Common Drug Review

Pharmacoeconomic Review Report (Resubmission)

November 2015

Drug	Rotigotine (Neupro)
Indication	Treatment of the signs and symptoms of idiopathic Parkinson's disease. Neupro may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.
Listing request	As adjunctive therapy to levodopa for the treatment of patients with advanced Parkinson's disease.
Dosage form	Transdermal Patch
NOC date	March 21, 2013
Manufacturer	UCB Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

TABLE OF CONTENTS

Tables

ABBREVIATIONS

APD	advanced Parkinson's disease
CDR	CADTH Common Drug Review
DA	dopamine agonist
EPD	early Parkinson's disease
IR	immediate release
NMA	network meta-analysis
ODB	Ontario Drug Benefit
PD	Parkinson's disease
RLS	restless legs syndrome
TRUST	Transdermal Rotigotine User Surveillance Trial

SUMMARY

Background

Rotigotine (Neupro) is a once-daily transdermal delivery system (patch) indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD), both in early Parkinson's disease (EPD) without concomitant levodopa therapy, or in advanced Parkinson's disease (APD) as an adjunct to levodopa therapy. Rotigotine is a non-ergolinic dopamine agonist (DA).[1]

Rotigotine was reviewed for the same indication by the CADTH Common Drug Review (CDR) in 2013, and received a "do not list" recommendation by the Canadian Drug Expert Committee (CDEC).[2] This review is a resubmission based on new clinical data and a reduced price.

Rotigotine patches are available in 1 mg/24 h, 2 mg/24 h, 3 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h strengths. The recommended dosing for PD is to initiate at 2 mg/24 h and increase in weekly increments of 2 mg/24 h to an effective dose of up to 8 mg/24 h for EPD and up to 16 mg/24 h for APD. The manufacturer has submitted a confidential price of [redacted] daily. This is the [redacted].

The 1 mg/24 h and 3 mg/24 h patches are recommended for restless legs syndrome (RLS) rather than for PD,[1] and are marketed at prices of $3.54 and $6.50 per patch, respectively.[3]

For this resubmission, the manufacturer is requesting a listing as adjunctive therapy to levodopa for the treatment of patients with APD; this review will thus focus on the APD indication.

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost comparison of rotigotine (up to 8 mg/24 h in patients with EPD and 16 mg/24 h in patients with APD) to the non-ergolinic DAs, pramipexole immediate release (IR) (up to 4.5 mg daily[4]) and ropinirole IR (up to 24 mg daily).[5] The perspective was that of a public health care payer with a time horizon of one year. Similar efficacy between comparators was assumed on the basis of a published network meta-analysis (NMA),[6,7] while similar safety was assumed based on a pairwise meta-analysis by Zhou et al.[8] The manufacturer assumed a rotigotine to pramipexole comparative dosage ratio of 2.666:1, and a rotigotine to ropinirole dosage ratio of 1:1.5.[9-13] Only drug costs were considered. Ontario Drug Benefit (ODB) Formulary list prices from April 2015 were used to estimate the costs of generic pramipexole IR and generic ropinirole IR; the ODB markup of 8% was included, and a dispensing fee of $8.83 was applied every 30 days for each prescription. Patient dosage distributions were estimated using manufacturer forecasts.

The manufacturer concluded that the weighted average annual cost of rotigotine was [redacted] per APD patient, [redacted] more than that of pramipexole ([redacted] per patient per year) and [redacted] more than that of ropinirole ([redacted] per patient per year). For EPD patients, the manufacturer concluded that the weighted average annual cost of rotigotine was [redacted] per patient, [redacted] more than that of pramipexole ([redacted] per patient per year) and [redacted] more than that of ropinirole ([redacted] per patient per year).

Key Limitations

- **Mathematical errors in the analysis:** The manufacturer-submitted analysis contained several mathematical errors which, when corrected, without alteration of any assumptions, lead to an estimated weighted average annual cost of rotigotine for APD patients of [redacted], which was [redacted] more than that of pramipexole ([redacted] per APD patient per year) and [redacted] more than the corrected cost of ropinirole ([redacted] per APD patient per year). For EPD patients, these mathematical corrections lead to a weighted average annual cost of rotigotine of [redacted] per patient, which remained [redacted] more than that of pramipexole ([redacted] per patient per year), but increased to [redacted] more than that of ropinirole ([redacted] per patient per year). (See CDR reanalyses in Appendix 2 for details.)
- **Generalizability of NMA results to population using lower rotigotine doses:** The average rotigotine dose assumed by the manufacturer in the pharmacoeconomic submission ([redacted] mg/24 h for APD and [redacted] mg/24 h for EPD) is similar to the average daily doses seen in European sales data for PD patients (2014 range: [redacted] mg/24 h to [redacted] mg/24 h), but less than the average dose seen in a large observational trial[14] or the mean or median doses used in the clinical trials included in the NMA (APD range: 7.2 mg/24 h to 12.9 mg/24 h).[6,15-17] It is therefore unclear if the NMA findings (i.e., similar efficacy to ropinirole and pramipexole) can be generalized to the lower doses of rotigotine used in the manufacturer's pharmacoeconomic submission.
- **Assumption of similar safety:** As the NMA[6,7] did not assess safety outcomes and the pairwise meta-analysis by Zhou et al. included only one rotigotine trial for each PD subpopulation,[8] the relative safety of rotigotine to pramipexole and ropinirole is uncertain.
- **Comparator dispensing assumptions:** While the manufacturer's assumptions of how doses of pramipexole and ropinirole might be dispensed are technically accurate,[9-12] it is likely that pharmacists will minimize the number of claims required to achieve each dose in order to simplify dosing for patients, as they would only need to take one dose strength. Thus a 0.75 mg, three-times-daily dose of pramipexole is likely to be dispensed as three 0.25 mg tablets three times daily rather than as one 0.25 mg tablet + one 0.5 mg tablet, while the 8 mg dose is more likely to be dispensed as four 2 mg tablets three times daily rather than as 1 mg, 2 mg, and 5 mg tablets. These changes reduce the drug costs as well as the number of dispensing fees required. Additionally, the 0.5 mg pramipexole tablet is not reimbursed in some jurisdictions, while the 1 mg tablet is scored for splitting. If these substitutions are assumed, the weighted average annual cost of pramipexole is reduced to [redacted] ([redacted] less per APD patient per year than rotigotine) and that of ropinirole is reduced to [redacted] ([redacted] less per APD patient per year than rotigotine). For EPD patients, these substitutions reduced the weighted annual cost of pramipexole to [redacted] ([redacted] less per EPD patient per year than rotigotine) and that of ropinirole to [redacted] ([redacted] less per EPD patient per year than rotigotine). (See CDR reanalyses in Appendix 2 for details.)
- **Unclear source of information on patient distribution:** Despite the availability of rotigotine dosing information from the observational Transdermal Rotigotine User Surveillance Trial (TRUST) and the higher rotigotine doses used in clinical trials, the manufacturer assumed a distribution based on internal forecasting of unknown methodology, with a mean dose of [redacted] mg/24 h for APD patients and [redacted] mg/24 h for EPD patients. With only [redacted] of APD patients and [redacted] of EPD patients assumed to be using doses greater than 8 mg/24 h, [redacted] assumed to use 16 mg/24 h, it is likely that the number of patients who will use more than one patch daily has been underestimated (along with, consequently, the cost of rotigotine). Of particular interest is the Mizuno et al. 2014 trial, where 50% of APD patients in the rotigotine group had been titrated to the maximum dose of rotigotine (16 mg/24 h) by the start of the maintenance phase.[18,19]

