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An Open-Label Conversion Study of Pramipexole to Ropinirole Prolonged Release in Parkinson's Disease

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Abstract: Ropinirole prolonged release (PR) is a once daily oral dopamine agonist approved for the treatment of Parkinson's disease (PD). The goal of this 4 week, open-label study was to determine the most effective conversion ratio with the fewest adverse effects (AEs) when switching from pramipexole to ropinirole PR. Sixty patients with PD taking pramipexole were converted overnight to ropinirole PR at ratios of 1:3, 1:4, or 1:5 such that 20 consecutive subjects were enrolled in each group. Ropinirole PR dose adjustments were allowed to maintain efficacy or to reduce AEs. An overnight switch from pramipexole to ropinirole PR was found to be well tolerated and AEs were typical for a dopamine agonist. The most common AEs were worsening of PD symptoms, dizziness, somnolence, and nausea, the majority of which resolved after dose adjustments. Thirteen subjects discontinued ropinirole PR before 4 weeks. These subjects were taking a significantly greater dose of pramipexole, the majority greater than 4 mg/day, and tended to have longer disease durations. A conversion ratio of 1 mg of pramipexole to 4 mg of ropinirole PR resulted in the fewest discontinuations of ropinirole PR, the fewest dose adjustments and the largest percentage of subjects that preferred ropinirole PR. © 2009 Movement Disorder Society

Key words: Parkinson's disease; ropinirole prolonged release; dopamine agonists; dopamine agonist conversion

The nonergot dopamine agonists, ropinirole and pramipexole, are effective treatments for Parkinson's disease (PD) both as monotherapy and as adjuncts to levodopa (L-dopa).[1–3] Both medications are generally administered three times daily. Ropinirole prolonged release (PR) is a once daily 24-hour formulation of ropinirole that provides more stable blood plasma levels compared with immediate release ropinirole.[4] Once daily dosing may also improve medication compliance and ultimately improve outcomes.[5] Ropinirole PR has been shown to be effective as monotherapy in early PD[6] and as an adjunct to l-dopa.[7] In a double-blind, crossover study comparing ropinirole immediate release and ropinirole PR as monotherapy in patients with early PD, the two formulations had comparable efficacy and an overnight switch using comparable daily dosages were shown to be well tolerated.[6] There are currently no data examining the safety and efficacy of the conversion from multiple daily doses of pramipexole to once daily ropinirole PR. However, in a 6-week conversion study, subjects taking pramipexole were converted to immediate release ropinirole. The final conversion ratio was 1 mg of pramipexole to 3.8 mg of ropinirole.[8] Based on these findings and other studies examining the conversion between various dopamine agonists, it was determined that the conversion ratio between pramipexole and immediate release ropinirole ranged between 1:3 and 1:5.[9,10] The objective of this study was to determine the most effective conversion ratio and the tolerability of an overnight switch from pramipexole to ropinirole PR.

PATIENTS AND METHODS

Patients

A total of 61 patients with PD were enrolled at the University of Kansas Medical Center. The first subject

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TABLE 1. *Exact and assigned conversion doses of ropinirole prolonged release (PR) for each pramipexole to ropinirole PR conversion group*

	Ropinirole PR daily dosages					
	1:3 Conversion pramipexole: ropinirole PR		1:4 Conversion pramipexole: ropinirole PR		1:5 Conversion pramipexole: ropinirole PR	
Pramipexole (mg/day)	Exact (mg/day)	Assigned (mg/day)	Exact (mg/day)	Assigned (mg/day)	Exact (mg/day)	Assigned (mg/day)
0.375	1.125	2	1.5	2	1.875	2
0.75	2.25	2	3	4	3.75	4
1.5	4.5	4	6	6	7.5	8
2.25	6.75	6	9	8	11.25	12
3	9	8	12	12	15	16
3.75	11.25	12	15	16	18.75	20
4.5	13.5	16	18	20	22.5	24

Ropinirole PR was available in dosages of 2, 4, and 8 mg which did not allow for exact dosage conversions.

was enrolled in January 2006 and the last subject completed the study in February 2008. Men and women over 18 years of age with a diagnosis of idiopathic PD participated in the study. All subjects were taking a stable dose of pramipexole for at least 4 weeks. There were no restrictions on other antiparkinsonian therapies as long as the treatments remained stable throughout the study. Patients with atypical forms of parkinsonism, prior exposure to ropinirole PR, current use or significant adverse effects (AEs) related to immediate release ropinirole, concurrent use of a monoamine oxidase inhibitor other than selegiline or rasagiline, or significant uncontrolled medical conditions were excluded from the study. All subjects provided written informed consent approved by the University of Kansas Medical Center's Institutional Review Board.

