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Abbreviated Class Update: Parkinson's Drugs

Month/Year of Review: November 2013
New Drug: rotigotine transdermal system **(**Neupro®)

End of literature search: September 2013
Manufacturer: UCB Pharmaceuticals, Inc.

Current Preferred Agents	Current Non-Preferred Agents
Anticholinergics	
Benztropine tablets	
Trihexyphenidyl tablets/elixir	
COMT Inhibitors*	
Entacapone tablets	Tolcapone (Tamsar®) tablets
Dopaminergic Agents	
Carbidopa/Levodopa tablets	Carbidopa/Levodopa ER tablets
Dopamine Agonists	
Amantadine capsules/syrup/tablets	Bromocriptine (Parlodel®) tablets/capsules
Pramipexole DI-HCL tablets	Ropinirole (Requip®) IR and XL tablets
*MAO- B** Inhibitors*	
Selegiline capsules	Rasagaline (Azilect®) tablets
Combination Product	
	Carbidopa/Levodopa/Entacapone

*COMT = Catechol-O-methyl transferase; **MAO-B = Monoamine oxidase B

PA Criteria: All non-preferred agents require prior authorization to cover preferred products when feasible for covered diagnosis (Appendix 1). OHP does not cover treatment for restless leg syndrome.

Research Questions:

- Is there any evidence about comparative effectiveness of rotigotine transdermal versus other agents for the treatment of Parkinson's Disease (PD) in reducing disability, motor complications, and associated symptoms?
- Is there any evidence about comparative harms of rotigotine transdermal versus other agents in the treatment of PD?
- Are there subpopulations of patients (specifically by race, age, sex, or comorbidities) for which rotigotine is more effective or associated with less harm?

Conclusions:

- There is moderate quality evidence that, compared to placebo, more patients on rotigotine achieve a 20% or greater decrease in UPDRS ADL + Motor scores at 24 weeks (48% vs. 19%; ARR 29%, NNT 4) in the treatment of early Parkinson's Disease (PD).
- There is low quality evidence that rotigotine did not meet non-inferiority in responder rate(at least a 20% decrease in UPDRS ADL + Motor scores) compared to ropinirole in patients with early PD (52% vs. 68%).
- There is moderate quality evidence, that compared to placebo, patients on rotigotine achieved a greater change in total hours "off" from baseline (-2.7 vs. -0.9, $p<0.0001$) in the treatment of advanced PD over 24 weeks with adjunct levodopa.
- There is low quality evidence that there is no difference between rotigotine and pramipexole in responder rate (at least a 30% decrease in "off" time) in patients with advanced PD over 16 weeks (59.7% vs. 67%; RR 0.9, 95% CI 0.7-1.0); p=0.125).
- Rotigotine is generally well tolerated for up to 6 years with similar side effects as other dopamine agonists, including somnolence, dizziness, nausea, and insomnia. In addition, more patients experienced application site reactions with transdermal rotigotine compared to placebo.
- There is insufficient evidence that rotigotine is more efficacious or safer than other oral dopamine agonists in the treatment of PD. It may be a reasonable option for patients with difficulty swallowing that may be addressed by use of the patch.

Recommendations:

- Rotigotine transdermal patch should be evaluated in executive session for relative cost.

Reason for Review: Oregon reviewed the literature in this class in September 2013 and recommended adding rotigotine transdermal to complete the class

Background:

Rotigotine patch was originally approved for the treatment of PD in 2007 and was the first non-ergot dopamine agonist delivered continuously through a transdermal system. The formation of rotigotine crystals in the transdermal patch resulted in the product being withdrawn from the market in 2008 due to concerns of the impact on the bioavailability and effects on efficacy.[1] It was re-approved by the FDA in April 2012 for the treatment of PD and restless legs syndrome after the manufacturer reformulated the patch. Non-oral routs of delivery can be useful in PD patients scheduled for surgery or those with dysphagia.[2] This review will evaluate its efficacy and safety only in the treatment of PD, as restless leg syndrome is not a covered diagnosis under the Oregon Health Plan.

