Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CADTH CANADIAN DRUG EXPERT COMMITTEE
FINAL RECOMMENDATION

ROTIGOTINE — RESUBMISSION
(Neupro — UCB Canada Inc.)
Indication: Parkinson's Disease

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that rotigotine be listed for the treatment of Parkinson's disease (PD), if the following clinical criterion and condition are met:

Clinical criterion
- For adjunctive therapy to levodopa for the treatment of patients with advanced stage Parkinson's disease (APD).

Condition
- Total daily drug plan cost for rotigotine should be comparable to the drug plan costs of ropinirole or pramipexole.

Reasons for Recommendation:
1. One randomized controlled trial (RCT) (Mizuno 2014 [N = 420]) demonstrated that rotigotine was non-inferior to ropinirole and superior to placebo for improving motor function in patients with APD who are taking levodopa, and one RCT (Study SP515 [N = 506]) demonstrated that rotigotine was non-inferior to pramipexole and superior to placebo for change from baseline in time spent *off*.
2. Additional placebo-controlled RCTs demonstrated that treatment with rotigotine resulted in statistically significant and clinically meaningful improvements in motor function in patients with APD (Study SP650 [N = 351] and Nomoto 2014 [N = 174]) and a mixed population of PD patients (Study SP889 [N = 336]).
3. At the submitted price ([redacted]), the annual cost of rotigotine ranges from [redacted] per patient, which is more costly than generic pramipexole immediate release (IR) (1.5 mg to 4.5 mg daily) and generic ropinirole IR (3 mg to 24 mg daily).

Of Note:
CDEC noted that patients living with PD have indicated that there is a need for a non-oral treatment option for APD; however, rotigotine should be used in combination with an oral medication (i.e., levodopa) when used in patients with APD.

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Background:
Rotigotine transdermal patches are approved for the following indications: the treatment of the signs and symptoms of idiopathic PD (as monotherapy or in combination with levodopa), and the symptomatic treatment of moderate to severe idiopathic restless leg syndrome in adults. The current CADTH Common Drug Review (CDR) resubmission is for the treatment of early idiopathic PD (EPD) with rotigotine monotherapy and the treatment of advanced idiopathic PD (APD) with rotigotine in combination with levodopa.

Rotigotine is available in the following transdermal patch doses for use in the treatment of PD: 2 mg/24 h, 4 mg/24 h, 6 mg/24 h, and 8 mg/24 h. Rotigotine is applied once a day and should remain on the skin for 24 hours. The maximum recommended dose for EPD is 8 mg/24 h and for APD is 16 mg/24 h. Multiple patches are required to achieve doses higher than 8 mg/24 h.

Submission History:
Rotigotine was previously reviewed by CDEC for treatment of idiopathic PD and received a "do not list" recommendation (see *CDEC Final Recommendation*, May 28, 2014). The reason for the recommendation was as follows: Two RCTs failed to consistently demonstrate that rotigotine is non-inferior to ropinirole in EPD (Study SP513; N = 561) and pramipexole in APD (Study SP515; N = 506); therefore, the comparative clinical benefit of rotigotine versus other less costly non-ergolinic dopamine agonists is uncertain.

In the EPD trial, rotigotine failed to show non-inferiority against ropinirole for improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) Part II (activities of daily living) plus III (motor function) subtotal score and for the number of responders achieving at least a 20% reduction in the subtotal score. In the APD trial, non-inferiority against pramipexole was demonstrated for the absolute reduction in time spent *off*, but not for the number of responders achieving a 30% or more reduction in *off* time. CDEC noted there were insufficient data to confirm the benefit of transdermal administration compared with oral administration, with respect to patient adherence and clinical end points, and that application site reactions were the most commonly reported adverse event leading to discontinuation by rotigotine-treated patients in both Studies SP512 (5%) and SP513 (8%). CDEC also noted there was insufficient evidence about the long-term efficacy of rotigotine.

The basis of the manufacturer's resubmission is new clinical information, specifically two RCTs in the subgroup of patients with APD, including one active comparator trial, and a change in price for the incremental doses of rotigotine ([redacted]). There is also a change in the manufacturer's requested listing, which is now restricted to use of rotigotine as adjunctive therapy to levodopa for the treatment of patients with APD.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR:
- The final CDR clinical and pharmacoeconomic review reports from the initial rotigotine submission
- A critique of the manufacturer's pharmacoeconomic evaluation
- New clinical data from three RCTs
- A network meta-analysis (NMA) submitted by the manufacturer
- Patient group input.