- **Underestimation of comparator dose equivalence:** As presented in the CDR Clinical Report (Table 27), the comparative dose ratio used by the manufacturer for rotigotine compared with pramipexole (2.666:1) and ropinirole (1:1.5)[9-13] differed from that reported in other clinical trials. In Study SP515 (Poewe et al., 2007[20]), the authors noted that the failure to show non-inferiority of rotigotine versus pramipexole for the responder rates might indicate the need for a higher dose of rotigotine versus pramipexole than reflected by the 4:1 ratio reached in this trial. Further, the mean dose ratio in the Mizuno et al. 2014 trial[18] was 1.4:1 for rotigotine to ropinirole. Therefore, the incremental cost of rotigotine compared with pramipexole and ropinirole in APD was likely underestimated. See Appendix 1 for price reduction scenarios.

Issues for Consideration

- **Patient convenience/increased adherence:** As a once-daily transdermal patch, the dosing schedule for rotigotine is less complicated than those for pramipexole or ropinirole, which may increase adherence or convenience for some patients (an observational study found high adherence rates among PD patients on rotigotine maintenance therapy, although no comparative data are available).[21] Additionally, the transdermal mode of administration may have an advantage for PD patients (particularly APD patients) who experience difficulty swallowing, although no data for this subpopulation are available (See CDR Clinical Report, Section 5.1, and Clinical Report Appendix 1: Patient Input.)
- **Potential use of 1 mg/24 h and 3 mg/24 h patches:** While the recommended dosing for PD patients includes titration increments of 2 mg/24 h, some PD patients may be prescribed doses requiring the use of the 1 mg/24 h or 3 mg/24 h patches, although these strengths are recommended for RLS rather than for PD (Appendix 3, Table 10). The 1mg/24 h patch is priced [redacted], however the 3 mg/24 h ex-factory price is [redacted].[3] Patients using the 3 mg/24 h or the 1 mg/24 h patch in combination with another dose (i.e., to achieve an odd-numbered dose) would [redacted] in jurisdictions that reimburse the 1 mg/24 h or 3 mg/24 h patches.

Results and Conclusions

At the confidential submitted price of [redacted], the weighted average annual cost of rotigotine under the manufacturer's assumed APD patient dose distribution and CDR's dose dispensing assumptions, not including markups or dispensing fees, is [redacted], which is [redacted] more expensive than that of generic pramipexole IR [redacted] per APD patient per year) and [redacted] more expensive than that of generic ropinirole IR ([redacted] per APD patient per year). The listing of rotigotine would result in increased expenditures.

The long-term comparative effectiveness and dose equivalence of rotigotine with pramipexole and ropinirole remain unknown. Several methods of estimating the weighted average or range of plausible costs for each non-ergolinic DA comparator were explored by CDR by altering the comparator dispensing assumptions and dose equivalence ratios, and using the upper and lower mean trial dosing rather than the manufacturer's forecasted distribution. Rotigotine was more expensive than generic pramipexole IR and generic ropinirole IR in all scenarios. The extent to which the price of rotigotine would have to be reduced to be equal to the cost of comparators varied from [redacted] to [redacted] for pramipexole and from [redacted] to [redacted] for ropinirole. Similarly, in EPD patients, rotigotine led to increased expenditures for drug plans compared with pramipexole and ropinirole.

Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE FOR DRUGS IN EARLY AND ADVANCED IDIOPATHIC PARKINSON'S DISEASE

Drug/ Comparator	Strength	Form	Price ($)	Recommended Daily Dose[a]	Daily Drug Cost ($)	Annual Cost ($)
Non-ergolinic DAs (as monotherapy in EPD or in combination with levodopa/decarboxylase inhibitor in APD)						
Rotigotine (Neupro)	**2 mg/24 h 4 mg/24 h 6 mg/24 h 8 mg/24 h**	**Patch**	[redacted][b]	**EPD: 2 mg to 8 mg APD: 4 mg to 16 mg**	[redacted]	[redacted]
Pramipexole (generics)	0.25 mg 0.50 mg 1 mg 1.5 mg	Tablet	0.2628 0.5257[c] 0.5257 0.5257	1.5 mg to 4.5 mg in three equal doses	0.79[d] to 2.37	288 to 864
Ropinirole (generics)	0.25 mg 1 mg 2 mg 5 mg	Tablet	0.0710 0.2838 0.3122 0.8596	3 mg to 24 mg in three equal doses	0.85 to 3.75[e]	310 to 1,369[e]
Oral levodopa/decarboxylase inhibitor combinations (as monotherapy in EPD or in combination with other drugs in APD)						
Levodopa/ carbidopa (generics)	100 mg/10 mg 100 mg/25 mg 250 mg/25 mg	Tablet	0.1877 0.2803 0.3129	300 mg to 1,500 mg of levodopa in three to four daily doses	0.56 to 1.88	204 to 686
	100 mg/25 mg 200 mg/50 mg	Controlled release tablet	0.3857 0.7115	200 mg to 1,600 mg of levodopa in two to four daily doses	0.77 to 5.69	282 to 2,078
Levodopa/ benserazide (Prolopa)	50 mg/12.5 mg 100 mg/25 mg 200 mg/50 mg	Capsule Capsule Capsule	0.2855 0.4701 0.7891	400 mg to 800 mg of levodopa daily in four to six doses	1.88 to 3.16	686 to 1,152
COMT inhibitors (in combination with levodopa/decarboxylase inhibitor in APD)						
Entacapone[f] (generics)	200 mg	Tablet	0.4010	200 mg to 1,600 mg daily in multiple doses	0.40 to 3.21	146 to 1,171
Levodopa/ carbidopa/ entacapone (Stalevo)	50 mg/ 12.5 mg/ 200 mg 75 mg/ 18.75 mg/	Tablet	1.6882	600 mg to 1,600 mg of entacapone daily in multiple doses	5.06 to 13.51	1,849 to 4,930

