensives and neuroleptics were not allowed for at least 28 days prior to study entry. All subjects were started on 4 mg/24 hours or placebo and titrated up to optimal doses over a 5 week period in 2mg /24 hour weekly increments to target doses of 8 mg or 12 mg respectively. A 24 week maintenance period followed this titration period. At the end of the maintenance period, a dose de-escalation period was undertaken in which subjects decreased their dose by 2 mg/24 hours every 2 days until they reached the starting dose of 4 mg/24 hours. At that point, all subjects were allowed to enter an open-label treatment phase. The primary efficacy endpoint was the change in the absolute number of daily hours in the off state from baseline to the end of the 24 week maintenance. A secondary efficacy endpoint was the percent of responders, defined as those achieving a 30% improvement in absolute time spent in daily off time. Safety assessments were performed throughout the study.
Results	<p><u>Safety and tolerability:</u></p> <p>Forty six subjects withdrew from the study due to adverse effects although no differences were seen between groups. Adverse effects that were noted to be 5% greater in the active treatment group versus placebo included nausea and vomiting (26% vs 20%), dyskinesia (15% vs 7%), peripheral edema (11% vs 6%), hallucinations (11% vs <1%), and skin reactions (41% vs 13%). These effects were not noted to be dose related.</p> <p><u>Efficacy</u></p> <p>The mean doses of rotigotine in the active arm at the end of the maintenance period were 7.16 mg in the 8 mg arm and 9.51 mg in the 12 mg arm. The absolute change in daily off time between baseline and end of 24 week maintenance period was -0.9 hours for placebo, -2.7 hours for 8 mg, and -2.1 hours for 12 mg. A statistical difference was noted between active treatment groups and placebo. The percent of responders from baseline to end of maintenance period was 34.5% in the placebo arm, 56.6% in 8 mg arm, and 55.1% in 12 mg arm.</p>
Conclusion	A statistically significant decrease in daily off time was noted in advanced PD subjects receiving 8 mg or 12 mg of rotigotine versus placebo over a 24 week period.
Comments	Schwarz Pharma was responsible for the funding, study design, and statistical analysis of this trial.

Pharmacokinetics

Approximately 45% of the rotigotine from the patch is released within 24 hours (0.2 mg/cm²), independent of patch size. Similar absorption per cm² was observed in healthy subjects and patients with early stage Parkinson's disease. There is a lag time of 3 hours (range 1-8 hours) until the drug is detected in plasma. T_{min} occurs most commonly between 0-7 hours post dose. T_{max} typically occurs between 15-18 hours post dose, but can occur from 4-27 hours post dose. There is no characteristic peak concentration observed. Rotigotine displays dose-proportionality over a daily dose range of 2mg/24 hours to 8mg/24 hours. Rotigotine is primarily eliminated in the urine (71%) and feces (11%) as inactive metabolites. After removal of the patch, plasma levels decreased with an initial half-life of 3 hours and a terminal half-life of 5-7 hours.

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Price = (Drugstore.com 9-4-07)

Parlodel (bromocriptine)

Generic

2.5 mg caps: \$169.98/90

5 mg caps: \$231.98/90

Mirapex

0.125 mg, 0.25mg: \$172.36/90

0.5 mg: \$203.82/90

1 mg: \$214.98/90

1.5 mg: \$212.52/90

Requip

0.25 mg, 0.5mg, 1mg: \$201.36/90

2 mg: \$199.12/90

3 mg, 4mg, 5mg: \$216.06/90

Sinemet CR

Sinemet CR 300mg am, 300mg pm and 200mg later \$162.46/month

Sinemet CR 400mg am, 400mg pm and 200mg later \$ 221.99/month

Neupro (no drugstore.com listing)

AWP 4mg and 8mg \$9.62 each

Simplicity + (once daily dosing vs. multiple daily dosing)

Rotigotine is supplied as a 2mg/24 hours, 4mg/24 hours, and 6mg /24 hours transdermal patch. Starting at 2mg/24 hours the dosage is increased weekly by 2mg/24 hours based on individual patient clinical response and tolerability. Patients wear the patch continuously for 24 hours, then remove it and immediately apply a new patch to a different site. 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. Sites of application are the front of the abdomen, thigh, hip, flank, shoulder or upper arm. The same site should not be used within 14 days. If it is necessary to discontinue Neupro therapy, it should be discontinued gradually. The daily dose should be reduced by 2 mg per 24 hours with a dose reduction preferably every other day, until complete withdrawal.

Because of the transdermal delivery food does not affect absorption and the patch can be applied irrespective of the time of meals.

References

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