CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-514

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	3/19/2010
From	Gerald D. Podskalny, DO
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22514
Applicant	Boehringer Ingelheim
Date of Submission	21 May 2009
PDUFA Goal Date	22 March 2010
Proprietary Name / Established (USAN) names	Pramipexole Dihydrochloride Extended-Release Tablets MIRAPEX ER
Dosage forms / Strength	Extended Release Tablets 0.375, 0.75, 1.5, 3.0, and 4.5 mg
Proposed Indication(s)	1. Adults with Advance Parkinson's Disease
Recommended:	***APPROVAL***

1. Introduction

Immediate release (IR) pramipexole (Mirapex™) was approved for the treatment of the signs and of idiopathic Parkinson's disease (PD), as monotherapy or adjunctive therapy levodopa on July 1, 1997.

Boehringer decided to divide the submission to the FDA for Mirapex ER in 2 separate NDA applications, one for early and another for advanced Parkinson's disease indications rather that to file a single applications for the entire PD indication. Pramipexole was approved for the treatment for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) On November 7, 2006 (NDA-20-667). MIRAPEX ER (NDA 22421) was approved by the US FDA for the treatment of the signs and symptoms of early Parkinson's disease on February 19, 2010. The initial action taken by the agency for the Pramipexole ER in early Parkinson's disease was a complete response. The reason for the complete response action was the agency's safety concerns regarding the potential for medication errors caused by the similar appearance shared between the different strength tablets for pramipexole ER and similarities between pramipexole ER and immediate release pramipexole tablets. The sponsor altered the appearance of pramipexole ER by changing the debossing on the ER tablets to "ER" on one side and the tablet strength in milligrams on the other. Dissolution data for the reimaged tablets was reviewed by the agency, the CMC review division concluding the tablet performance on dissolution testing was adequate. In addition, the carton and container labeling was revised to further reduce the potential for medication errors prior to approval of pramipexole ER for early PD.

The approval of the second application for advanced PD would complete the approval for a global PD indication similar to the indication for the immediate release pramipexole. Unlike pramipexole IR, pramipexole ER is not approved for the treatment of the signs and symptoms of moderate to severe Restless Legs Syndrome.

2. Background

Pramipexole ER is expected to have a similar efficacy and safety profile as the IR product, which has been approved since 1997. The recently completed NDA review for pramipexole ER in the Early PD indication did not reveal any new safety concerns for the ER formulation. The ER product also did not demonstrate a significant efficacy advantage over the IR product. The main advantage of the ER product is the convenience of once daily dosing.

3. CMC/Device

No New CMC or Quality data was presented in this NDA.

Summary of CMC/Quality Recommendations for Approval of NDA 22421 (Early PD)

The CMC drug quality review for pramipexole ER was completed prior to the approval of the early PD indication. The review of the drug substance and drug product was complete with no unresolved issues with the sponsor and there were not unresolved issues within the agency. T The drug product was recommended for approval pending the changes in tablet appearance as noted above. Pramipexole ER was assigned a 24 month expiry.

Facilities review/inspection NDA 22421 (Early PD)
Mirapex ER (NDA 22421) was approved by the US FDA for the treatment of the signs and symptoms of early Parkinson's disease on February 19, 2010. This product was investigated under IND 75,961 and CMC/Quality rendered an overall recommendation of acceptable on 10-JUN-2009 for the Establishment Inspection relevant to pramipexole ER.

There are no outstanding CMC or drug quality issues for pramipexole ER.

4. Nonclinical Pharmacology/Toxicology

There were no new animal or non-clinical studies included in this application. There were no unresolved Pharmacology Toxicology issues or differences of opinion relating to the advanced PD indication or the prior application for early PD.

5. Clinical Pharmacology/Biopharmaceutics

There were no new Clinical Pharmacology study results contained in this application.

A labeling issue that re-emerged during labeling negotiations with Boehringer Ingelheim for the Advanced PD application that was also negotiated in the early PD application related to elevations in BP and pulse observed in healthy volunteers enrolled in the Thorough QTc study.

Based on observations of a modest increase in pulse and BP in healthy volunteers participating in the QTc Study, (b) (4)

(b) (4) IRT made the following comment on the observed change in vital signs:

> "A modest rise in supine SBP (10 mmHg), DBP (7mmHg) and HR (10 bpm) were noted in these normal subjects compared to placebo; this is effect is felt to be due to the forced titration schedule, one not used in the patient population. The increase in HR was noted to a more modest degree in the trial. The BP elevation was seen in some subjects but many had a drop with change in posture. These do not appear to be clinically important".

The sponsor proposed changes to the clinical pharmacology section of the Mirapex label and proposed a CBE days after the Mirapex ER label was approved for early Parkinson's disease.