Study Design and Procedures

This was a single center, 4 week, open-label conversion study from pramipexole to ropinirole PR. The primary investigator (RP) received approval of an Investigational New Drug application from the Food and Drug Administration before conducting the study. Subjects were enrolled into one of three conversion groups such that the first 20 subjects were converted from pramipexole to ropinirole PR at a ratio of 1 mg of pramipexole to 3 mg of ropinirole PR, the next 20 subjects were converted at a ratio of 1:4 and the final 20 subjects were converted at a ratio of 1:5. To maximize safety, each conversion group was filled completely ($n = 20$) and adverse events were reviewed before enrolling subjects into the higher conversion group.

Subjects completed a baseline visit and returned 4 weeks later for the final visit. All subjects were converted from pramipexole to ropinirole PR overnight. To maximize safety, the first five subjects in each conversion group received their initial dose of ropinirole PR in the clinic where they were closely monitored for orthostatic changes. These subjects completed the baseline assessments and within 1 week, returned to the clinic without taking their morning dose of pramipexole. Blood pressure was assessed after sitting for 10 minutes and again 1 minute after standing, ropinirole PR was taken, and sitting and standing blood pressures were monitored every hour for 4 hours. The remaining 15 subjects in each group completed the baseline assessments and were instructed to discontinue pramipexole the next morning and initiate the assigned dosage of ropinirole PR. For each of 5 days following the conversion, all subjects were contacted by phone to evaluate AEs and efficacy. Ropinirole PR could be increased or decreased as necessary to maintain efficacy or reduce AEs. The maximum dose of ropinirole PR could not exceed 24 mg/day. Ropinirole PR was available in dosages of 2, 4, and 8 mg; therefore, the actual conversion factor was as close to the assigned conversion ratio as possible. Table 1 illustrates conversion ratios used in the study.

Before the initiation of ropinirole PR, all subjects were assessed with the complete Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr, Schwab and England, PDQ-39 quality of life assessment, Epworth Sleepiness Scale (ESS), Mini-Mental State Examination (MMSE), and global ratings of disease. Subjects returned after 4 weeks and all assessments were repeated and global impressions of change and drug preferences were obtained. Sitting and standing blood pressures were measured at each visit. AEs and changes in ropinirole PR dose were collected throughout the study.

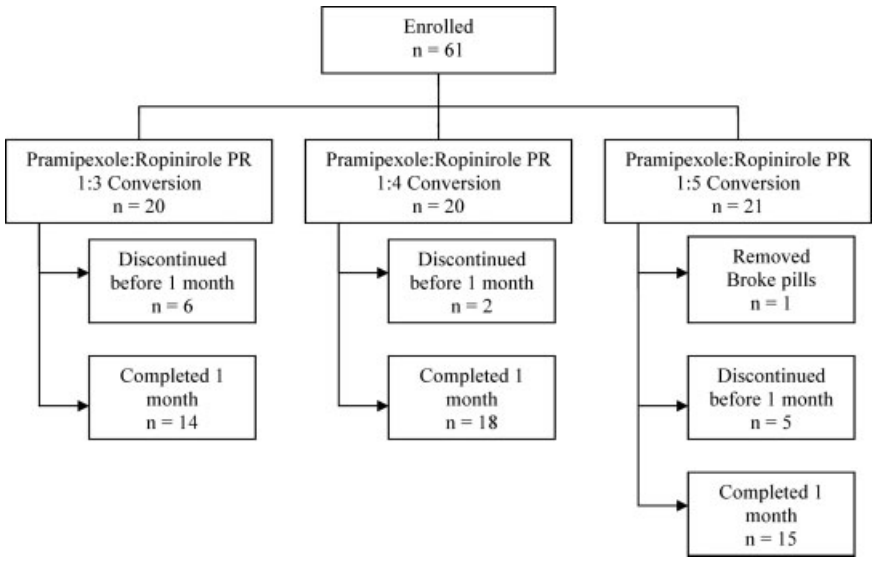

FIG. 1. Patient flow diagram.

