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Literature Scan: Anti-Parkinson's Agents

Date of Review: July 2016

Date of Last Review: September 2014
Literature Search: August 2014 – May 2016

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- Since the previous Parkinson's disease drug class scan, there is limited new comparative evidence from one systematic review with meta-analysis and three randomized controlled trials. There are also two new levodopa and carbidopa formulations approved by the U.S. Food and Drug Administration (FDA) for the treatment of Parkinson's disease and one new FDA safety alert.
- There is low quality evidence that levodopa monotherapy is more effective than levodopa-sparing therapy for improving activities of daily living and motor symptoms as measured by the unified Parkinson's disease rating scale (UPDRS)[Scale 0-176, 0 = no disability, 176 = worst disability; mean difference 0.95 (52 point scale), 95% CI, 0.51 to 1.39; p<0.0001 and 2.89 (108 point scale), 95% CI, 1.56 to 4.21; p<0.0001, respectively] but less effective than levodopa-sparing therapy for improvement of mental functioning [mean change from baseline -0.30 (16 point scale), 95% CI, -0.51 to -0.09; p=0.0005]. The clinical significance of these differences remain unclear.
- There is low quality evidence that levodopa monotherapy results in a worsening of motor complications compared to levodopa-sparing treatment (33.7% vs. 24.4%, respectively; p<0.0001), has increased risk of dyskinesia (RR 1.88, 95% CI, 1.37 to 2.59; p<0.0001), and higher incidence of wearing-off phenomenon (41.2% vs. 29.6%; p<0.00001). There is insufficient evidence of no difference in self-reported quality of life measurement scores between levodopa and levodopa-sparing therapy in the treatment of PKD.

Recommendations:

- No further review or research needed at this time. After the executive session, no changes in the PDL were made.

Previous Conclusions and Recommendations:

- Evidence does not support a difference in efficacy or effectiveness between agents for PD.
- Make tolcapone non-preferred due to reported liver toxicity.
- Make carbidopa/levodopa ER preferred on PDL.
- 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. Make rotigotine transdermal (Neupro) non-preferred on the PDL.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A systematic review with meta-analysis by Xie, et al. evaluated the use of levodopa monotherapy versus levodopa sparing therapy for initial treatment of Parkinson's disease (PKD).[1] The American Academy of Neurology (AAN) and European Federation of Neurological Societies/Movement Disorder Society-European Section (EFNS/MDS-ES) have recommended either levodopa or dopamine agonists as first-line agents for symptomatic treatment of early PKD, with the initial choice dependent upon patient age, disease stage, symptoms, and preferences.[2,3] Treatment of PKD with levodopa monotherapy has been widely used to ameliorate symptoms, however, it has also been associated with motor fluctuations and dyskinesias with prolonged use. Eleven RCTs (n=3584) were identified and included in the meta-analysis with 35 to 1406 subjects in each study. Follow-up ranged from 1 year to 10 years. Of the eleven levodopa-sparing groups, five trials used the dopamine agonist pramipexole, cabergoline was used in three trials, ropinirole in two trials, and bromocriptine was used in one trial.[1] The outcomes measured included the Unified Parkinson's disease Rating Scale (UPDRS, parts 1-3), motor complications (dyskinesia, wearing off phenomenon and on-off fluctuation), and health-related quality of life measures through the Parkinson's disease questionnaire (PDQ-39), and EuroQol (EQ-5D).

The UPDRS effects were assessed through tests of mental functioning (part 1), activities of daily living [ADL] (part 2), and motor symptoms (part 3). The total UPDRS scoring scale ranged from zero to 176 (0 = no disability, 176 = worst disability). Pooled data for three of the trials compared mental functioning (UPDRS part 1: score 0 to 16 points) and showed a slight but statistically significant difference and worsening of overall symptoms with levodopa monotherapy versus levodopa-sparing treatment (mean change from baseline: -0.30, 95% CI, -0.51 to -0.09; p=0.0005).[1] However, pooled data of six trials comparing activities of daily living (UPDRS part 2: score 0 to 52 points) showed that levodopa monotherapy resulted in significant improvements over the levodopa-sparing group (mean difference: 0.95, 95% CI, 0.51 to 1.39; p<0.0001). Motor symptoms (UPDRS part 3: score 0 to 108 points) and UPDRS total scores were improved with levodopa monotherapy (mean change 2.89, 95% CI, 1.56 to 4.21; p<0.0001, and 3.33, 95%CI, 1.04 to 5.61; p=0.004, respectively).