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Patient Input Information

One patient group, Parkinson Society Canada (PSC), responded to the CDR call for patient input. Information was obtained from Canadian guidelines and from a national survey of patients and caregivers. The following is a summary of information provided by the patient group:

- PD is characterized by motor manifestations such as slowness of movement, loss of dexterity, rigidity, tremor, restless legs, gait problems, and postural instability; by neuropsychiatric symptoms that include depression, dementia, psychosis, and cognitive impairment; and by speech impairment, sleep disorders, fatigue, autonomic dysfunction, urinary dysfunction, orthostatic hypotension, constipation, nausea, and erectile dysfunction.
- PD poses a significant physical, emotional, and financial burden on the lives of patients and caregivers. Patients are often unable to work, experience progressive loss of their ability to perform basic daily tasks, and participate less and less in family, social, and recreational activities.
- Those affected with PD and their caregivers reported that current medications for PD can be associated with side effects including nausea, vomiting, dizziness, sleep disruption, mood changes, visual hallucinations, and obsessive compulsive behaviour. In addition, currently available therapies can be associated with a significant pill burden, which can negatively impact adherence to treatment, especially for patients who have difficulty swallowing.
- "*Off* periods" (time without medication effect) were identified by people living with PD as one of the more significant concerns with currently available medications.

Clinical Trials

The updated CDR systematic review included three new double-blind RCTs. Two trials enrolled patients with APD (Mizuno 2014 [N = 420] and Nomoto 2014 [N = 174]) and one enrolled patients with PD of all stages but predominantly APD (Study SP889 [N = 336]). The three trials were of ≤ 16 weeks duration and were of similar overall design with a titration phase of eight to 12 weeks, depending on the trial, followed by a maintenance phase of four weeks, during which the test drug dose could not be changed. Rotigotine was initiated at 2 mg/24 h and titrated up on the basis of symptom control and tolerability to a maximum of 16 mg/24 h. Mizuno 2014 was a 16-week, three-group, phase 3 trial conducted in Japan that compared rotigotine with placebo and ropinirole as adjunct therapy to levodopa in APD. The study was designed to demonstrate superiority to placebo and non-inferiority to ropinirole for UPDRS Part III sum score. Nomoto 2014 was a phase 2, placebo-controlled trial conducted in Japan of 12 to 14 weeks. Study SP889 was a 12-week, placebo-controlled trial in patients with EPD and APD (about 80% of all participants were on levodopa and met the criteria for APD).

The initial CDR submission included the following two studies conducted in patients with APD:

- SP515 (N = 506) compared rotigotine (4 mg/24 h titrated weekly up to 16 mg/24 h) with pramipexole capsules (0.375 mg/day titrated to 4.5 mg/day) or placebo transdermal patches or capsules over 32 weeks. Rotigotine was assessed for superiority versus placebo and for non-inferiority compared with pramipexole.
- SP650 (N = 351) was a three-group trial comparing rotigotine at a target dose of 8 mg/24 h, rotigotine at a target dose of 12 mg/24 h, and placebo transdermal patches for 38 weeks.

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Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- UPDRS (Part III) — assesses speech, tremors, rigidity, repeated movements (e.g., rapidly alternating movements of the hands), as well as gait, postural stability, and other kinetic parameters, with total score ranging from 0 (no disability) to 56 (worst). Estimates for the minimal clinically important difference (MCID) in the UPDRS Part III range from 2.4 to 6.6 points.
- Time spent *off* (loss of optimum effects of treatment) — reduction in absolute time spent *off* was measured by self-completed PD home diaries. Estimated MCIDs for *off* time range from 1.3 hours to 1.9 hours.
- Response to therapy — defined as a ≥ 30% decrease in the sum of the UPDRS (Parts II and III) subtotal scores from baseline to the end of the double-blind maintenance phase.
- Health-related quality of life — assessed using the EuroQol 5-Dimensions Questionnaire (EQ-5D) visual analogue scale, the Parkinson Disease Questionnaire 39 (PDQ-39), and the Parkinson Disease Questionnaire 8 (PDQ-8).
- Nocturnal sleep — assessed with the Parkinson Disease Sleep Scale (PDSS) at baseline and at the end of the maintenance phase or at withdrawal assessment. The MCID for the PDSS is unknown.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The UPDRS Part III (*on* state) sum score was the primary efficacy outcome for Mizuno 2014 and for Nomoto 2014. The co-primary outcomes in both Studies SP515 and SP650 were change from baseline in absolute time spent *off* and response to therapy.