The primary outcome was the determination of the pramipexole to ropinirole PR conversion ratio that led to the fewest AEs and fewest dose adjustments while maintaining comparable efficacy to that with pramipexole. The primary efficacy variables were PDQ-39 and global impressions of change from baseline to week 4. Secondary efficacy variables were changes in UPDRS activities of daily living (ADLs) and motor scores, MMSE, and ESS from baseline to week 4. Safety variables included orthostatic blood pressure measurements and AEs reported throughout the study.

The target enrollment was 20 in each conversion group for a total of 60 subjects. Study conclusion was either the completion of 4 weeks of ropinirole PR treatment or the discontinuation of ropinirole PR. For the primary analysis, descriptive statistics were used to determine the final conversion factors, the number of dose adjustments and subject drug preference. Changes from baseline to week 4 in PDQ-39 scores were analyzed with paired *t*-tests and changes from baseline to week 4 in UPDRS, MMSE, and ESS scores were analyzed using Wilcoxon signed rank comparisons for nonparametric data. Comparisons between groups that preferred pramipexole or ropinirole PR were analyzed with Mann–Whitney tests for nonparametric data and independent *t*-tests for parametric data.

RESULTS

Subjects

A total of 61 subjects were enrolled in the study (Fig. 1). One subject in the 1:5 conversion group was replaced after reporting he broke the ropinirole PR tablets in half. Therefore, there were 20 subjects in each conversion group. Table 2 shows baseline demographic characteristics for the full cohort and each conversion group. There were no significant baseline differences between conversion groups ($P > 0.19$ for all comparisons).

Early Discontinuations of Ropinirole PR

Thirteen subjects (21.7%) discontinued ropinirole PR before week 4. This group was comprised of eight males and five females with a mean age of 67 years, mean disease duration of 11 years, and mean pramipexole dose of 3.3 mg/day, ranging from 0.75 to 5.0 mg/day. The majority (n = 12) were on L-dopa therapy at a mean daily dose of 625 mg, ranging from 300 to 1800 mg/day and one subject was not taking l-dopa. Disease duration (11 vs. 7 years, $P < 0.01$) and daily pramipexole dose (3.3 mg vs. 2.1 mg, $P < 0.03$) were significantly greater in the group that discontinued ropinirole PR early compared to the 47 subjects that completed the week 4 visit. Furthermore, in the group that discontinued early, 54% (7/13) were taking a daily dose of at least 4 mg of pramipexole compared to 6% (3/47) of those that completed the week 4 visit. The majority who discontinued ropinirole PR before week 4 reported worsening of PD (n = 9) as the reason for discontinuation, other reasons included dizziness (n = 3), sleepiness (n = 2), gastrointestinal disturbances (n = 2), insomnia (n = 1), disorientation (n = 1), confusion (n = 1), and hallucinations (n = 1).

TABLE 2. *Subject demographics and baseline characteristics for the full cohort and each conversion group [mean (SD)]*

	All (n = 60)	1:3 (n = 20)	1:4 (n = 20)	1:5 (n = 20)
Age (yr)	64.7 (9.7)	64.1 (10.1)	63.9 (9.7)	66.2 (9.7)
Gender	42M 18F	12M 8F	15M 5F	15M 5F
Disease duration (yr)	7.9 (5.0)	8.6 (5.1)	6.4 (4.0)	8.8 (5.8)
Pramipexole dose (mg/day)	2.4 (1.2)	2.4 (1.3)	2.2 (1.1)	2.6 (1.2)
UPDRS ADL	12.4 (6.1)	13.2 (4.9)	11.0 (6.2)	12.9 (6.9)
UPDRS Motor	23.0 (8.9)	22.4 (8.9)	22.4 (8.1)	24.2 (10.0)
Hoehn and Yahr	2.2 (0.6)	2.3 (0.5)	2.1 (0.7)	2.4 (0.7)
Schwab and England	82.4 (8.4)	82.3 (9.4)	83.2 (8.3)	81.8 (7.7)
PDQ-39 Total	21.7 (13.4)	25.4 (15.9)	18.6 (11.1)	21.1 (12.6)
ESS	11.2 (4.7)	12.2 (5.2)	10.1 (4.0)	11.4 (5.0)
MMSE	28.5 (1.7)	28.0 (1.9)	28.9 (1.5)	28.6 (1.5)

UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-39, Parkinson's disease quality of life questionnaire; ESS, Epworth sleepiness scale; MMSE, Mini-Mental State Examination.