Drug/ Comparator	Strength	Form	Price ($)	Recommended Daily Dose[a]	Daily Drug Cost ($)	Annual Cost ($)
	200 mg 100 mg/ 25mg/ 200 mg 150 mg/ 37.5 mg/ 200 mg					
MAO-B inhibitors (in combination with levodopa/decarboxylase inhibitor in APD)						
Rasagiline (Azilect)	0.5 mg 1 mg	Tablet Tablet	7.0000[g]	0.5 mg to 1 mg daily	7.00	2,555
Selegiline (generics)	5 mg	Tablet	0.5021	5 mg twice daily	1.00	367

APD: advanced Parkinson's disease; COMT = catechol-O-methyl transferase; DA = dopamine agonist; EPD: early Parkinson's disease; MAO-B: monoamine-oxidase B; PD = Parkinson's disease.
[a] Based on product monograph unless otherwise specified.
[b] Manufacturer's confidential submitted price.
[c] Saskatchewan Formulary (August 2015).
[d] The 0.5 mg tablet is not a benefit of the ODB Formulary. However, the 1 mg tablet is scored.
[e] The 24 mg daily dose can be achieved with 5 mg + 2 mg + 1 mg three times daily for $4.46 daily ($1,575 annually), or more simply with 4 tablets of 2 mg three times daily for $3.75 daily ($1,369 annually).
[f] Entacapone is indicated only when used as an adjunct to levodopa/carbidopa or levodopa/benserazide.
[g] ODB Exceptional Access Program (August 2015).
Source: Prices are from the ODB Formulary (August 2015) unless stated otherwise.

APPENDIX 1: PRICE REDUCTION ANALYSES

Since therapeutic doses of non-ergolinic dopamine agonists (DAs) are individualized, calculating the average dose for each comparator is complex. CADTH Common Drug Review (CDR) explored several methods of estimating the weighted average or range of plausible costs for each non-ergolinic DA comparator. Rotigotine was more expensive than generic pramipexole immediate release (IR) and generic ropinirole IR in all scenarios; however, the extent to which the cost of rotigotine would have to be reduced to equal that of the comparators varied.

The range of daily costs for the three comparators by scenario for early Parkinson's disease (EPD) is shown in Table 2; the weighted average or estimated cost per patient per day of rotigotine would need to be reduced by [redacted] to [redacted] to equal that of pramipexole, and by [redacted] to [redacted] to equal that of ropinirole for EPD patients, depending on the scenario assumed.

For advanced Parkinson's disease (APD) patients, the estimated daily cost of rotigotine would need to be reduced by [redacted] to [redacted] to equal that of pramipexole, and by [redacted] to [redacted] to equal that of ropinirole, depending on the scenario assumed (Table 3).

Dosing Equivalence Ratios

In an additional analysis, CDR estimated the daily cost reduction for APD patients required for rotigotine to be equivalent to the cost of pramipexole if the 4:1 equivalence ratio for APD suggested by Poewe et al.[20] is assumed, when the average APD dose range of pramipexole of 3 mg/day to 3.75 mg/day from the clinical trials included in the network meta-analysis (NMA)[6,7,22] and expert feedback are considered. In this scenario, the cost of 12 mg/24 h and 16 mg/24 h rotigotine would need to be reduced by [redacted] and [redacted], respectively, to be equivalent to 3 mg and 3.75 mg of pramipexole daily (markups and dispensing fees excluded). Similarly, in a scenario where the dose ratio is assumed to be similar to the 1.4:1 rotigotine to ropinirole ratio seen in the mean doses at the start of the maintenance phase of the Mizuno et al.[18] trial, the cost of 12 mg/24 h rotigotine would need to be reduced by [redacted] to be cost-neutral to 9 mg/day of ropinirole.

TABLE 2: PRICE REDUCTION ESTIMATES FOR DAILY COST OF ROTIGOTINE TO EQUAL PRAMIPEXOLE AND ROPINIROLE IN EARLY PARKINSON'S DISEASE

Scenario Assumption EPD	Weighted Average Daily Cost Rotigotine ($)	Weighted Average Daily Cost Pramipexole ($)	Price Reduction for Rotigotine to Equal Pramipexole	Daily Cost Ropinirole ($)	Price Reduction for Rotigotine to Equal Ropinirole ($)
Not including markup or dispensing fees					
Base case CDR math corrections only[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case CDR dispensing assumptions[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis with CDR math corrections; lower range of trial doses[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis with CDR math corrections; upper range of trial doses[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CDR = CADTH Common Drug Review; EPD = early Parkinson's disease; NA = not applicable.
[a] Based on manufacturer's assumed patient distribution; see Table 5 in Appendix 2.
[b] Sensitivity analyses refer to the clinical trial with the lowest and highest mean or median dose for each comparator; see Table 7.

TABLE 3: PRICE REDUCTION ESTIMATES FOR DAILY COST OF ROTIGOTINE TO EQUAL PRAMIPEXOLE AND ROPINIROLE IN ADVANCED PARKINSON'S DISEASE

Scenario Assumption APD	Weighted Average Daily Cost Rotigotine ($)	Weighted Average Daily Cost Pramipexole ($)	Price Reduction for Rotigotine to Equal Pramipexole	Daily Cost Ropinirole ($)	Price Reduction for Rotigotine to Equal Ropinirole ($)
Not including markup or dispensing fees					
Base case CDR math corrections only[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case CDR dispensing assumptions[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis with CDR math corrections; lower range of trial doses[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis with CDR math corrections; upper range of trial doses[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assuming 4:1 rotigotine to pramipexole equivalence in APD based on Poewe et al.[20] (no fees/markups)					
12 mg/24 h (2 × 6 mg) rotigotine and 3 mg/day	[redacted]	1.58	[redacted]	NA	NA

Scenario Assumption APD	Weighted Average Daily Cost Rotigotine ($)	Weighted Average Daily Cost Pramipexole ($)	Price Reduction for Rotigotine to Equal Pramipexole	Daily Cost Ropinirole ($)	Price Reduction for Rotigotine to Equal Ropinirole ($)
(3 × 1 mg) pramipexole					
16 mg/24 h (2 × 8 mg) rotigotine and 3.75 mg/day (3 × 1.25 mg)	[redacted]	2.37	[redacted]	NA	NA
Assuming 1.33:1 rotigotine to ropinirole to approximate Mizuno et al.[18] (no fees/markups)					
12 mg/24 h (2 × 6 mg) rotigotine and 9 mg/day (1 mg + 2 mg three times daily) ropinirole	[redacted]	NA	NA	1.58	[redacted]

APD = advanced Parkinson's disease; CDR = CADTH Common Drug Review; NA= not applicable.
[a] Based on manufacturer's assumed patient distribution; see Table 5 in Appendix 2.
[b] Sensitivity analyses refer to the clinical trial with the lowest and highest mean or median dose for each comparator; see Table 7.