The Unified Parkinson's Disease Rating Scale (UPDRS) is the most widely used clinical rating scale for PD.[3] It evaluates the key areas of disability and evaluates response to therapy. Many practitioners find it too complicated to use in clinical practice. A total of 199 points are possible with 0 representing no disability and 199 representing total disability. A recent analysis showed that a minimal clinically important difference was 2.3 to 2.7 points on the UPDRS motor score and 4.1 to 4.5 on the UPDRS total score. A moderate clinically important difference was 4.5 to 6.7 points on the UPDRS motor score and 8.5 to 10.3 on the total score. A large difference was 10.7 to 10.8 points on the UPDRS motor score and 16.4 to 17.8 on the UPDRS total score.[4]

Methods:

A MEDLINE OVID search was conducted using rotigotine for Parkinson's disease (PD) and limited to randomized controlled trials (RCTs) and meta-analysis, English language, and conducted in humans since the date of the literature search conducted for the previous OHA P & T review. The Agency for Healthcare

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Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. From the literature search, two systematic reviews were identified as well as 9 randomized controlled trials. Three were excluded due to wrong outcome and/or wrong study design.[5–7]

New Systematic Reviews:

1) A systematic review was conducted to evaluate rotigotine's efficacy in PD, including randomized controlled trials up to July 2012.[2] Trials that used the Unified Parkinson's Disease Rating Scale (UPDRS) score were included. Two authors evaluated trials for quality using the Jadad scale. Six RCTs including 1789 patients were included in the meta-analysis and had Jadad scores that ranged from 4 to 5 (5 being rated as the strongest score). Four trials demonstrated a greater response in UPDRS ADL score with rotigotine compared to placebo (weighted mean difference [WMD] -1.69; 95% CI -2.18 to -1.19; p<0.0001), as well as a greater reduction in motor score (WMD -3.86; 95% CI -4.86 to -2.86; p<0.0001). There was no difference between rotigotine and placebo in overall number of withdrawals (RR 0.88; 95% CI 0.64-1.21; p=0.44) with evidence of heterogeneity (p=0.037, I^2=57.7%). However, rotigotine was associated with a significantly higher rate of withdrawals due to adverse events compared to placebo (11.4% vs. 6.4%, respectively; RR 1.82, 95% CI 1.29-2.59; p=0.0008). Both application site reactions (RR 2.92; 95% CI 2.29-3.72; p<0.0001) and dizziness (RR 1.47, 95% CI 1.12-1.95; p=0.006) occurred with rotigotine significantly more than placebo. The overall magnitude reduction in UPDRS ADL score (-1.69) was slightly greater than that in early PD patients (-1.64) but smaller than that in advanced PD patients (-2.2) when compared to results of previous meta-analyses of dopamine agonists. This review met the DARE scientific quality criteria for a systematic review.

2) Another systematic review evaluated the tolerability and safety of ropinirole versus other dopamine agonists, including rotigotine, in the treatment of PD.[8] A literature search through November 2008 was conducted to identify double-blind randomized clinical trials. Guidelines on systematic reviews from the Cochrane Collaboration were followed and quality of the evidence was assessed using the Jadad criteria. A total of 40 RCTs were identified, including 1 trial comparing ropinirole to rotigotine and 5 trials comparing rotigotine to placebo. In all of the included studies, dopamine agonists exhibited a higher incidence of adverse events than placebo. Rotigotine showed statistically significantly more nausea (RR 2.08, 95% CI 1.30-3.34), dizziness (RR 1.35, 95% CI 1.02-1.9), dyskinesia ((RR 2.29, 95% CI 1.10-4.78), insomnia (RR 1.90, 95% CI 1.22-2.95), vomiting (RR 5.31, 95% CI 2.30-12.27), and hallucinations (RR 4.02, 95% CI 1.23-13.11) compared to placebo. There was not a statistically significant difference in somnolence, headache, confusion, constipation or abdominal pain between rotigotine and placebo. When a direct comparison was made between rotigotine and ropinirole, no significant differences for either dyskinesia or constipation were found.

Guidelines:

National Guideline Clearinghouse (NGC) released treatment guideline on early (uncomplicated) Parkinson's disease. This guideline is an updated version of the therapeutic management of Parkinson's disease by the joint task force of the European Federation of Neurological Societies and the Movement Disorder Society-European Section.[9] Agents available in the US that carried **level A** recommendation for controlling PD's symptoms including Levodopa IR and CR,

pramipexole, ropinirole IR and CR, selegiline and rasagliline. Levodopa also has **level A** recommendation as the most effective symptomatic antiparkinsonian drug; however after a few years of treatment, levodopa is frequently associated with the development of motor complications. Rotigotine is not included in these guidelines.