Eight trials reported motor complication outcomes (n=3269) which were found to be higher in the levodopa monotherapy groups than levodopa-sparing therapy (33.7% vs. 24.4%, respectively; risk ratio (RR) 1.53, 95% CI, 1.25-1.87; p<0.0001).[1] Dyskinesia incidence was higher with levodopa monotherapy (RR 1.88; 95% CI, 1.37 to 2.59; p<0.0001). Incidence of wearing-off phenomenon was higher with levodopa monotherapy (41.2% vs. 29.6%; RR 1.36, 95% CI, 1.20 to 1.55; p<0.00001) but there was no statistically significant difference detected in on-off fluctuations (6.5% vs 3.1%; RR 2.07, 95% CI, 0.70 to 6.16; p=0.19).[1]

The PDQ-39 (39 questions, each scored 0 to 4) or EQ-5D (5 questions, 3 response types plus 0 – 100 point visual analog scale) were quality of life assessment tools utilized in 5 of the 11 studies. PDQ-39 scores from the individual trials revealed no significant difference between levodopa monotherapy and levodopa-sparing therapy in three of the five trials, while the remaining two trials showed statistically significant average score improvement of 1.8 ($p<0.05$) for levodopa monotherapy. The clinical significance of this difference is unclear. EQ-5D results were only available for four of the eleven trials, and all but one of the studies assessed did not show a statistically significant difference between treatment groups ($p>0.05$).

New Guidelines:
None identified**.**

New Formulations/Indications:
Rytary® (carbidopa and levodopa) extended release capsules for oral use was approved by the FDA in January 2015 based on pharmacokinetic studies.[4] The new formulation of carbidopa/levodopa joins the carbidopa/levodopa formulation already marketed under various product names. Rytary® is indicated for the treatment of PKD, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

Duopa® (carbidopa and levodopa) enteral suspension was approved by the FDA in January 2015.[5] The new formulation of carbidopa/levodopa has the same active ingredient but is supplied as a solution for administration via percutaneous endoscopic gastrostomy with jejunal tube (PEG-J). Duopa® is indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease.

There is insufficient comparative data that these new formulations provide any improved efficacy or safety over other agents available in the class.

New FDA Safety Alerts:
In February 2015, the FDA Center for Drug Evaluation and Research (CDER) issued a safety labeling change warning about increased risk of adverse events in patients using Neupro® (rotigotine) Transdermal System.[6] For patients with advanced PKD on maximum doses of Neupro®, incidence of orthostasis was higher for Neupro® than placebo (32% vs 27%, respectively), resulted in more weight gain and fluid retention (Neupro 9% vs. placebo 1%), had a higher incidence of dyskinesia (Neupro 14% vs. placebo 7%), and more application site reactions (36% Neupro vs. 13% placebo). Notable increases in systolic blood pressure (>20 mmHg) and diastolic blood pressure (>10 mmHg) was at least 5% higher in all patients taking Neupro® versus placebo. Patients with early-stage PKD on Neupro® therapy had an increased risk for low hemoglobin (Neupro 8% vs placebo 5%) and low serum glucose (Neupro 15% vs. placebo 6%) at levels below normal reference range. Specific reference ranges and interpretive details were unavailable.

References:

1. Xie C, Zhang Y, Wang X, et al. "Levodopa Alone Compared with Levodopa-Sparing Therapy as Initial Treatment for Parkinson's Disease: A Meta-Analysis." *Neurological Sciences* 2015;36:1319–29. doi:10.1007/s10072-015-2253-7.