(b) (4)

CDTL Comment
The sponsor's proposed label change is based on the observations from the Thorough QTc Study that was conducted in healthy volunteers who were administered pramipexole using a rapid (not recommended) titration schedule. These findings do not inform prescribers about a potential risk associated with the recommended use of pramipexole in the intended population. The mild increases in BP and pulse were not considered clinically relevant. (b) (4)

(b) (4)

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The NDA application relies on a single trials to support effectiveness in patients with advanced PD. The safety and efficacy of Mirapex ER in PD is supported by the results of the Mirapex ER trial (248.524) in early PD that served as the pivotal trial for that recently approved NDA.

Clinical Trial Design Study 248.525 in Patients with Advanced PD

This study evaluated the efficacy and safety of pramipexole ER in patients with advanced PD over a treatment period of up to 33 weeks, in comparison to placebo and pramipexole IR. The primary efficacy endpoint was the change from baseline in the UPDRS Parts II and III combined. The primary efficacy analysis was performed after 18 weeks of treatment and to descriptively assess maintenance of efficacy at 33 weeks. The key secondary efficacy endpoint was the change from baseline in the percentage off-time during waking hours (assessed on a patient's diary). Overall, 517 patients (PPX ER: 164, PPX IR: 175 and placebo: 178, according to the 1:1:1 randomization ratio) were treated in this study conducted in 14 countries from Europe and Asia. This 33-week study was concluded after the last patient completed 18 weeks of treatment

In both 248.524 and 248.525 trials, patients were randomized in a DB, double-dummy manner to pramipexole ER (given once a day in the morning), pramipexole IR (given in equally divided doses t.i.d.), or placebo. Depending on efficacy and tolerability, pramipexole doses were up-titrated to an optimal dose (based on efficacy and safety), at weekly intervals from 0.375 mg to 4.5 mg/day. The total treatment period was 33 weeks (7-week titration and 26 weeks on maintenance dose Mirapex ER).

Endpoints

Primary endpoint:

- UPDRS (Unified Parkinson's Disease Rating Scale) parts II+III score (change from baseline to week 18. Originally, the endpoint was to end of the maintenance period (33 weeks), but this was changed in an amendment approved by the agency).

Key secondary endpoint

- Percentage of off-time during wakefulness –change from baseline (diary based)

Other secondary endpoints:

- Proportion of patients with at least a 20% improvement relative to baseline in the percentage off-time during waking hours (diary based)
- Percentage on-time:
    - without dyskinesia
    - with non troublesome dyskinesia
    - without dyskinesia or with non-troublesome dyskinesia ("good on-time")
    - with troublesome dyskinesia
    - during waking hours – diary based (change from baseline)
- Responder rate for Clinical Global Impression of Improvement (CGI-I)
- Responder rate for Patient Global Impression of Improvement (PGI-I)
- Responder rate for Patient Global Impression of Improvement (PGI-I) of early morning symptoms

- Proportion of patients with at least a 20% improvement relative to baseline in the UPDRS II+III total score
- UPDRS I, II, III and IV scores separately (change from baseline)
- BDI (Beck's Depression Inventory) version IA (change from baseline)
- PDSS (Parkinson's Disease Sleep Scale) (change from baseline)
- Likert scale for pain related to PD (change from baseline)
- PDQ-39 (Parkinson Disease Questionnaire- 39 items)
- EQ-5D (EuroQoL) (change from baseline)
- L-Dopa daily dose (change from baseline)
- Cost-effectiveness analysis will be conducted to compare treatments

Safety endpoints:

- Incidence of Adverse Events
- Proportion of withdrawals due to adverse events
- Vital signs (blood pressure and pulse rate)
- Weight
- Epworth Sleepiness Scale (ESS)
- Modified Minnesota Impulsive Disorders Interview (MMIDI)
- Clinical laboratory parameters

Analysis Plan

Primary analysis:
ANCOVA analysis for change from baseline at the end of the maintenance treatment period in the UPDRS II+III total score, adjusting for center (fixed effect) and baseline UPDRS II+III (covariate). The primary analysis will be based on the Full Analysis Set (using LOCF) for the comparison of PPX ER vs. placebo.

Secondary analyses:
The percentage off-time during waking hours (key secondary endpoint) will be tested using an ANCOVA model. ANCOVA or non-parametric treatment group comparisons as appropriate for secondary efficacy endpoints. The secondary analyses will be based on the Full Analysis Set (using LOCF). Aside from declaring the Percentage of off-time during wakefulness as "Key Secondary Endpoint" there was no adjustment made for multiple comparisons for the analysis of the remaining secondary endpoints.

Key Inclusion Criteria

- Idiopathic Parkinson's disease diagnosed by UK Brain Bank criteria for at least 2 years with a modified Hoehn and Yahr scale of II to IV at "on time'.
- Must be treated with levodopa with or without dopa-decarboxylase inhibitor and/or entacapone, at an optimized dose, stable for at least 4 weeks prior to baseline

- Must have documented motor fluctuations with at least 2 cumulative hours of off-time every day during waking hours
- No exposure to dopamine agonists within 8 weeks prior to baseline.

Key Exclusion Criteria

- Atypical parkinsonian syndromes
- Dementia with MMSE < 24 at baseline
- Psychosis except drug induced hallucinations
- History of deep brain stimulation
- Any dopamine blocking concomitant treatments within 4 weeks of the baseline visit.