Study Completers

Forty-seven subjects (34 males/13 females) with a mean age of 64 years, mean disease duration of 7 years and mean pramipexole dose of 2.1 mg/day (range 0.75-4.5 mg/day) completed 4 weeks of ropinirole PR therapy. Forty-one (87%) were taking l-dopa at an average daily dose of 594 mg, ranging from 150 to 1700 mg/day. The remaining six subjects were not taking l-dopa. There were no significant differences in PDQ-39 quality of life total or subscores, MMSE, ESS, UPDRS ADL, or UPDRS motor scores from baseline to week 4.

Overall Drug Preference

For the entire cohort (n = 60), 55% (n = 33) preferred ropinirole PR and 45% (n = 27) pramipexole. There were no differences between the two groups in baseline PDQ-39 total score (ropinirole PR 23; pramipexole 20; $P > 0.20$) or any PDQ-39 subscores, UPDRS ADLs (ropinirole PR 12.5; pramipexole 12.2; $P > 0.90$), UPDRS motor scores (ropinirole PR 22.9; pramipexole 23.2; $P > 0.09$), ESS (both groups 11.2; $P > 0.90$) or daily L-dopa dosage (ropinirole PR 553 mg; pramipexole 478 mg; $P > 0.40$). The only significant baseline differences between the two groups were disease duration, which was 6.7 years in the ropinirole PR group and 9.4 in the pramipexole group ($P < 0.04$), and MMSE scores which were 29 in the ropinirole PR group and 28 in the pramipexole group ($P < 0.01$).

There were 24 males and nine females with a mean age of 63 years who preferred ropinirole PR. According to global impressions of change, 15% (n = 5) had marked improvement, 21% (n = 7) moderate improvement, 33% (n = 11) mild improvement, 27% (n = 9) no change, and 3% (n = 1) moderate worsening. In the subject with moderate worsening, tremor was worsened; however, a significant reduction in somnolence led to the preference for ropinirole PR. Forty-five percent (n = 15) reported increased efficacy with less "off" time with ropinirole PR, 33% (n = 11) reported comparable efficacy and preferred the convenience of once daily dosing and 33% (n = 11) reported less daytime somnolence. Other reasons for preference of ropinirole PR included reductions in dyskinesia, edema, and impulsivity each reported by two subjects, reductions in nausea, dizziness, and anxiety each reported by one subject and a faster treatment effect in one subject.

There were 18 males and nine females with a mean age of 67 years who preferred pramipexole. According to global impressions of change, 4% (n = 1) had mild improvement, 22% (n = 6) no change, 26% (n = 7) mild worsening, 15% (n = 4) moderate worsening, and 15% (n = 4) marked worsening. Five subjects that discontinued ropinirole PR before week 4 did not report global impressions of change. The reasons for preference of pramipexole included greater efficacy in 13 (48%), decreased dizziness in six (22%), decreased daytime somnolence in five (19%), reduced gastrointestinal upset in three (11%), reduced dyskinesia and edema each in one, and faster treatment effect and increased energy each in one subject.

Dose Adjustments and Conversion Ratio

A conversion ratio of 1 mg of pramipexole to 4 mg of ropinirole PR resulted in the fewest dose adjustments, fewest early discontinuations and the largest percentage of subjects preferring ropinirole PR (Table 3). In the 1:4 conversion group, 10% (n = 2) discontinued ropinirole PR before the week 4 visit compared with 30% (n = 6) in the 1:3 group and 25% (n = 5) in the 1:5 group. With respect to dose adjustments, 65% of the subjects in the 1:4 group and 50% in the 1:5 group did

TABLE 3. *Number of dose adjustments, pramipexole and ropinirole PR daily dosages and final conversion factors for each conversion group and the total cohort based on final drug preference*