Clinical Trials:

Early-Stage Parkinson's Disease

A RCT by Giladi et al evaluated the efficacy and safety of the rotigotine patch in the treatment of early PD in 561 patients randomized to rotigotine, ropinirole, or placebo. [10] Patients had mild to moderate disease with a baseline UPDRS ADL score of 9.0 and motor score of 23.2. The primary efficacy variable was the proportion of patients who responded to treatment which was defined as a 20% or greater decrease in the UPDRS parts II (ADL) + parts III (motor) scores from baseline. Compared to placebo, both rotigotine and ropinirole resulted in a significantly higher proportion of responders compared to placebo. The mean decrease from baseline in UPDRS subtotal score was -7.2 for patients receiving rotigotine compared with -2.2 for patients receiving placebo (P<0.0001) and -11.0 for ropinirole (p<0.0001). The changes in motor score and subtotal score are considered clinically significant as well as statistically significant. Results did not show noninferiority of rotigotine and ropinirole (RR 0.8, 95% CI 0.65-0.90); however the study was not powered to show superiority of any active treatment over the other and only 26% of ropinirole patients received the maximum allowed dose of 24mg/day. There were a significant more number of discontinuations due to adverse events in the rotigotine group compared to placebo (17% vs. 5.1%; RR 3.4, 95% CI 1.4-8.8). The majority of those in the rotigotine group were due to application-site reactions (8%). Common adverse events included application-site reactions, nausea, vomiting, somnolence, dizziness, and headache. There was an imbalanced titration (4 weeks vs. 13 weeks) and maintenance (24 weeks vs. 33 weeks) period between the treatment groups, making them hard to compare. This is a short term study; because progression of PD is estimated to be 3 UPDRS points per year, a longer study period is needed to examine long-term effects.

Watts, et al compared rotigotine patch (max dose 6 mg/24h) to placebo for 6 months in patients with early-stage PD.[11] Results demonstrated statistically significant improvements in motor function and activities of daily living (UPDRS II + III score) with rotigotine compared to placebo (-3.98 vs. +1.31; p<0.000.1; mean difference of 5.28 points). The mean rotigotine dose was 5.7 mg/24 h. Superior scoring in the motor examination was the largest contributor to the subtotal improvements. The proportion of responders (at least 20% improvement in UPDRS scores) was higher in the rotigotine group (48% vs. 19%; p<0.0001). Because patients included in the trial were so early in respect to PD disease, it may be difficult to see drastic motor fluctuations as measured by the primary endpoint.

A total of 216 subjects from the Watts trial were enrolled in an open-label long term study with a mean follow-up of 5.3 years. At 2 years, the UPDRS ADL plus motor scores were not different from the double-blind baseline.[12] For the following 4 years, scores worsened but remained within 4 points of the baseline scores. Adjunctive levodopa was started in 74% of patients, making it difficult to determine the long-term efficacy of rotigotine monotherapy.

Advanced Parkinson's Disease:

The PREFER study evaluated the efficacy of rotigotine compared to placebo in patients with suboptimal control of symptoms and significant motor complications.[13] Patients were randomized to rotigotine 8mg/24h, 12mg/24h, or placebo for 24 weeks. Rotigotine 8mg/24h and 12mg/24 hr resulted in a statistically significant reduction in absolute "off" time (-2.7 hrs vs. -2.1 hrs, -0.9hrs, respectively) and an increase in daily "on" time without troublesome dykinesias (3.5 hrs vs. 2.2 hrs vs. 1.1 hrs, respectively) compared to placebo. The primary outcome of changes in daily off time was measured by patient diaries, which can be subjective. UPDRS ADL and motor scores were also significantly increased with both rotigotine doses compared to placebo.

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The CLEOPATRA-PD trial[14] was a 24-week randomized trial in PD patients with at least 2.5 hours of daily off-time (advanced PD). Subjects were randomized to rotigotine (max dose of 16mg/24hr), pramipexole (max dose 4.5mg/day), and placebo. The mean daily dose of rotigotine was 12.95 mg/24 h. Daily off-time was reduced by 2.5 hours with rotigotine, 2.8 hours with pramipexole, and 0.9 hours with placebo. Both rotigotine and pramipexole demonstrated statistical significance compared to placebo; however, there was no difference between the two treatment groups. There was also no difference between the rotigotine and ropinirole groups in UPDRS ADL and motor scores or in responder rates.