Efficacy

<u>New Studies in the CDR Resubmission (Mizuno 2014, Nomoto 2014, and SP889)</u>

- Rotigotine was statistically superior to placebo and non-inferior to ropinirole for change from baseline UPDRS Part III (motor examination). The adjusted mean differences in change from baseline were:
  - Rotigotine versus ropinirole: −1.4 (95% confidence interval [CI], −3.2 to −0.6)
  - Rotigotine versus placebo: −6.4 (95% CI, −8.6 to −4.2) in Mizuno 2014, −5.7 (95% CI, −8.2 to −3.2) in Nomoto 2014, and −3.6 (95% CI, −5.4 to −1.7) in SP889
- A statistically significantly greater proportion of rotigotine-treated patients were considered UPDRS Part III responders compared with placebo and ropinirole. The differences in proportion were:
  - Rotigotine versus ropinirole: 11.4% (95% CI, 2.1 to 20.7)
  - Rotigotine versus placebo: 23.9% (95% CI, 11.6 to 36.1) in Mizuno 2014, and 30.2% (95% CI, 16.2 to 44.3) in Nomoto 2014
- Rotigotine was statistically superior to placebo for reducing *off* time in Mizuno 2014 and Nomoto 2014; however, there was no statistically significant difference between rotigotine and ropinirole. The adjusted mean differences for change from baseline in *off* time were:
  - Rotigotine versus ropinirole: 0.5 h (95% CI, −0.2 to 1.2)
  - Rotigotine versus placebo: −1.1 h (95% CI, −1.9 to −0.3) in Mizuno 2014 and −1.4 h (95% CI, −2.5 to −0.3) in Nomoto 2014.

[redacted]

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[redacted]

- For change from baseline in UPDRS Part II sum score (activities of daily living), rotigotine was statistically superior to placebo and there was no significant difference between rotigotine and ropinirole. The mean differences in change from baseline were:
  - Rotigotine versus ropinirole: −0.6 (95% CI, −1.4 to 0.1)
  - Rotigotine versus placebo: −2.4 (95% CI, −3.3 to −1.5) in Mizuno 2014, −2.2 (95% CI, −3.1 to −1.2) in Nomoto 2014, and −1.5 (95% CI, −2.3 to −0.7) in SP889.
- For change from baseline in PDSS-2, rotigotine was statistically superior to placebo and there was no significant difference between rotigotine and ropinirole. The adjusted mean differences for change from baseline in PDSS-2 were:
  - Rotigotine versus ropinirole: −0.7 (95% CI, −1.9 to 0.6)
  - Rotigotine versus placebo: −2.6 (95% CI, −4.1 to −1.1) in Mizuno 2014, and −4.3 (95% CI, −6.1 to −2.5) in SP889.

<u>Studies from Initial CDR Submission (SP515 and SP650)</u>

- Rotigotine was superior to placebo for change from baseline in time spent *off*, with mean differences reported as follows:
  - Rotigotine 8 mg/24 h versus placebo: −1.6 h (95% CI, −2.3 to −0.9) in SP515
  - Rotigotine 8 mg/24 h versus placebo: −1.8 h (95% CI, –2.6 to –1.0) in SP650
  - Rotigotine 12 mg/24 h versus placebo: –1.2 h (95% CI, –2.0 to –0.4) in SP650.
- Rotigotine was non-inferior to pramipexole for change from baseline in time spent *off* with a mean difference of 0.35 h (95% CI, –0.21 to 0.92) in the full analysis set and 0.44 h (95% CI, –0.15 to 1.03) in the per-protocol analysis.
- Response to therapy was reported for a greater proportion of rotigotine-treated patients compared with placebo-treated patients in both SP515 (60% versus 35%) and SP650 (57% with rotigotine 8 mg/24 h, 55% with rotigotine 12 mg/24 h, and 34% with placebo). The between-group differences were reported as follows:
  - Rotigotine versus placebo: 24.7% (95% CI, 13.2 to 36.3) in SP515
  - Rotigotine 8 mg/24 h versus placebo: 22.2% (95% CI, 9.7 to 34.7) in SP650
  - Rotigotine 12 mg/24 h versus placebo: 20.6% (95% CI, 7.9 to 33.3) in SP650.
- Rotigotine failed to demonstrate non-inferiority against pramipexole for response to therapy, based on the non-inferiority margin of –15%. The between-group difference for rotigotine versus pramipexole was –7.3% (95% CI, –16.7% to 2.1%) in the full analysis set and –6.4% (–16.4% to 3.6%) in the per-protocol set.
- Nocturnal sleep improved in the rotigotine and pramipexole groups with mean (standard deviation) changes from baseline in PDSS of 4.4 (21.07) and 4.8 (19.30), respectively, while the mean change in the placebo group was –2.9 (21.78).