APPENDIX 2: REVIEWER WORKSHEETS

TABLE 4: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug Product	Rotigotine (Neupro) transdermal system
Treatment	Rotigotine 2 mg to 16 mg per 24 hours
Comparators	Pramipexole (up to 4.5 mg in three daily doses) Ropinirole (up to 24 mg in three daily doses)
Study Question	From the Ministry of Health perspective, what is the cost of rotigotine relative to alternative non-ergolinic DAs in patients with EPD and in patients with APD as an adjuvant to levodopa?
Type of Economic Evaluation	Cost comparison
Target Population	Patients with EPD or APD
Perspective	Ministry of Health (public payer)
Outcome(s) Considered	Costs
Key Data Sources	
Cost	ODB Formulary, RAMQ Liste des médicaments, manufacturer's confidentially submitted price
Clinical Efficacy	Network meta-analysis based on randomized controlled trials[6,7,15]
Harms	Zhou et al. pairwise meta-analysis[8]
Dose Distribution	Manufacturer's internal forecasts; TRUST observational study
Time Horizon	1 year
Results for Base Case (note corrections below)	**EPD per-patient annual cost** Rotigotine: [redacted] Pramipexole: [redacted] ([redacted] less than rotigotine) Ropinirole: [redacted] ([redacted] less than rotigotine) **APD per-patient annual cost** Rotigotine: [redacted] Pramipexole: [redacted] ([redacted] less than rotigotine) Ropinirole [redacted] ([redacted] less than rotigotine)

APD = advanced Parkinson's disease; DA = dopamine agonist; EPD = early Parkinson's disease; ODB = Ontario Drug Benefit; RAMQ = Régie de l'assurance maladie du Québec; TRUST = Transdermal Rotigotine User Surveillance Trial.

Manufacturer's Results

The manufacturer submitted a cost comparison of rotigotine (up to 8 mg/24 h in patients with early Parkinson's disease [EPD] and 16 mg/24 h in patients with advanced Parkinson's disease [APD]) to generic pramipexole immediate release (IR) (up to 4.5 mg daily) and generic 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. The Ontario Drug Benefit (ODB) Formulary markup of 8% was included, and a dispensing fee of $8.83 was applied every 30 days for each prescription. The CADTH Common Drug Review (CDR) focuses mainly on the APD population as per the listing request, although EPD results are also summarized.

Of note, CDR identified several calculation errors in the manufacturer's model, leading to overestimates in the cost of both rotigotine and ropinirole. The corrected values are included in Table 5 and Table 6.

TABLE 5: MANUFACTURER'S WEIGHTED AVERAGE DOSE AND COST PER DAY PER ADVANCED PARKINSON'S DISEASE PATIENT

	Treatment	Unit Dose (mg)	Unit Cost[a]	Daily Dosage (mg)	Cost per Day (Includes Markup and Dispensing Fee)	Patient Distribution[b]	Weighted Average Daily Dose (mg)	Weighted Average Cost per Day
Rotigotine‡	2 mg/24 h	2.0	[redacted]	2.0	[redacted]	[redacted]	[redacted]	[redacted]
	4 mg/24 h	4.0	[redacted]	4.0	[redacted]	[redacted]	[redacted]	[redacted]
	6 mg/24 h	6.0	[redacted]	6.0	[redacted]	[redacted]	[redacted]	[redacted]
	8 mg/24 h	8.0	[redacted]	8.0	[redacted]	[redacted]	[redacted]	[redacted]
	16 mg/24 h	2 × 8.0	[redacted]	16.0	[redacted][d]	[redacted]	[redacted]	[redacted]
	Weighted total for rotigotine						[redacted]	[redacted][d]
Pramipexole	0.25 mg t.i.d.	0.25	$0.2628	0.75	$1.15	[redacted]	[redacted]	[redacted]
	0.5 mg t.i.d.	0.50	$1.0909	1.5	$3.83	[redacted]	[redacted]	[redacted]
	0.75 mg t.i.d.	0.25 + 0.50	$1.3537	2.25	$4.97	[redacted]	[redacted]	[redacted]
	1 mg t.i.d.	1.00	$0.5257	3.0	$2.00	[redacted]	[redacted]	[redacted]
	1.5 mg t.i.d.[c]	1.50	$0.5257	4.5	$2.00	[redacted]	[redacted]	[redacted]
	Weighted total for pramipexole						[redacted]	[redacted]
Ropinirole	1.0 mg t.i.d.	1.0	$0.2838	3.0	$1.21	[redacted]	[redacted]	[redacted]
	2.0 mg t.i.d.	2.0	$0.3122	6.0	$1.31	[redacted]	[redacted]	[redacted]
	3.0 mg t.i.d.	1.0 + 2.0	$0.5960	9.0	$2.52	[redacted]	[redacted]	[redacted]
	4.0 mg t.i.d.	2 × 2.0	$0.6244	12.0	$2.32[e]	[redacted]	[redacted]	[redacted]
	8.0 mg t.i.d.[c]	1.0 + 2.0 + 5.0	$1.4556	24.0	$5.60[f]	[redacted]	[redacted]	[redacted]
	Weighted total for ropinirole						[redacted]	[redacted][g]

APD = advanced Parkinson's disease; CDR = CADTH Common Drug Review; EPD = early Parkinson's disease; ODB = Ontario Drug Benefit; t.i.d. = three times daily.

Source: Adapted from manufacturer's pharmacoeconomic submission; see Table 7.[23]

[a] Rotigotine unit costs reflect the manufacturer's confidential submitted price; costs shown for pramipexole and ropinirole are ODB Formulary list prices (April 2015). The 0.5 mg pramipexole unit price is from the RAMQ Liste des médicaments (April 2015).

[b] Based on manufacturer's "forecasting assumptions". Distribution used for EPD patients is [redacted], except that [redacted] of patients were assumed to use the second-highest listed dose for each comparator and [redacted] used the highest listed dose.