Open-label extensions of both the CLEOPATRA-PD (n=395) and PREFER (n=258) studies were conducted to evaluate rotigotine over several years of follow-up in patients with advanced PD.[15] Patients were re-titrated do optimal dose (up to 16mg/24h) for 7 weeks. Most patients had moderately severe PD. The majority of subjects reported at least one adverse event, however only 8 and 9% were recorded as severe. The long term efficacy data demonstrated continuing disease progression over the course of studies. UPDRS scores gradually increased over the maintenance periods and were 0.8 points higher than baseline in one study, and 4.1 points higher than baseline in the other. Responder rates also decreased over time to 36% and 25% respectively.

Safety:

Most common adverse events were typical of a dopamine agonist and include nausea, somnolence, dizziness, and headache. Application site reactions also occurred more frequently than placebo in clinical trials. Long term trials have demonstrated rotigotine is generally well tolerated for up to 6 years with the most common adverse reactions of somnolence (54%), falls (33%), peripheral edema (37%), application site reactions (32%), nausea (31%), and dizziness (27%).[12] Case reports of patients experiencing sudden onset of sleep have been reported. In one study of 242 patients, one subject fell asleep while driving a motor vehicle and another reported a brief loss of consciousness while driving. A post-hoc analysis of patients taking low dose rotigotine demonstrated that 4 patients experienced a sleep attack or sudden onset of sleep.

Evidence Table

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Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias, External Validity Concerns
Giladi et al[10] DB, PC, RCT	Rot: Rotigotine Rop: Ropinirole Pla: Placebo	Mean age: 61 Male: 58% Caucasian: 97% Mean UPDRS score: -ADL: 9.0 -Motor: 23.2 Mean rotigotine dose 7.2mg/24h Inclusion Criteria: Adults 30 years or older with mild to moderate PD, a score of at least 10 on the UPDRS Exclusion Criteria: Psychiatric disease, h/o skin sensitivity, levodopa use for longer than 6 months, hepatic, renal or cardiac dysfunction, elevated QTc interval	N=215 N=228 N=118 Minimum duration of 33 weeks for rotigotine and 24 weeks for ropinirole based on dose-titration period	<u>Proportion of patients who responded to treatment:</u> Rot: 110 (52%) Rop: 154 (68%) Pla: 35 (30%) P<0.0001 for Rot vs. Pla RR 1.7, 95% CI 1.2-2.4 P<0.0001 for Rop vs. Pla RR 2.3, 95% CI 1.7-3.1 P=0.001 for Rot vs. Rop RR 0.8, 95% CI 0.65-0.90	ARR 22% NNT 5 ARR 38% NNT 3 N/A	<u>Withdrawals due to AEs:</u> Rot: 37(17.2%) Rop: 29 (12.8%) Pla: 6 (5.1%) P=0.002 for Rot vs. Pla RR 3.4, 95% CI 1.4-8.8	ARI= 12.1% NNH 9	**Quality Rating: Fair** **Internal Validity Review of Bias:** <u>Selection:</u> Randomization occurred via interactive voice response system. Patients similar at baseline. <u>Performance:</u> Double-blinded with placebo patches and capsules. Unclear if investigator were blinded during dose titration phase. <u>Detection:</u> Unclear if outcome assessors were blinded. <u>Attrition:</u> Overall high attrition at 29% PLA, 29% ROT, 23% ROP. Mostly due to lack of efficacy and adverse events. **External Validity Review of Bias:** <u>Patient Characteristics:</u> Patients with very mild disease included in study; only 26% of ropinirole patients received the maximum allowed dose of 24 mg/day. <u>Setting:</u> There was an imbalanced titration and maintenance periods between treatment groups, making them hard to compare <u>Outcomes:</u> A responder was defined as a patient with a 20% or greater decrease in the UPDRS parts II + III (ADL + motor) from baseline.