2. Suchowersky, O., G. Gronseth, J. Perlmutter, et al. "Practice Parameter: Neuroprotective Strategies and Alternative Therapies for Parkinson Disease (an Evidence-Based Review) Report of the Quality Standards Subcommittee of the American Academy of Neurology." *Neurology* 2006; 66:976–82. doi:10.1212/01.wnl.0000206363.57955.1b.

3. Ferreira, J. J., R. Katzenschlager, B. R. Bloem, et al. "Summary of the Recommendations of the EFNS/MDS-ES Review on Therapeutic Management of Parkinson's Disease." *European Journal of Neurology* 2013; 20: 5–15. doi:10.1111/j.1468-1331.2012.03866.x.

4. Rytary (carbidopa and levodopa) extended-release capsules [Prescribing Information]. Hayward, CA: Impax Pharmaceticals, a division of Impax Laboatories, Inc., January 2015.

5. Duopa (carbidopa and levodopa) enteral suspension [Prescribing Information]. North Chicago, IL: AbbVie, Inc. January 2015.

6. U.S. Food and Drug Administration. Safety Information - Neupro (Rotigotine) Transdermal System. FDA Drug Safety Communication. 2015. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm302528.htm. Accessed June 13, 2016.

7. Olanow CW, Kieburtz K, Odin P, et al. "Continuous Intrajejunal Infusion of Levodopa-Carbidopa Intestinal Gel for Patients with Advanced Parkinson's Disease: A Randomised, Controlled, Double-Blind, Double-Dummy Study." *The Lancet Neurology* 2014;13:141–49. doi:10.1016/S1474-4422(13)70293-X.

8. Stocchi F, Hsu A, Khanna S, et al. "Comparison of IPX066 with Carbidopa–levodopa plus Entacapone in Advanced PD Patients." *Parkinsonism & Related Disorders* 2014;20:1335–40. doi:10.1016/j.parkreldis.2014.08.004.

9. Mizuno Y, Masahiro N, Kazuko H, et al. "Rotigotine vs Ropinirole in Advanced Stage Parkinson's Disease: A Double-Blind Study." *Parkinsonism & Related Disorders* 2014;20:1388–93. doi:10.1016/j.parkreldis.2014.10.005.

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	BENZTROPINE MESYLATE	BENZTROPINE MESYLATE	Y
ORAL	TABLET	CARBIDOPA-LEVODOPA	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET	SINEMET 10-100	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET	SINEMET 25-100	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET	SINEMET 25-250	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET ER	CARBIDOPA-LEVODOPA ER	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET ER	SINEMET CR	CARBIDOPA/LEVODOPA	Y
ORAL	TABLET	CARBIDOPA-LEVODOPA-ENTACAPONE	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 100	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 125	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 150	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 200	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 50	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	STALEVO 75	CARBIDOPA/LEVODOPA/ENTACAPONE	Y
ORAL	TABLET	COMTAN	ENTACAPONE	Y
ORAL	TABLET	ENTACAPONE	ENTACAPONE	Y
ORAL	TABLET	MIRAPEX	PRAMIPEXOLE DI-HCL	Y
ORAL	TABLET	PRAMIPEXOLE DIHYDROCHLORIDE	PRAMIPEXOLE DI-HCL	Y
ORAL	CAPSULE	SELEGILINE HCL	SELEGILINE HCL	Y
ORAL	ELIXIR	TRIHEXYPHENIDYL HCL	TRIHEXYPHENIDYL HCL	Y
ORAL	TABLET	TRIHEXYPHENIDYL HCL	TRIHEXYPHENIDYL HCL	Y
ORAL	CAPSULE	AMANTADINE HCL	AMANTADINE HCL	N
ORAL	SYRUP	AMANTADINE HCL	AMANTADINE HCL	N
ORAL	TABLET	AMANTADINE HCL	AMANTADINE HCL	N
ORAL	CAPSULE	BROMOCRIPTINE MESYLATE	BROMOCRIPTINE MESYLATE	N
ORAL	CAPSULE	PARLODEL	BROMOCRIPTINE MESYLATE	N
ORAL	TABLET	PARLODEL	BROMOCRIPTINE MESYLATE	N
ORAL	TABLET	BROMOCRIPTINE MESYLATE	BROMOCRIPTINE MESYLATE	N
ORAL	TABLET	CARBIDOPA	CARBIDOPA	N
ORAL	TABLET	LODOSYN	CARBIDOPA	N
ORAL	CAPSULE ER	RYTARY	CARBIDOPA/LEVODOPA	N
ORAL	TAB RAPDIS	CARBIDOPA-LEVODOPA	CARBIDOPA/LEVODOPA	N
ORAL	TAB ER 24H	MIRAPEX ER	PRAMIPEXOLE DI-HCL	N
ORAL	TAB ER 24H	PRAMIPEXOLE ER	PRAMIPEXOLE DI-HCL	N
ORAL	TABLET	AZILECT	RASAGILINE MESYLATE	N