[c] Represents the maximum daily dose in APD: rotigotine 16 mg/24 h, pramipexole 4.5 mg/day, ropinirole 24 mg/day.

[d] Reported by manufacturer as [redacted], due to doubling the 8 mg drug cost and also doubling the number of units required to achieve 16 mg (i.e., quadrupling the cost rather than doubling); correction of this error by CDR led to a reduction in weighted average cost per day, from [redacted] to [redacted].

[e] Reported by manufacturer as $4.34 due to doubling the unit cost of the 2 mg tablet and then also doubling the number of units needed to achieve 4 mg (i.e., quadrupling the cost rather than doubling).

[f] Reported by manufacturer as $6.48 due to the erroneous inclusion of six dispensing fees every 30 days rather than three (one for each of the 1 mg, 2 mg, and 5 mg tablets assumed to be dispensed to achieve the 8 mg dose).

[g] Corrections described in footnotes e and f led to a reduction in the weighted average cost per day from [redacted] to [redacted].

Using the dose distribution assumption for APD patients provided by the manufacturer yields weighted average daily costs of [redacted], [redacted], and [redacted] for rotigotine, pramipexole, and ropinirole respectively when CDR's mathematical corrections and ODB markup and dispensing fees are included (Table 5). When extrapolated, the average weighted annual cost of rotigotine ([redacted] per patient per year) is [redacted] more than pramipexole ([redacted] per patient per year) and [redacted] more than ropinirole ([redacted] per patient per year).

The manufacturer also reported a "blended" incremental cost where rotigotine (corrected to [redacted] from [redacted]) was compared with a mix of [redacted]% pramipexole and [redacted]% ropinirole use. CDR did not consider this blended incremental cost to be useful, because:

- The [redacted]% pramipexole/[redacted]% ropinirole market share used in the analysis did not match the IMS Brogan Compustat data provided by the manufacturer (84% pramipexole/16% ropinirole in Figure 6 of the manufacturer's pharmacoeconomic submission[23] when bromocriptine was removed, which was consistent with more recent IMS Brogan PharmaStat data retrieved by CDR).
- The total claims data included prescriptions used by patients with restless legs syndrome (RLS); thus, it may not accurately reflect market share in a Parkinson's disease (PD) population.
- The blended incremental cost is only relevant if rotigotine replaces pramipexole and ropinirole in the exact ratio assumed in the analysis.

TABLE 6: MANUFACTURER'S CALCULATION OF THE TOTAL AND INCREMENTAL COSTS OF COMPARATORS FOR ADVANCED PARKINSON'S DISEASE

Comparator	Weighted Average Daily Cost	Weighted Average Annual Cost	Incremental Cost of Rotigotine – Comparator
Rotigotine	[redacted] (corrected from [redacted])	[redacted] (corrected from [redacted])	**Ref**
Pramipexole	[redacted]	[redacted]	[redacted] (corrected from [redacted])
Ropinirole	[redacted] (corrected from [redacted])	[redacted] (corrected from [redacted])	[redacted] (corrected from [redacted])

Note: Adapted from manufacturer's pharmacoeconomic submission (Table 10).[23] Includes 8% markup and $8.83 dispensing fee every 30 days per prescription.

For EPD patients, similar mathematical corrections led to a weighted average annual cost of rotigotine of [redacted] per patient, which remained [redacted] more than that of pramipexole ([redacted] per patient per year) but increased to [redacted] more than the cost of ropinirole ([redacted] per patient per year). The manufacturer's forecasted patient dose distribution for EPD was [redacted] for APD (Table 5), except that [redacted]% of patients were assumed to use the second-highest dose of each comparator listed (i.e., 8 mg/24 h of rotigotine, 1 mg three times daily of pramipexole, 4 mg three times daily of ropinirole), and [redacted]% were assumed to use the highest listed dose.

The manufacturer also conducted sensitivity analyses incorporating the upper and lower mean or median doses reported in the clinical trials included in the NMA for each comparator to explore the effects of alternate dosing possibilities, which also included mathematical errors (Table 7). For EPD patients, when CDR's mathematical corrections were incorporated, rotigotine cost [redacted] and [redacted] more per patient per year than pramipexole and ropinirole, respectively, when the lowest mean or median doses from clinical trials included in the NMA were used, and [redacted] and [redacted] more per

patient per year than pramipexole and ropinirole, respectively, when the highest mean or median clinical trial doses were used. Similarly, for APD patients, rotigotine cost [redacted] and [redacted] more per patient per year than pramipexole and ropinirole, respectively, when the lowest mean and median trial doses were assumed, while rotigotine cost [redacted] and [redacted] more per patient per year than pramipexole and ropinirole, respectively, when the highest mean or median clinical trial doses were used.

TABLE 7: MANUFACTURER'S SENSITIVITY ANALYSES EXPLORING THE IMPACT OF USING MEAN AND MEDIAN DOSES FROM CLINICAL TRIALS ON THE ANNUAL COST OF COMPARATORS

	Manufacturer's Results				CDR's Mathematical Corrections			
	EPD Lower Range[a]	EPD Upper Range[b]	APD Lower Range[c]	APD Upper Range[d]	EPD Lower Range[a]	EPD Upper Range[b]	APD Lower Range[c]	APD Upper Range[d]
Rotigotine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pramipexole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ropinirole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

APD = advanced Parkinson's disease; CDR = CADTH Common Drug Review; EPD = early Parkinson's disease.
[a] The EPD lower range refers to the lowest mean or median doses from EPD clinical trials, which were rotigotine: 5.7 mg/24 h; pramipexole: 2.2 mg/day; and ropinirole: 9.0 mg/day.
[b] The EPD upper range refers to the highest mean or median doses from EPD clinical trials, which were rotigotine: 8.2 mg/24 h; pramipexole: 3.8 mg/day; and ropinirole: 16.5 mg/day.
[c] The APD lower range refers to the lowest mean or median doses from APD clinical trials, which were rotigotine: 10.0 mg/24 h; pramipexole: 3.1 mg/day; and ropinirole: 10.7 mg/day.
[d] The APD upper range refers to the highest mean or median doses from APD trials, which were rotigotine: 16.0 mg/24 h; pramipexole: 3.9 mg/day; and ropinirole: 15.0 mg/day.
Note: Annual costs include 8% markup and a single $8.83 dispensing fee every 30 days. CDR corrections include cost per mg corrections to several doses similar to those described above, as well as including the highest dose cost per mg in all unweighted cost per mg calculations for both EPD and APD. This is because the manufacturer's base-case dose distribution assumption was not used in these sensitivity analyses, thus, the assumption that no EPD patient used the highest doses is invalid. These CDR corrections do not include the dispensing format assumption changes discussed in the next section.