Watts et al.[11] Phase III, MC, R, DB, PC	Rot: Rotigotine Pla: Placebo Rotigotone was started at 2mg/24 hours and titrated to max tolerable dose up to 6 mg/24 hours	Mean age: 63 Males 64% Mean rotigotone dosage: 5.7mg/24 h Inclusion: Age>30, UPDRS motor score of at least 10, MMSE score >25 Exclusion: Prior or current dopamine agonist therapy, epilepsy, seizure history, stroke, TIA, or clinically relevant renal, hepatic, or cardiac dysfunctions	N=181 N=96 24 weeks	<u>Change in UPDRS II+III from baseline:</u> Rot: -3.98 Pla: +1.31 Treatment effect -5.3 P<0.0001 for Rot vs. Pla <u>% of responders</u> Rot: 87 (48%) Pla: 18 (19%) P<0.0001 for Rot vs. Pla RR 2.5, 95% CI 1.6-4.2	N/A ARR 29% NNT 4	<u>Withdrawals due to AEs:</u> Rot: 25 (14%) Pla: 6 (6%) P=0.06 for Rot vs. Pla RR 2.2, 95% CI 0.9-5.9	NS	**Quality Rating: Fair** **Internal Validity Review of Bias:** <u>Selection:</u> Unclear method of randomization. Patients similar at baseline. <u>Performance:</u> Double-blinded with placebo patches and capsules. Unclear if investigator were blinded during dose titration phase. <u>Detection:</u> Unclear if outcome assessors were blinded. <u>Attrition:</u> Overall attrition at 16% PLA, 22% ROT. High rate due to AE in Rot group. **External Validity Review of Bias:** <u>Recruitment:</u> Unknown <u>Patient Characteristics:</u> Patients had very earl PD <u>Setting:</u> 50 clinical study sites in the US and Canada <u>Outcomes:</u> Primary endpoint was combination of motor and ADL scores, however these patients may be too early in PD disease course to see such drastic motor fluctuations Study funded by Schwarz Pharma

CLEOPATRA PD[14] **(Poewe, et al).** MC, R, DB, DI	Rot: Rotigotine Pram: Pramipexol Pla: Placebo Rotigotine up to 16mg/24 hr Pramipexole up to 3.5mg/day Titration up to 7 weeks Maintenance: 16 weeks	Inclusion Criteria: 30 years or older, stable treatment with levodopa, motor fluctuations of the wearing-off type with an average of at least 2.5 hr per day in the off stage Exclusion criteria: Previous surgery for PD, MMSE <25, hallucinatior or psychosis, h/o MI, prolonged QTc interval	N= 204 N=201 N=101	<u>Absolute change in total hours "off" from baseline</u> Rot: -2.5 Pram: -2.8 Pla: -0.9 P<0.0001 Rot vs. Pla P<0.0001 Pram vs. Pla P=0.003 Rot vs. Pram <u>Responder rate (>30% decrease in off time):</u> Rot: 122 (59.7%) Pram: 135 (67%) Pla: 35 (35%) P<0.0001 Rot vs. Pla RR 1.7, 95% CI 1.3-2.4 P<0.0001 Pram vs. Pla RR 1.9, 95% CI 1.5-2.6 P=0.125 Rot vs. Pram RR 0.9, 95% CI 0.7-1.0	N/A ARR 24.7%/ NNT 4 ARR 32% NNT 3 NS	<u>Withdrawals due to AE:</u> Rot: 11 (5%) Pram: 14 (6%) Pla: 6 (6%) NS One report of sleep attack in pramipexole group	NS	**Quality Rating: Fair** **Internal Validity Review of Bias:** <u>Selection:</u> Randomization occurred via interactive voice response system. Slightly lower number of men in pramipexole group than other groups. <u>Performance:</u> Double-blinded with placebo patches and capsules. <u>Detection:</u> Unclear if outcome assessors were blinded. <u>Attrition:</u> Overall attrition at 27% PLA, 12% ROT, 17.5% PRAM. Mostly due to lack of efficacy and adverse events. **External Validity Review of Bias:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Patients with more advanced disease; on stable levodopa; almost all patients were white <u>Setting:</u> 77 centers in Europe, South Africa, Australia, and New Zealand <u>Outcomes:</u> Primary outcome of on/off time measured by patient diaries which is very subjective Members of Schwarz Pharma involved in steering committee for the trial design and submitted the manuscript for publication