ORAL	TABLET	REQUIP	ROPINIROLE HCL	N
ORAL	TABLET	ROPINIROLE HCL	ROPINIROLE HCL	N
ORAL	TAB ER 24H	REQUIP XL	ROPINIROLE HCL	N
ORAL	TAB ER 24H	ROPINIROLE ER	ROPINIROLE HCL	N
TRANSDERM	PATCH TD24	NEUPRO	ROTIGOTINE	N
ORAL	TABLET	SELEGILINE HCL	SELEGILINE HCL	N
ORAL	TAB RAPDIS	ZELAPAR	SELEGILINE HCL	N
ORAL	TABLET	TASMAR	TOLCAPONE	N
ORAL	TABLET	TOLCAPONE	TOLCAPONE	N

Anticholinergics: *benztropine; trihexyphenidyl*
COMT* Inhibitors: *entacapone; tolcapone*
Dopaminergic Agents: *carbidopa/levodopa*
Dopamine Agonists: *amantadine; bromocriptine; pramipexole; ropinirole; rotigotine*
MAO- B** Inhibitors: *selegiline; rasagaline*

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

Appendix 2: New Clinical Trials

A total of 120 citations were manually reviewed from the literature search. After manual review, 117 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 3 trials are briefly described in the table below. The full abstracts are included in **Appendix 3**.

Table 1. Description of Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Olanow CW et al., 2014[7] RCT, DB, DD, PC	Levodopa-carbidopa intestinal gel (LCIG) vs levodopa-carbidopa Immediate-release oral (LCIRO)	≥30 y/o w/ PKD dx ≥ 10 years Mean age 64 y/o 65% male 93% white (n=71)	Change in mean number of off-time hours 3 days prior to both baseline and 12-week final visit normalized to a 16 hour waking day	Treatment Difference: LCIG vs LCIRO -1.91(95% CI, -3.05 to -0.76) P=0.0015
Stocchi F et al., 2014[8] RCT, DB, DD, CS	IPX066 (ER Carbidopa-levodopa) plus entacapone vs Carbidopa-levodopa IR plus entacapone (CL+E)	≥30 y/o w/ advanced idiopathic PKD dx ≥ 10 years Mean age 64 75% male 98% white (n=91)	Mean percent "off-time" during waking hours during last 3 days of each treatment period	Mean percent "off-time": IPX066: 24.0% (95% CI, 7.8% to 40.2%) CL+E: 32.5% (95% CI, 10.6% to 54.4%) P<0.0001
Mizuno Y et al., 2014[9] RCT, DB, DD, PC, PG	Rotigotine (RTG) vs ropinirole (ROP)	Japanese subjects with diagnosis of PKD Mean age 66 y/o 61% female (n=414)	Change in UPDRS Part III "ON" state sum score from baseline to week 16	Treatment Difference: ROT vs PBO -6.4(95% CI, -8.6 to -4.2); p<0.001 ROP vs PBO -5.1(95% CI, -7.4 to -2.8); p<0.001 ROT vs ROP -1.4(95% CI, -3.2 to 0.4); p=0.137 (NS)

Abbreviations: CS = crossover study; DB = double blind; DD = double dummy; dx = diagnosis; PKD = Parkinson's disease; PC = placebo controlled; PG = parallel group; RCT=randomized controlled trial; UPDRS = Unified Parkinson's disease Rating Scale; y/o = years old

Appendix 3: Abstracts of Clinical Trials

1. Olanow, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. *Lancet Neurol.* 2014 Feb;13(2):141-149.

BACKGROUND: Levodopa is the most effective therapy for Parkinson's disease, but chronic treatment is associated with the development of potentially disabling motor complications. Experimental studies suggest that motor complications are due to non-physiological, intermittent administration of the drug, and can be reduced with continuous delivery. We aimed to assess efficacy and safety of levodopa-carbidopa intestinal gel delivered continuously through an intrajejunal percutaneous tube.