Key Limitations and CADTH Common Drug Review Results

Comparator Dispensing Assumptions

Pramipexole: While the dispensing assumptions used by the manufacturer are technically accurate and in accordance with comparator dosage regimens provided by the Patented Medicine Prices Review Board (PMPRB) Human Drug Advisory Panel (HDAP) report for rotigotine,9-12 as proposed by Chen et al., 2009,13 the pramipexole 0.5 mg tablet is not reimbursed by some jurisdictions (e.g., Ontario) and is more expensive than the other doses of pramipexole in other jurisdictions (e.g., Saskatchewan, Quebec). In order to achieve the 0.5 mg three-times-daily dose, it is likely that pharmacists will dispense it as half of the scored pramipexole 1 mg tablet. This reduces the cost of the 0.5 mg three-times-daily dose to $1.15 per patient per day. Additionally, the 0.75 mg three-times-daily dose is more likely to be dispensed as three 0.25 mg tablets, leading to a cost of $2.85 per day (or alternately, $2.29 per day if one 0.25 mg tablet and one-half of a 1 mg tablet are used instead). This change alters the weighted average cost per day of pramipexole from [redacted] to [redacted] (Table 8), and reduces the weighted average annual cost of pramipexole to [redacted] from [redacted] (Table 9).

Ropinirole: Similarly, rather than dispensing 1 mg, 2 mg, and 5 mg tablets to patients requiring the 8 mg three-times-daily dose of ropinirole, it is likely that pharmacists will simplify the prescription to four 2 mg tablets three times daily. This change reduces the cost per day of ropinirole 8 mg three times daily

to $4.34 (Table 8) and thus reduces the weighted average cost per day of ropinirole to [redacted] and the weighted average annual cost per APD patient to [redacted] (Table 9).

TABLE 8: CADTH COMMON DRUG REVIEW WEIGHTED AVERAGE DOSE AND COST PER DAY PER ADVANCED PARKINSON'S DISEASE PATIENT, MANUFACTURER'S ASSUMED PATIENT DISTRIBUTION

	Treatment	Unit Dose (mg)	Unit Cost[a]	Daily Dosage (mg)	Cost per Day (Includes Markup and Dispensing Fee)	Patient Distribution[b]	Weighted Average Daily Dose (mg)	Weighted Average Cost per Day
Rotigotine‡	2 mg/24 h	2.0	[redacted]	2.0	[redacted]	[redacted]	[redacted]	[redacted]
	4 mg/24 h	4.0	[redacted]	4.0	[redacted]	[redacted]	[redacted]	[redacted]
	6 mg/24 h	6.0	[redacted]	6.0	[redacted]	[redacted]	[redacted]	[redacted]
	8 mg/24 h	8.0	[redacted]	8.0	[redacted]	[redacted]	[redacted]	[redacted]
	16 mg/24 h[c]	2 × 8.0	[redacted]	16.0	[redacted]	[redacted]	[redacted]	[redacted]
	Weighted total for rotigotine						[redacted]	[redacted]
Pramipexole	0.25 mg t.i.d.	0.25	$0.2628	0.75	$1.15	[redacted]	[redacted]	[redacted]
	0.5 mg t.i.d.	½ × 1.0	$0.2629	1.5	$1.15	[redacted]	[redacted]	[redacted]
	0.75 mg t.i.d.	3 × 0.25	$0.5257	2.25	$2.85[d]	[redacted]	[redacted]	[redacted]
	1 mg t.i.d.	1.00	$0.5257	3.0	$2.00	[redacted]	[redacted]	[redacted]
	1.5 mg t.i.d.[c]	1.50	$0.5257	4.5	$2.00	[redacted]	[redacted]	[redacted]
	Weighted total for pramipexole						[redacted]	[redacted]
Ropinirole	1.0 mg t.i.d.	1.0	$0.2838	3.0	$1.21	[redacted]	[redacted]	[redacted]
	2.0 mg t.i.d.	2.0	$0.3122	6.0	$1.31	[redacted]	[redacted]	[redacted]
	3.0 mg t.i.d.	1.0 + 2.0	$0.5960	9.0	$2.52	[redacted]	[redacted]	[redacted]
	4.0 mg t.i.d.	2 × 2.0	$0.6244	12.0	$2.32	[redacted]	[redacted]	[redacted]
	8.0 mg t.i.d.[c]	4 × 2.0	$1.2488	24.0	$4.34	[redacted]	[redacted]	[redacted]
	Weighted total for ropinirole						[redacted]	[redacted]

APD = advanced Parkinson's disease; EPD = early Parkinson's disease; ODB = Ontario Drug Benefit; t.i.d. = three times daily.
[a] Rotigotine unit costs are the manufacturer's confidential submitted price, pramipexole and ropinirole are ODB Formulary list prices (April 2015). The 0.5 mg pramipexole unit price is from the RAMQ Liste des médicaments (April 2015).
[b] Based on manufacturer's "forecasting assumptions". Distribution used for EPD patients is [redacted], except that [redacted] of patients were assumed to use the second-highest listed dose for each comparator, and [redacted] used the highest listed dose.
[c] Represents the maximum daily dose in APD: rotigotine 16 mg/24 h, pramipexole 4.5 mg/day, ropinirole 24 mg/day.
[d] Alternately, the pramipexole 0.75 mg three-times-daily dose can be dispensed as one-half of 1 mg + 0.25 mg three times daily, which yields a daily cost of $2.29 and leads to a weighted average cost per day for pramipexole of [redacted].

TABLE 9: CADTH COMMON DRUG REVIEW TOTAL AND INCREMENTAL COSTS OF COMPARATORS FOR ADVANCED PARKINSON'S DISEASE, MANUFACTURER'S ASSUMED PATIENT DISTRIBUTION

	With 8% Markup and $8.83 Dispensing Fee Every 30 Days per Prescription			Without Markup or Dispensing Fees		
Comparator	Weighted Average Daily Cost	Weighted Average Annual Cost	Incremental Rotigotine — Comparator	Weighted Average Daily Cost	Weighted Average Annual Cost	Incremental Rotigotine — Comparator
Rotigotine	[redacted]	[redacted]	Ref	[redacted]	[redacted]	Ref
Pramipexole	[redacted][a]	[redacted][a]	[redacted][a]	[redacted][b]	[redacted][b]	[redacted][b]
Ropinirole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] If the 0.75 mg three-times-daily dose of pramipexole is assumed to be taken as one-half of 1.0 mg + 0.25 mg tablets, the weighted average cost of pramipexole is [redacted] per patient per day, yielding a weighted average annual cost of [redacted], and an incremental cost of [redacted] (rotigotine – pramipexole).

