CDEC FINAL RECOMMENDATION

ROTIGOTINE
(Neupro — UCB Canada Inc.)
Indication: Idiopathic Parkinson Disease (early and advanced)

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that rotigotine not be listed for the treatment of idiopathic Parkinson disease (PD).

Reason for the Recommendation:
Two randomized controlled trials (RCTs) failed to consistently demonstrate that rotigotine is non-inferior to ropinirole (SP513; N = 561) and pramipexole (SP515; N = 506); therefore, the comparative clinical benefit of rotigotine versus other less costly non-ergolinic dopamine agonists is uncertain.

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 legs syndrome in adults. The current Common Drug Review (CDR) submission 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 in Canada: 2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours. 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 hours and 16 mg/24 hours for APD. Multiple patches may be used to achieve doses higher than 8 mg/24 hours.

Summary of CDEC Considerations
CDEC considered the following information prepared by CDR: a systematic review of RCTs focused on rotigotine in the treatment of EPD and APD, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of information provided by one patient group that responded to the CDR call for patient input.

- The most common symptoms of PD identified by the patient group included: loss of motor control/dexterity, muscle stiffness, nausea, tremors, fatigue, sleep disturbances, mood changes, reduced mobility, memory and cognitive impairment, speech impairment, balance problems, and restless legs.
- 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.
- As PD progresses, individuals become more reliant on medication to maintain their ability to function. Medication schedules increase in complexity, and the timing of the administration of medications becomes crucial because "off-periods" (time without medication effect) can strike quickly and at any time, leaving patients immobilized. These "off" times were identified by people living with PD as one of the more significant concerns around current medications.

Clinical Trials

Four phase 3, double-blind RCTs met the inclusion criteria for the CDR systematic review. Two studies were conducted in patients with EPD (SP512 and SP513) and two were conducted in patients with APD (SP515 and SP650).

- SP512 (N = 277) compared rotigotine (2 mg/24 hours titrated weekly up to 6 mg/24 hours) with placebo transdermal patches over 38 weeks.
- SP513 (N = 561) compared rotigotine (4 mg/24 hours titrated weekly up to 8 mg/24 hours) with ropinirole capsules (0.75 mg/day titrated to 24.0 mg/day) or placebo transdermal patches/capsules over 48 weeks. Rotigotine was assessed for superiority versus placebo and for non-inferiority compared with ropinirole.
- SP515 (N = 506) compared rotigotine (4 mg/24 hours titrated weekly up to 16 mg/24 hours) with pramipexole capsules (0.375 mg/day titrated to 4.5 mg/day) or placebo transdermal patches/capsules over 32 weeks. Rotigotine was assessed for superiority versus placebo and for non-inferiority compared with pramipexole.
- SP650 (N = 351) was a three-arm trial comparing rotigotine at a target dose of 8 mg/24 hours, rotigotine at a target dose of 12 mg/24 hours, and placebo transdermal patches for 38 weeks.

Outcomes

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

<u>Early PD:</u>

- Change from baseline in Unified Parkinson Disease Rating Scale (UPDRS) subscale score (parts II and III) — assesses disability and impairment in PD with part II focusing on activities of daily living (13 items) and part III focusing on motor examination (14 items).
- Response to therapy — defined as a ≥ 20% 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 EQ-5D visual analogue scale (VAS).
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

Advanced PD:

- Time spent "off" (loss of optimum effects of treatment) — reduction in absolute time spent "off" was measured by self-completed Parkinson disease home diaries.
- 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 EQ-5D VAS and the Parkinson Disease Questionnaire 39 (PDQ-39).
- Nocturnal sleep — assessed with the Parkinson Disease Sleep Scale (PDSS) at baseline and at the end of the maintenance phase or at withdrawal assessment.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The co-primary outcomes in both EPD studies were change from baseline in UPDRS subscale score (parts II and III) and response to therapy. The co-primary outcomes in both APD studies were change from baseline in absolute time spent "off" and response to therapy. Only the co-primary outcomes were analyzed for statistical significance.

Efficacy

Early PD

- Rotigotine was superior to placebo for change from baseline in UPDRS subscale scores, with between-group mean differences of –5.28 (95% confidence interval [CI], −7.60 to −2.96) in SP512 and –4.49 (95% CI: −6.64 to −2.35) in SP513.
- Rotigotine failed to demonstrate non-inferiority against ropinirole for change from baseline in UPDRS subscales based on the non-inferiority margin of 2.9. The mean difference for rotigotine versus ropinirole was 3.96 (95% CI: 2.18 to 5.73) in the full-analysis set and 5.54 (95% CI: 3.37 to 7.71) in the per-protocol set.
- Response to therapy was reported for a greater proportion of rotigotine-treated patients compared with placebo-treated patients in both SP512 (48% versus 19%) and SP513 (52% versus 30%). The between-group differences were 28.7% (95% CI: 18.0 to 39.4) in SP512 and 21.7% (95% CI: 11.1 to 32.4) in SP513.
- Rotigotine failed to demonstrate non-inferiority against ropinirole for response to therapy, based on a non-inferiority margin of –15%. The between-group difference for rotigotine versus ropinirole was –16.6% (–25.7% to –7.6%) in the full-analysis set and –20.0 (–30.5% and –9.4%) in the per-protocol set.
- Mean (SD) change from baseline in EQ-5D VAS was reported as follows:
  - rotigotine 0.0 (12.2) and placebo −1.2 (15.0) in SP512
  - rotigotine 3.6 (15.76), ropinirole 5.5 (16.12), and placebo −0.8 (17.40) in SP513.