PREFER[13] (LeWitt, et al) RCT, DB, PG	Rot 8: Rotigotine 8mg/24 hr Rot12: Rotigotine 12mg/24 hr Pla: Placebo	Mean Age: 66 Male 78% PD duration – 7.7 yr Daily "off" – 6.5 hr Inclusion Criteria: at least 30 years old, PD for at least 3 years, on at least 200mg/day of levodopa, inadequate relief of parkinsonism, at least 2.5 hours of "off time"	N=120 N=111 N=120 24 week maintenance phase	<u>Absolute change in total hours "off" from baseline</u> Rot 8: -2.7 Rot 12: -2.1 Pla: -0.9 P<0.0001 Rot 8 vs. Pla P<0.0001 Rot 12 vs. Pla <u>Responder rate (>30% decrease in off time):</u> Rot8: 56.6% Rot12: 55.1% Pla: 34.5% P<0.0001 for both Rot doses compared to placebo	N/A	<u>D/C due to AE</u> Rot8: 18 (15.3%) Rot12: 17 (15.3%) Pla: 11 (9.2%)%	NS	**Quality Rating: Fair** **Internal Validity Review of Bias:** <u>Selection:</u> Appropriate randomization method and allocation concealment. Similar groups at baseline <u>Performance:</u> Subjects blinded <u>Detection:</u> Unclear if outcome assessors blinded <u>Attrition:</u> Overall attrition of 27.5% ROT 8mg, 27% ROT 12mg, 23% Pla. Mostly due to adverse events in ROT groups and inefficiency in placebo group. **External Validity Review of Bias:** <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Limited baseline patient characteristics provided; more advanced disease on stable levodopa. Mean dose in 12mg group only 9.5mg. <u>Setting:</u> Clinical sites in the US and Canada <u>Outcomes:</u> Primary outcome of on/off time measured by patient diaries which is very subjective

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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16. Neupro. (rotigotine) prescribing information. Smyrna, GA; UCB, Inc; March 2012.

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Appendix 1: Current PA Criteria

Anti-Parkinsons Agents

Goal(s):

- Cover preferred products when feasible for covered diagnosis. Preferred products are selected on evidence based reviews.
- OPH does not cover treatment for restless leg syndrome (Coverage line 624)

Length of Authorization: 12 months

Requires PA:

Non-preferred drugs

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis Parkinson's disease or another chronic neurological condition?	**Yes:** Go to #5.	**No:** Go to #3
3. Is the diagnosis Restless Leg Syndrome (ICD9-333.94)?	**Yes:** Pass to RPH; Deny, (Not covered by OHP)	**No:** Go to #4
4. RPH only All other indications need to be evaluated as to whether they are above the line or below the line	**Above:** Go to #5	**Below:** Deny, (Not covered by the OHP)
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class.	**No:** Approve for the shorter of 1 year or length of prescription

DUR/P&T Board Action: 9/06/10 (DO)
Revision(s):
Initiated: 1/1/11

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Appendix 2: Specific Drug Information

PHARMACOKINETICS[16]

Parameter	Result
Oral Bioavailability	Transdermal Formulation
Protein Binding	92%
Elimination	Renally as inactive conjugates
Half-Life	5-7 hours
Metabolism	Multiple CYP isoenzymes, sulfotransferases, and two UDP-glucoronosyltransferases catalyze the metabolism of rotigotine

DOSE & AVAILABILITY[16]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
1mg/24h 2mg/24h 3mg/24h 4mg/24h 6mg/24h 8mg/24h	Transdermal	Q24H	Initially, 2mg/24h for early-stage PD or 4mg/24hr for advanced PD. The dose may be increase as needed by 2mg/24 hours at weekly intervals, up to 6 mg/24 hours for early-stage PD and up to 8 mg/24h for advanced-stage disease.	No adjustment needed	No guidance available for patients with severe hepatic impairment.	No information available..	No differences in safety, efficacy or response have been observed among patients of varying age. Skin changes with advanced age may lead to increased rug exposure.	Should be applied to clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm; the application site should be moved on a daily basis. For discontinuation, the daily dose should be reduced by 2mg/24 hours with a dose reduction preferably every other day, until complete withdrawal.

Author: Megan Herink, Pharm.D.

DRUG SAFETY[16]

Contraindications: Rotigotine is contraindicated in patients who are hypersensitive to rotigotine or any component of the transdermal delivery system.

Warnings and Precautions:

- Sulfite Sensitivity: Rotigotine contains sodium metabisulfite and patient with sulfite sensitivity may experience allergic reactions.
- Falling asleep during activities of daily living/somnolence: Instances of patients falling asleep while engaged in ADL, including operating a motor vehicle, have been reported.
- Hallucinations/Psychotic-like Behavior
- Symptomatic Hypotension
- Syncope
- Impulse Control
- Elevation of blood pressure/heart rate
- Weight gain/fluid retention
- Dyskinesia
- Application Site Reactions: Rotigotine should be discontinued if a generalized skin reaction is observed.
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Look-alike/Sound-alike Potential:

Rotigotine may be confused with : *rasagiline, rivastigmine, ropinirole*
Neupro may be confused with: *Neupogen, Neurontin*

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