[b] If the 0.75 mg three-times-daily dose of pramipexole is assumed to be taken as one-half of 1.0 mg + 0.25 mg tablets, the weighted average cost of pramipexole without markup or dispensing fees is [redacted] per patient per day, yielding a weighted average annual cost of [redacted], and an incremental cost of [redacted] (rotigotine — pramipexole).

For EPD patients, when markups and dispensing fees are included, these dosing assumptions similarly lead to a weighted average annual cost of pramipexole of [redacted] per patient ([redacted] less than rotigotine), while that of ropinirole remained at [redacted] per patient ([redacted] less than rotigotine). When markups and dispensing fees are not included, the weighted average annual cost of rotigotine was [redacted] ([redacted] daily per patient), which was [redacted] more than that of pramipexole under these dosing assumptions ([redacted] per patient) and [redacted] more than that of ropinirole ([redacted] per patient).

Generalizability of Network Meta-analysis Results to Population Using Lower Rotigotine Doses

In the economic submission, the manufacturer assumes that real-world APD patients will use an average dose of [redacted] mg/24 h ([redacted] mg/24 h for EPD patients). This forecasted assumption is similar to average doses for PD patients (calculated from annual sales in mg per annual treatment days) from six European countries, which in 2014 ranged from [redacted] to [redacted] mg/24 h[23], but is lower than the average dose seen in the observational Transdermal Rotigotine User Surveillance Trial (TRUST), where the average daily APD dose was [redacted] mg/24 h. However, the NMA[6,7] used to establish the similar efficacy of rotigotine to pramipexole or ropinirole included trials where the mean daily dose of rotigotine ranged from 7.2 mg/24 h to 12.9 mg/24 h for the APD population (CDR Clinical Report, Appendix 8). Thus, it is unclear if the results of the NMA can be generalized to the lower average rotigotine dose assumed in the economic submission.

Assumption of Similar Safety

While the NMA provided some evidence of similar efficacy between rotigotine, pramipexole, and ropinirole, it did not assess safety outcomes. The manufacturer submitted an unsponsored, published, pairwise meta-analysis[8] to support its assumption of similar safety and tolerability among the three drugs, which concluded that long-acting, non-ergolinic DAs were non-inferior to standard non-ergolinic DAs. However, the majority of studies included in this meta-analysis were of pramipexole IR versus pramipexole extended release (ER), or ropinirole IR versus ER; only one trial comparing rotigotine with ropinirole in EPD patients[24] and one trial comparing rotigotine with pramipexole in APD patients[20] was included. In the absence of more data specifically comparing the safety of rotigotine with that of ropinirole or pramipexole, or of a well-conducted NMA including safety outcomes, the relative safety profile of rotigotine versus pramipexole and ropinirole remains uncertain.

Unclear Patient Distribution Source

In its base case, the manufacturer assumed the APD patient distribution by rotigotine dose described in Table 5 and Table 8. Patients using the comparators were assumed to be distributed in the same way across equivalent doses. This APD distribution and resultant weighted average daily dose ([redacted] mg/24 h) is lower than that seen in the clinical trials (average daily dose: 7.2 to 12.9 mg/24 h[6,7,15]) or in the TRUST study (average APD daily dose: [redacted] mg/24 h[14,23]); however, it and the EPD weighted average are consistent with global European sales data for patients with PD provided by the manufacturer.

In its submitted pharmacoeconomic submission, the manufacturer stated that the weighted average daily dose per patient used was calculated from the distribution of doses, which were based on internal forecast assumptions (manufacturer's pharmacoeconomic submission,[23] page 20). When queried for more detail on the methods of forecasting used, the manufacturer indicated that the internal forecast projected the average daily dose, and that the distribution percentages were calculated to align with this average.[3] Therefore, the methodology used to forecast the distribution assumption remains unclear.

The manufacturer's distribution assumes that only [redacted] patients will use the 16mg/24 h dose, and that [redacted] patients will use doses of 10 mg/24 h, 12 mg/24 h, or 14 mg/24 h, despite such doses being explicitly described in the product monograph: *"For doses higher than 8 mg/24h multiple patches may be used to achieve the final dose (e.g., 10 mg/24h may be reached by combination of a 6 mg/24h and a 4 mg/24 patch)."*[1] Of particular note, [redacted] of APD patients in the eight-year observational TRUST study had average daily rotigotine doses of more than 8 mg/24 h. In assuming that [redacted] patients using more than one patch per day are on the 16 mg/24 h dose, the manufacturer unrealistically minimizes the number of patients required to achieve the assumed higher daily average dose for APD ([redacted] mg/24 h versus the [redacted] mg/24 h assumed for EPD patients), thus minimizing the increase in daily cost. This assumption also eliminates the cost of the second dispensing fee that any patient requiring a 10 mg/24 h or 14 mg/24 h dose would incur due to the multiple patch sizes required to achieve those doses (i.e., the 2 mg/24 h + 8 mg/24 h or 8 mg/24 h + 6mg/24 h doses would cost [redacted] daily rather than [redacted] assuming dispensing fees are charged every 30 days).

Using the distribution of doses for APD patients in the TRUST study[14] (Appendix 3, Table 10, Table 11, and Table 12) and including an 8% markup and dispensing fee leads to a weighted average daily cost for rotigotine of [redacted] if doses are rounded down (e.g., patients in the > 8 mg/24 h to 10 mg/24 h category are assumed to use 8 mg/24 h; those in the 0 mg/24 h to 2 mg/24 h and 2 mg/24 h to < 4 mg/24 h ranges are assumed to use 1 mg/24 h or 2 mg/24 h) to a weighted daily cost of [redacted] if they are rounded up (e.g., patients in the > 8 mg/24 h to 10 mg/24 h category are assumed to use 10 mg/24 h; those in the 2 mg/24 h to 4 mg/24 h range are assumed to use 4 mg/24 h). This extrapolates to a weighted average annual cost of rotigotine per APD patient of [redacted] to [redacted] when markups and dispensing fees are included (Appendix 3). Using the TRUST dose distribution data for EPD patients yields a weighted average daily cost of [redacted] to [redacted] when markups and dispensing fees are included.