Advanced PD

- Rotigotine was superior to placebo for change from baseline in time spent "off," with mean differences reported as follows:
  - rotigotine 8 mg/24 hours versus placebo: −1.6 hours (95% CI: −2.3 to −0.9) in SP515
  - rotigotine 8 mg/24 hours versus placebo: −1.8 hours (95% CI: –2.6 to –1.0) in SP650
  - rotigotine 12 mg/24 hours versus placebo: –1.2 hours (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 hours (95% CI: –0.21 to 0.92) in the full-analysis set and 0.44 hours (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 hours, 55% with rotigotine 12 mg/24 hours, 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 hours versus placebo: 22.2% (95% CI: 9.7 to 34.7) in SP650
  - rotigotine 12 mg/24 hours 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.
- Mean (SD) changes from baseline in EQ-5D VAS were: rotigotine 8 mg/24 hours 4.3 (15.62) rotigotine 12 mg/24 hours 3.6 (20.43) placebo –1.2 (18.51) in SP650.
- Mean (SD) changes from baseline in PDQ-39 were: rotigotine –5.0 (9.07), pramipexole –6.1 (9.45), and placebo –2.1 (9.52) in SP515.
- Nocturnal sleep improved in the rotigotine and pramipexole groups with mean (SD) 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)

Early PD

- The proportion of patients with at least one adverse event was reported as follows:
  - rotigotine (90%) and placebo (89%) in SP512
  - rotigotine (85%), ropinirole (82%), and placebo (77%) in SP513.
- The proportion of patients with at least one serious adverse event was reported as follows:
  - rotigotine (7%) and placebo (4%) in SP512
  - rotigotine (13%), ropinirole (10%), and placebo (8%) in SP513.
- Withdrawals due to adverse events were reported as follows:
  - rotigotine (14%) and placebo (6%) in SP512
  - rotigotine (17%), ropinirole (13%), and placebo (5%) in SP513.

Application site reactions were the most commonly reported reason for withdrawal with rotigotine in SP512 and SP513.

Advanced PD

- The proportion of patients who reported at least one adverse event was reported as follows:
  - rotigotine (69%), pramipexole (69%), and placebo (66%) in SP515
  - rotigotine 8 mg/24 hours (93%), rotigotine 12 mg/24 hours (93%), and placebo (91%) in SP650.
- The proportion of patients with at least one serious adverse event was reported as follows:
  - rotigotine (9%), pramipexole (7%), and placebo (9%) in SP515
  - rotigotine 8 mg/24 hours (7%), rotigotine 12 mg/24 hours (10%), and placebo (8%) in SP650.

- Withdrawals due to adverse events were reported as follows:
  - rotigotine (5%), pramipexole (7%), and placebo (5%) in SP515
  - rotigotine 8 mg/24 hours (7%), rotigotine 12 mg/24 hours (15%), and placebo (8%) in SP650.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing drug costs of rotigotine with generic pramipexole and generic ropinirole, assuming similar clinical efficacy among these three non-ergolinic dopamine agonists in EPD (as monotherapy) and APD (as an adjunct to levodopa) based on the results of a manufacturer-sponsored network meta-analysis (NMA). The NMA showed that for both EPD and APD, the efficacy of rotigotine, ropinirole, and pramipexole appeared similar at 11 to 16 weeks and 24 to 28 weeks after completion of a titration period. It is unclear if the findings of the NMA can be generalized to a longer time period, or to a population using different dosages than those used in the clinical trials. Furthermore, the NMA did not assess the comparative safety profile of rotigotine with that of pramipexole and ropinirole. The expected average maintenance doses of rotigotine and incremental cost compared with generic pramipexole used in the manufacturer's base-case scenario were likely underestimated, especially in APD.

At recommended doses, CDR estimated that rotigotine (2 mg/24 hours to 8 mg/24 hours in EPD, $3.54 to $7.27; and 4 mg/24 hours to 16 mg/24 hours in APD, $6.50 to $14.54) is more costly than generic pramipexole (1.5 mg to 4.5 mg daily, $0.79 to $2.37) and generic ropinirole (3 mg to 24 mg daily, $0.85 to $4.37); as well as other drugs used for the management of EPD and APD, such as oral levodopa-decarboxylase inhibitor combinations ($0.84 to $8.00 daily), entacapone ($0.40 to $3.21 daily), or monoamine-oxidase B inhibitors ($1 to $7 daily).

Other Discussion Points:

CDEC noted the following:

- The clinical expert consulted by CDR noted that the dose of ropinirole used in study SP513 (24 mg/day) was greater than the dosage typically prescribed for patients with EPD in routine clinical practice (10 mg/day to 15 mg/day). This may have biased the efficacy results in favour of ropinirole and the safety results in favour of rotigotine in that trial.
- CDEC considered the route of administration for rotigotine and noted that there was insufficient data to confirm the benefit of transdermal administration compared with oral administration with respect to patient adherence and clinical endpoints. In addition, it was noted that application site reactions were the most commonly-reported adverse events leading to discontinuation from both SP512 (5%) and SP513 (8%).

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.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets:
February 19, 2014: Two CDEC members could not attend this portion of the meeting.

May 21, 2014: None
Conflicts of Interest:
February 19, 2014: None

May 21, 2014: 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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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