	1:3 Conversion group		1:4 Conversion group		1:5 Conversion group		All subjects	
	Ropinirole PR (n = 9)	Pramipexole (n = 11)	Ropinirole PR (n = 14)	Pramipexole (n = 6)	Ropinirole PR (n = 10)	Pramipexole (n = 10)	Ropinirole PR (n = 33)	Pramipexole (n = 27)
No adjustments	2 (22%)	0	11 (79%)	2 (33%)	4 (40%)	6 (60%)	17 (52%)	8 (30%)
1 adjustment	5 (56%)	2 (18%)	2 (14%)	3 (50%)	5 (50%)	4 (40%)	12 (36%)	9 (33%)
2 adjustments	2 (22%)	4 (36%)	1 (7%)	1 (17%)	1 (10%)	0	4 (12%)	5 (18.5%)
≥3 adjustments	0	5 (45%)	0	0	0	0	0	5 (18.5%)
Mean adjustments	1.0 (0.7)	2.4 (0.9)*	0.3 (0.6)	0.8 (0.7)	0.7 (0.7)	0.4 (0.5)	0.6 (0.7)	1.3 (1.2)*
Pramipexole (mg/day)	2.3 (0.8)	2.6 (1.6)	1.8 (0.6)	3.1 (1.5)	2.7 (1.1)	2.5 (1.2)	2.2 (0.9)	2.6 (1.4)
Initial ropinirole PR (mg/day)	6.2 (2.1)	7.8 (5.5)	7.0 (2.3)	13.3 (6.4)	14.4 (6.0)	13.2 (6.8)	9.0 (5.2)	11.0 (6.6)
Final ropinirole PR (mg/day)	9.6 (4.7)	11.6 (6.8)	7.9 (3.2)	14.3 (7.8)	13.6 (5.4)	12.8 (7.4)	10.1 (4.9)	12.7 (7.1)
Final conversion factor	4.2	4.5	4.4	4.6	5.0	5.1	4.6	4.9
Age (yr)	60.2 (9.8)	67.2 (9.6)	63.2 (11.3)	65.6 (4.2)	65.9 (7.9)	66.6 (11.7)	63.2 (9.9)	66.6 (9.3)**
Disease duration (yr)	7.3 (3.7)	9.6 (5.9)	5.5 (3.7)	8.4 (4.3)	7.8 (4.5)	9.8 (6.9)	6.7 (4.0)	9.4 (5.8)**

*$P < 0.01$ comparing subjects who preferred pramipexole versus those who preferred ropinirole PR.
**$P < 0.04$ comparing subjects who preferred pramipexole versus those who preferred ropinirole PR.

TABLE 4. *Adverse effects based on drug preference and for the total cohort*

Adverse event	Preferred ropinirole PR (n = 33)	Preferred pramipexole (n = 27)	Total (n = 60)
PD worsening	6 (18%)	17 (63%)	23 (38%)
Dizziness	5 (15%)	6 (22%)	11 (18%)
Nausea	5 (15%)	4 (15%)	9 (15%)
Somnolence	4 (12%)	5 (19%)	9 (15%)
Anxiety	2 (6%)	0	2 (3%)
Constipation	1 (3%)	0	1 (2%)
Diarrhea	1 (3%)	1 (4%)	2 (3%)
Edema	1 (3%)	1 (4%)	2 (3%)
Headache	1 (3%)	0	1 (2%)
Heartburn	1 (3%)	0	1 (2%)
Insomnia	1 (3%)	1 (4%)	2 (3%)
Weakness	1 (3%)	0	1 (2%)
Confusion	0	1 (4%)	1 (2%)
Disorientation	0	1 (4%)	1 (2%)
Dyskinesia	0	2 (4%)	2 (3%)
Fatigue	0	1 (4%)	1 (2%)
Hallucinations	0	1 (4%)	1 (2%)
Leg cramps	0	1 (4%)	1 (2%)
Slow kick in	0	1 (4%)	1 (2%)

not require any dose adjustments compared with only 10% in the 1:3 group (Table 3). In the 1:4 group, 70% preferred ropinirole PR compared with 50% in the 1:5 group and 45% in the 1:3 group. The final conversion factor for subjects preferring ropinirole PR was 4.6, which ranged between 4.2 and 5.0 for the individual conversion groups. The final conversion factor for those preferring pramipexole was 4.9, ranging from 4.5 to 5.1 (Table 3).