In addition, in the recent Mizuno trial[18] comparing rotigotine with ropinirole in APD patients, 50% of patients in the rotigotine group (76 of 153) had been titrated to the maximum 16 mg/24 h dose at the start of the maintenance period.[19] The mean maintenance dose in the Mizuno trial was 12.9 mg/24 h in the rotigotine group,[18] which again suggests that the proportion of patients who will use a rotigotine dose higher than 8 mg/24 h in clinical practice may be substantially higher than the manufacturer's assumed [redacted].

Note that the manufacturer assumed in its pharmacoeconomic submission that EPD patients would use lower doses of non-ergolinic DAs than APD patients would use, while EPD patients in the TRUST study had higher mean, median, and maximum rotigotine doses than APD patients. Using the TRUST data to estimate a weighted average annual cost for EPD patients using rotigotine leads to a range of [redacted](if doses are rounded down) to [redacted](if doses are rounded up) per patient per year.

Underestimation of Dosage of Rotigotine Equivalent to Comparators in APD

The manufacturer assumed that the comparative dose ratio for rotigotine and pramipexole is 2.666:1, as proposed by Chen et al. 2009.[13] However, in Study SP515 (Poewe et al.[20]), the authors noted that the failure to show non-inferiority of rotigotine versus pramipexole for the responder rates might indicate the need for a higher dose of rotigotine versus pramipexole than reflected by the 4:1 ratio reached in this trial and cited in other sources (CDR Clinical Report, Section 5.3, Table 27). Therefore, the estimated incremental cost of rotigotine compared with pramipexole in APD may have been underestimated (Appendix 1: Price Reduction Analyses).

With regards to the dosing of rotigotine compared with ropinirole, the manufacturer assumed a ratio of 1:1.5;[9-13] ratios from 1:1 to 1:2 have been used in trials or cited in the literature (CDR Clinical Report, Section 5.3, Table 27). However, in the Mizuno trial,[18] the non-inferiority of rotigotine to ropinirole was demonstrated with mean doses of 12.9 mg/24 h rotigotine and 9.2 mg/day of ropinirole, a 1.4:1 ratio. The incremental cost of rotigotine compared with ropinirole may also have been underestimated (see Appendix 1).

APPENDIX 3: DOSING DISTRIBUTION FROM THE TRANSDERMAL ROTIGOTINE USER SURVEILLANCE TRIAL

Upon request from CADTH Common Drug Review (CDR) reviewers, the manufacturer provided information on the individual average daily rotigotine doses used by patients in the observational Transdermal Rotigotine User Surveillance Trial (TRUST) (Table 10 and Table 11).[14] CDR calculated a range of weighted average daily costs for rotigotine based on the advanced Parkinson's disease (APD) patient dose distribution within the TRUST study to contrast to the cost assumed by the manufacturer. The weighted average daily cost of rotigotine for APD patients was [redacted] to [redacted] when ODB markups and dispensing fees were included (Table 12), or [redacted] to [redacted] when no markup and fees were included. Use of the TRUST data to inform patient dose distributions increases the weighted average daily cost of rotigotine by [redacted]% to [redacted]% over that derived using the manufacturer's forecasted distribution.

The weighted average daily costs of rotigotine using the TRUST EPD population to inform patient dose distributions were [redacted]% to [redacted]% higher than those derived using the manufacturer's forecasted distribution for EPD patients. This was due to the higher proportion of patients using more than one patch per day.

TABLE 10: TRANSDERMAL ROTIGOTINE USER SURVEILLANCE TRIAL INDIVIDUAL AVERAGE DAILY ROTIGOTINE DOSE DESCRIPTIVE STATISTICS BY PARKINSON'S DISEASE POPULATION

Population	N	Mean (mg/24 h)	SD (mg/24 h)	Median (mg/24 h)	Minimum (mg/24 h)	Maximum (mg/24 h)
All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other-stage PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

APD = advanced Parkinson's disease; EPD = early Parkinson's disease; PD = Parkinson's disease; SD = standard deviation.
Note: The individual average daily rotigotine dose per patient is defined as: individual average daily dose level = sum (daily rotigotine doses taken)/number of days when rotigotine was taken. EPD is defined as dopaminergic monotherapy at baseline; APD is defined as L-dopa combination therapy with dopaminergic treatment; and other-stage PD is neither of the two defined stages (e.g., dopaminergic combination therapy). [redacted] patients treated with rotigotine did not have dose information available, and are not included in the table. Data from patients without valid dates of consent were not used for analysis.

TABLE 11: TRANSDERMAL ROTIGOTINE USER SURVEILLANCE TRIAL — INDIVIDUAL AVERAGE DAILY ROTIGOTINE DOSE BY PARKINSON'S DISEASE POPULATION

Dose	All patients (N = [redacted]) n (%)	EPD (N = [redacted]) n (%)	APD (N = [redacted]) n (%)	Other-stage PD (N = [redacted]) n (%)
0 to 2 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
> 2 to 4 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
> 4 to 6 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
> 6 to 8 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
> 8 to 10 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
> 10 to 12 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
> 12 to 14 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
> 14 to 16 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
> 16 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]

APD = advanced Parkinson's disease; EPD = early Parkinson's disease; PD = Parkinson's disease.
Note: The individual average daily rotigotine dose per patient is defined as: individual average daily dose level = sum (daily rotigotine doses taken)/number of days when rotigotine was taken. EPD is defined as dopaminergic monotherapy at baseline; APD is defined as L-dopa combination therapy with dopaminergic treatment; and other-stage PD is neither of the two defined stages (e.g., dopaminergic combination therapy). [redacted] patients treated with rotigotine did not have dose information available and are not included in the table. Data from patients without valid dates of consent were not used for analysis.

TABLE 12: WEIGHTED AVERAGE DAILY ROTIGOTINE COST BASED ON ADVANCED PARKINSON'S DISEASE POPULATION OF TRANSDERMAL ROTIGOTINE USER SURVEILLANCE TRIAL

Dose	Daily Cost of Dose ($)	APD Distribution Rounded Down	Weighted Daily Cost ($)	APD Distribution Rounded Up	Weighted Daily Cost ($)
1 mg/24 h or 2 mg/24 h[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL Weighted Average Daily Cost			[redacted]		[redacted]

APD = advanced Parkinson's disease; TRUST = Transdermal Rotigotine User Surveillance Trial.
Note: Includes 8% markup and $8.83 dispensing fee per prescription every 30 days. The weighted average daily cost based on APD TRUST data without fees or markup is [redacted] per patient when the distribution is rounded down and [redacted] per patient when it is rounded up.
[a] As the individual average daily doses were calculated based on the number of days rotigotine was used, individuals using less than 2 mg/24 h were assumed to be using 1 mg/24 h, which [redacted],[3] rather than no patch.

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