METHODS: In our 12-week, randomised, double-blind, double-dummy, double-titration trial, we enrolled adults (aged ≥ 30 years) with advanced Parkinson's disease and motor complications at 26 centres in Germany, New Zealand, and the USA. Eligible participants had jejunal placement of a percutaneous gastrojejunostomy tube, and were then randomly allocated (1:1) to treatment with immediate-release oral levodopa-carbidopa plus placebo intestinal gel infusion or levodopa-carbidopa intestinal gel infusion plus oral placebo. Randomisation was stratified by site, with a mixed block size of 2 or 4. The primary endpoint was change from baseline to final visit in motor off-time. We assessed change in motor on-time without troublesome dyskinesia as a prespecified key secondary outcome. We assessed efficacy in a full-analysis set of participants with data for baseline and at least one post-baseline assessment, and imputed missing data with the last observation carried forward approach. We assessed safety in randomly allocated patients who underwent the percutaneous gastrojejunostomy procedure. This study is registered with ClinicalTrials.gov, numbers NCT00660387 and NCT0357994.

FINDINGS: From baseline to 12 weeks in the full-analysis set, mean off-time decreased by 4.04 h (SE 0.65) for 35 patients allocated to the levodopa-carbidopa intestinal gel group compared with a decrease of 2.14 h (0.66) for 31 patients allocated to immediate-release oral levodopa-carbidopa (difference -1.91 h [95% CI -3.05 to -0.76]; p=0.0015). Mean on-time without troublesome dyskinesia increased by 4.11 h (SE 0.75) in the intestinal gel group and 2.24 h (0.76) in the immediate-release oral group (difference 1.86 [95% CI 0.56 to 3.17]; p=0.0059). In the safety analyses 35 (95%) of 37 patients allocated to the levodopa-carbidopa intestinal gel group had adverse events (five [14%] serious), as did 34 (100%) of 34 patients allocated to the immediate-release oral levodopa-carbidopa group (seven [21%] serious), mainly associated with the percutaneous gastrojejunostomy tube.

INTERPRETATION: Continuous delivery of levodopa-carbidopa with an intestinal gel offers a promising option for control of advanced Parkinson's disease with motor complications. Benefits noted with intestinal gel delivery were of a greater magnitude than were those obtained with medical therapies to date, and our study is, to our knowledge, the first demonstration of the benefit of continuous levodopa delivery in a double-blind controlled study.

2. Stocchi, et al. Comparison of IPX066 with carbidopa-levodopa plus entacapone in advanced PD patients. *Parkinsonism & Related Disorders.* 20(12):1335-40, 2014 Dec.

BACKGROUND: IPX066, an investigational extended-release carbidopa-levodopa (CD-LD) preparation, has demonstrated a rapid attainment and prolonged maintenance of therapeutic LD plasma concentrations in advanced Parkinson's disease (PD). This phase-3 crossover study assessed its efficacy and safety vs. CD-LD plus entacapone (CL + E).

METHODS: At baseline, all patients had motor fluctuations despite a stable regimen of CL + E or CD-LD-entacapone combination tablets (CLE). The study included a 6-week conversion from CL + E or CLE to IPX066, followed by two 2-week, double-blind crossover treatment periods in randomized order, one on IPX066 (and placebo CL + E), the other on CL + E (and placebo IPX066), separated by 1-week open-label IPX066 treatment. The primary efficacy measure was mean percent daily "off" time during waking hours (from patient diaries).