Harms (Safety and Tolerability)

- The most common adverse events associated with rotigotine were application site reactions, dyskinesia, nausea, perception disturbances or hallucination, vomiting, and somnolence.
- The proportion of patients who reported at least one adverse event was reported as follows:
  - Mizuno 2014: rotigotine (88.7%), ropinirole (77.8%), and placebo (69.4%)
  - Nomoto 2014: rotigotine (94.3%) and placebo (88.5%)
  - SP889: rotigotine (71.7%) and placebo (56.3%)
  - SP515: rotigotine (69%), pramipexole (69%), and placebo (66%)

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  - SP650: rotigotine (93%), rotigotine 12 mg/24 h (93%), and placebo (91%).
- The proportion of patients with at least one serious adverse event was reported as follows:
  - Mizuno 2014: rotigotine (4.2%), ropinirole (3.0%), and placebo (7.1%)
  - Nomoto 2014: 3.5% in both the rotigotine and placebo groups
  - SP889: rotigotine (5.2%) and placebo (3.1%)
  - SP515: rotigotine (9%), pramipexole (7%), and placebo (9%)
  - SP650: rotigotine (7%), rotigotine (10%), and placebo (8%).
- Withdrawals due to adverse events were reported as follows:
  - Mizuno 2014: rotigotine (7.7%), ropinirole (7.8%), and placebo (9.4%)
  - Nomoto 2014: rotigotine (10.3%) and placebo (8.1%)
  - SP889: 6.3% in both the rotigotine and placebo groups
  - SP515: rotigotine (5%), pramipexole (7%), and placebo (5%)
  - SP650: rotigotine (7%), rotigotine (15%), and placebo (8%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of rotigotine (up to 8 mg daily in patients with EPD and 16 mg daily in patients with APD) to the non-ergolinic dopamine agonists, pramipexole IR (up to 4.5 mg daily), and ropinirole IR (up to 24 mg daily). The perspective was that of a public health care payer with a time horizon of one year of therapy. Similar efficacy between comparators was assumed on the basis of a manufacturer-sponsored NMA.

Key limitations in the manufacturer's analyses included:

- Mathematical errors in the calculations
- NMA results generalized to a patient population that is assumed to use lower doses of rotigotine
- Lack of clarity regarding the source of the dose distribution used in the analysis
- Assumption of similar safety based on a pairwise meta-analysis that included few studies involving rotigotine
- Potential underestimation of the dose equivalency of rotigotine with comparators
- Assumptions regarding how doses of pramipexole and ropinirole would be dispensed did not consider the possibility that pharmacists would minimize the number of claims required to achieve each dose in order to simplify dosing for patients.

At the submitted price of [redacted], the annual cost of rotigotine, not including markups or dispensing fees, at recommended doses ranges from [redacted] per patient, which is more costly than that of generic pramipexole IR (1.5 mg to 4.5 mg daily in three equal doses; $288 to $864 per patient) and more than generic ropinirole IR (3 mg to 24 mg daily in three equal doses; $310 to $1,369 per patient).

Several methods of estimating the weighted average or range of plausible costs for each non-ergolinic dopamine agonist comparator were explored by CDR. Rotigotine was more costly than generic pramipexole IR and generic ropinirole IR for APD patients in all scenarios, including the manufacturer's analyses. Therefore, rotigotine would result in increased expenditures for drug plans.

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Other Discussion Points:
CDEC noted the following:
- Rotigotine is also indicated for use in the treatment of EPD; however, this indication was not specified in the manufacturer's requested listing criteria for the current resubmission.
- The once-daily non-oral dosing of rotigotine may be important to some patient populations, particularly those with problems swallowing.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:
- PD is a chronic condition and the long-term efficacy of rotigotine is uncertain.
- There is no evidence evaluating the efficacy of rotigotine for the following subpopulations of patients with PD:
  - Patients who have gastrointestinal problems such as dysphagia, gastroparesis, or malabsorption
  - Patients with PD who have experienced inadequate control on or intolerance to pramipexole or ropinirole.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

October 21, 2015 Meeting
Regrets:

None.

Conflicts of Interest:

None.

About This Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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