Adverse Effects

The most common adverse event throughout the study was worsening of PD symptoms during the titration phase, and other AEs were typical for a dopamine agonist and included dizziness, somnolence, and nausea (Table 4). There were no significant orthostatic changes. The majority of the adverse events in those who completed the study were initial effects and resolved with dose adjustments. AEs in those who discontinued ropinirole PR before week 4 resolved after pramipexole was resumed.

DISCUSSION

Ropinirole PR is a once daily oral dopamine agonist approved for the treatment of early and advanced PD.[6,7] It has been demonstrated that an overnight switch from comparable doses of immediate release ropinirole to ropinirole PR resulted in similar efficacy

without an increase in AEs.[6] However, there are no reports documenting the most appropriate conversion ratio when switching from pramipexole to ropinirole PR. This study demonstrated that the most efficacious conversion ratio with the fewest dose adjustments, adverse events, and study discontinuations was 1 mg of pramipexole to 4 mg of ropinirole PR. These results are comparable with those reported in a 6-week conversion study, in which subjects were switched from pramipexole to immediate release ropinirole, which reported a conversion factor of 1 mg of pramipexole to 3.8 mg of ropinirole.[8]

The 1:4 conversion ratio resulted in the early discontinuation of 10% of the subjects compared with 30% in the 1:3 group and 25% in the 1:5 group. Similarly, 65% of the 1:4 conversion group required no additional dose adjustments compared with 50% in 1:5 group and only 10% in the 1:3 group. The majority of the subjects (90%) in the 1:3 conversion group required a dose increase and a significantly greater number of adjustments (2.4 vs. 1.0) were made for those who preferred pramipexole versus those who preferred ropinirole PR. These results indicate that the conversion ratio of 1:3 was too low. In contrast, 40% of subjects in the 1:5 conversion group required a dose reduction indicating that this conversion ratio was too high for a large proportion of subjects. Although the conversion factor for all subjects preferring ropinirole PR was 4.6, the majority did not require additional adjustments and if necessary, one adjustment was generally sufficient. AEs were as expected with a dopamine agonist and the majority resolved after the optimal ropinirole PR dosage was achieved.

Fifty-five percent of the subjects preferred ropinirole PR and 45% preferred pramipexole. The most common reasons for preference of ropinirole PR were improved efficacy with reduced "off" time, the convenience of once daily dosing and decreased somnolence. The majority of subjects preferring pramipexole reported greater efficacy with less daytime somnolence and less dizziness. Thirteen subjects discontinued ropinirole PR before 4 weeks of therapy. In five of these subjects, their initial conversion resulted in the maximum dosage of 24 mg/day of ropinirole PR which could not be further increased in this study; they were taking a mean of 4.5 mg/day of pramipexole. In the remaining eight subjects that discontinued early, after several adjustments they chose to stop ropinirole PR treatment.

An examination of subjects that discontinued ropinirole PR before study completion revealed that they were taking a significantly higher dose of pramipexole, the majority greater than 4.0 mg/day compared with those who completed 4 weeks of ropinirole PR therapy. Similarly, when all subjects preferring pramipexole were compared with those who preferred ropinirole PR, those who preferred pramipexole had significantly more dose adjustments (1.3 vs. 0.6) and had a significantly longer mean duration of PD (9.4 vs. 6.7 years). There were no significant differences between preference groups in UPDRS, PDQ-39, ESS, or daily L-dopa dosages. Together, these results may suggest that patients with a longer disease duration who are taking daily doses of at least 4 mg of pramipexole are less likely to be successfully converted from pramipexole to ropinirole PR.

This study does have limitations. The open label design of the study allows for potential subject bias in trying a new medication and potential rater bias. In addition, ropinirole PR was available only in dosages of 2, 4, and 8 mg tablets that could not be broken, which did not allow for exact conversion values. There were no restrictions on other antiparkinsonian medications; however, the majority of subjects were on l-dopa therapy and there were no differences in l-dopa dosages based on drug preference.

In conclusion, when converting patients from pramipexole to ropinirole PR, an overnight switch is safe and well tolerated by the majority of patients. However, patients with longer disease duration who are taking daily dosages of pramipexole greater than 4 mg appear to be the most likely to have difficulty in tolerating a conversion from pramipexole to ropinirole PR. For the majority of subjects, the most effective conversion ratio was 1 mg of pramipexole to 4 mg of ropinirole PR followed by slow increases in ropinirole PR as needed.

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