RESULTS: Of 91 randomized patients, 84 completed the study. Their median daily LD dosage was 1495 mg from IPX066 and 600 mg from CL + E, corresponding, after correction for bioavailability, to an approximately 22% higher LD exposure on IPX066. Compared with CL + E, IPX066 demonstrated a lower percent "off" time (24.0% vs. 32.5%; $p < 0.0001$), lower "off" time (3.8 vs. 5.2 h/day; $p < 0.0001$), and higher "on" time without troublesome dyskinesia (11.4 vs. 10.0 h/day; $p < 0.0001$). Other endpoints, including patient-reported treatment preference, also favored IPX066 ($p < 0.05$). During double-blind treatment, 20.2% and 13.6% of patients reported adverse events on IPX066 and CL + E, respectively. The most common were dyskinesia (4 patients), insomnia (3), and confusional state (3) for IPX066, and fall (2) for CL + E.

CONCLUSIONS: In advanced PD, IPX066 showed improved efficacy, compared with CL + E, and appeared to be well tolerated.

3. Mizuno et al. Rotigotine vs ropinirole in advanced stage Parkinson's disease: a double-blind study. *Parkinsonism & Related Disorders*. 20(12):1388-93, 2014 Dec.

OBJECTIVE: To confirm the superiority of transdermal rotigotine up to 16 mg/24 h over placebo, and non-inferiority to ropinirole, in Japanese Parkinson's disease (PD) patients on concomitant levodopa therapy.

METHODS: This trial was a randomized, double-blind, double-dummy, three-arm parallel group placebo- and ropinirole-controlled trial. Four-hundred and twenty PD patients whose motor symptoms were not well controlled by levodopa treatment were randomized 2:2:1 to receive rotigotine, ropinirole (up to 15 mg/day) or placebo during a 16-week treatment period followed by a 4-week taper period. The primary variable was change in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (ON state) sum score from baseline to the end of the treatment period.

RESULTS: The difference in the change in the UPDRS Part III (ON state) sum score from baseline to the end of treatment between rotigotine and placebo groups was -6.4 +/- 1.2 (95% CI: -8.7 to -4.1; $p < 0.001$), indicating superiority of rotigotine over placebo. The difference between rotigotine and ropinirole groups was -1.4 +/- 1.0 (95% CI: -3.2 to 0.5), below the non-inferiority margin, indicating the non-inferiority of rotigotine to ropinirole. Application site reaction was seen in 57.7% of the patients in the rotigotine group and in 18.6% in the ropinirole group ($P < 0.001$). No other safety issue was noted.

CONCLUSIONS: Rotigotine was well tolerated at doses up to 16 mg/24 h and showed similar efficacy to ropinirole except that the application site reaction was much higher in the rotigotine group.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to April Week 4 2016

1. *benztropine.mp. or Benztropine/290*
2. *carbidopa.mp. or Carbidopa/1212*
3. *levodopa.mp. or Levodopa/10053*
4. *entacapone.mp./489*
5. *pramipexole.mp./1062*
6. *selegiline.mp. or Selegiline/1494*
7. *trihexyphenidyl.mp. or Trihexyphenidyl/292*
8. *amantidine.mp./19*
9. *bromocriptine.mp. or Bromocriptine/2305*
10. *rasagiline.mp./444*
11. *ropinirole.mp./682*
12. *rotigotine.mp./266*
13. *tolcapone.mp./331*
14. *Dopamine Agonists/ or Antiparkinson Agents/ or antiparkinson.mp./15147*
15. *1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13/15356*
16. *14 and 15/7249*
17. *limit 16 to (yr="2014 -Current" and english and humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))/120*

Anti-Parkinson's Agents

Goals:

- Promote preferred drugs for Parkinson's disease.
- Restrict use for non-funded conditions like restless leg syndrome.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 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?	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #4
4. RPh only: All other indications need to be evaluated to determine if treatment is for a funded condition.	**Funded:** Go to #5	**Not Funded:** Deny; not funded by the OHP.

Approval Criteria		
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 & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for the shorter of 1 year or length of prescription.

P&T Review: *7/16 (DE); 9/14; 9/13; 09/10*
Implementation: *1/1/14, 1/1/11*