Analysis Populations

Treated set 1 (TS 1) population was defined as all patients who were dispensed study medication, were documented to have at least one dose of study medication and were treated for 18 weeks (or had discontinued treatment prior to week 18). Data limited to visit 8 (or V11 in case of premature discontinuation before visit 8).

Treated set 2 (TS 2) population was defined as all patients who were dispensed study medication, were documented to have at least one dose of study medication and completed visit 11 (were treated for 33 weeks or had discontinued treatment prior to week 33).

Patient Demographics Data

Summary of Baseline Demographic Characteristics TS 1

	Placebo	PPX ER	PPX IR	Total
Number of patients	178	164	175	517
Gender [N (%)]				
Male	94 (52.8)	92 (56.1)	98 (56.0)	284 (54.9)
Female	84 (47.2)	72 (43.9)	77 (44.0)	233 (45.1)
Age [years]				
Mean (SD)	60.9 (9.7)	61.6 (9.7)	62.0 (10.3)	61.5 (9.9)
Age classes [N (%)]				
<65 years	104 (58.4)	94 (57.3)	100 (57.1)	298 (57.6)
>=65 years	74 (41.6)	70 (42.7)	75 (42.9)	219 (42.4)
Race [N (%)]				
White	92 (51.7)	81 (49.4)	87 (49.7)	260 (50.3)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	86 (48.3)	83 (50.6)	88 (50.3)	257 (49.7)
BMI [kg/m²]				
Mean (SD)	25.0 (4.6)	24.7 (3.9)	24.5 (4.2)	24.7 (4.3)

Source data: Table 15.1.4.1: 1

In general, it seems that the 3 treatment groups were comparable regarding demographic characteristics at baseline.

Baseline Disease Characteristics

Advanced PD Trial: Baseline disease characteristics (source: Sponsor)

	Placebo	PPX ER	PPX IR	Total
PD duration [years]				
Duration mean(SD) or median (IQR)	5.9 (3.8)	6.1 (4.0)	6.6 (4.4)	6.2 (4.1)
PD known since				
0-< 2 [y] N (%)	1 (0.6)	1 (0.6)	3 (1.7)	5 (1.0)
2-< 5 [y] N (%)	90 (50.6)	82 (50.0)	76 (43.4)	248 (48.0)
>= 5 [y] N (%)	87 (48.9)	81 (49.4)	96 (54.9)	264 (51.1)
UPDRS Part II+III total score				
Number of Patients	178	164	174	516
Mean (SD)	39.6 (18.2)	41.7 (17.9)	40.7 (17.6)	40.6 (17.9)
Percentage off-time				
Number of Patients	178	164	175	517
Mean (SD)	38.6 (15.6)	36.0 (15.7)	37.7 (13.2)	37.5 (14.9)
Off-time in hours				
Number of Patients	178	164	175	517
Mean (SD)	6.0 (2.5)	5.8 (2.8)	6.0 (2.2)	5.9 (2.5)
UPDRS Part I total score				
Number of Patients	178	164	175	517
Mean (SD)	1.9 (1.9)	2.1 (1.8)	1.9 (1.7)	1.9 (1.8)
UPDRS Part II total score (average on and off-period)				
Number of Patients	178	164	174	516
Mean (SD)	11.9 (6.1)	12.7 (6.5)	12.3 (5.7)	12.3 (6.1)
UPDRS Part III total score				
Number of Patients	178	164	175	517
Mean (SD)	27.7 (13.6)	29.0 (12.9)	28.3 (13.3)	28.3 (13.2)
PDSS				
Number of Patients	178	164	175	517
Mean (SD)	101.7 (25.3)	96.8 (27.7)	101.1 (26.2)	100.0 (26.4)

Source data: Table 15.1.4.1: 2, 15.1.4.1: 3, 15.1.4.1: 4

There did not appear to be any significant differences in baseline Parkinson's disease characteristics by comparing mean values for patients assigned the 3 treatment arms.

Efficacy Analysis

Primary Endpoint Sponsor's Analysis (Total n=507 in FAS)

Table 3.2.2.1.1: 1 UPDRS II+III, Trial 248.525, 18 weeks of treatment / FAS 1 (LOCF)

Primary efficacy endpoint	Placebo	PPX ER	PPX IR	PPX ER vs Placebo	PPX IR vs. Placebo
UPDRS II+III total score					
Number of patients	174	161	172		
Baseline, Mean (SD)	40.0 (18.1)	41.7 (17.7)	40.8 (17.4)		
Week 18, Mean (SD)	33.2 (17.4)	29.5 (17.3)	27.2 (16.4)		
LS Mean Change (SE) ANCOVA*	-6.1 (0.9)	-11.0 (1.0)	-12.8 (0.9)	0.0001	<0.0001

*ANCOVA with factors treatment and pooled country and covariate baseline
Source data: Appendix 6, Table 3.2.1.2.1.1 and trial 248.525 final report [U09-1270-01], Table 11.4.1.1.1: 1, Module 5.3.5.1

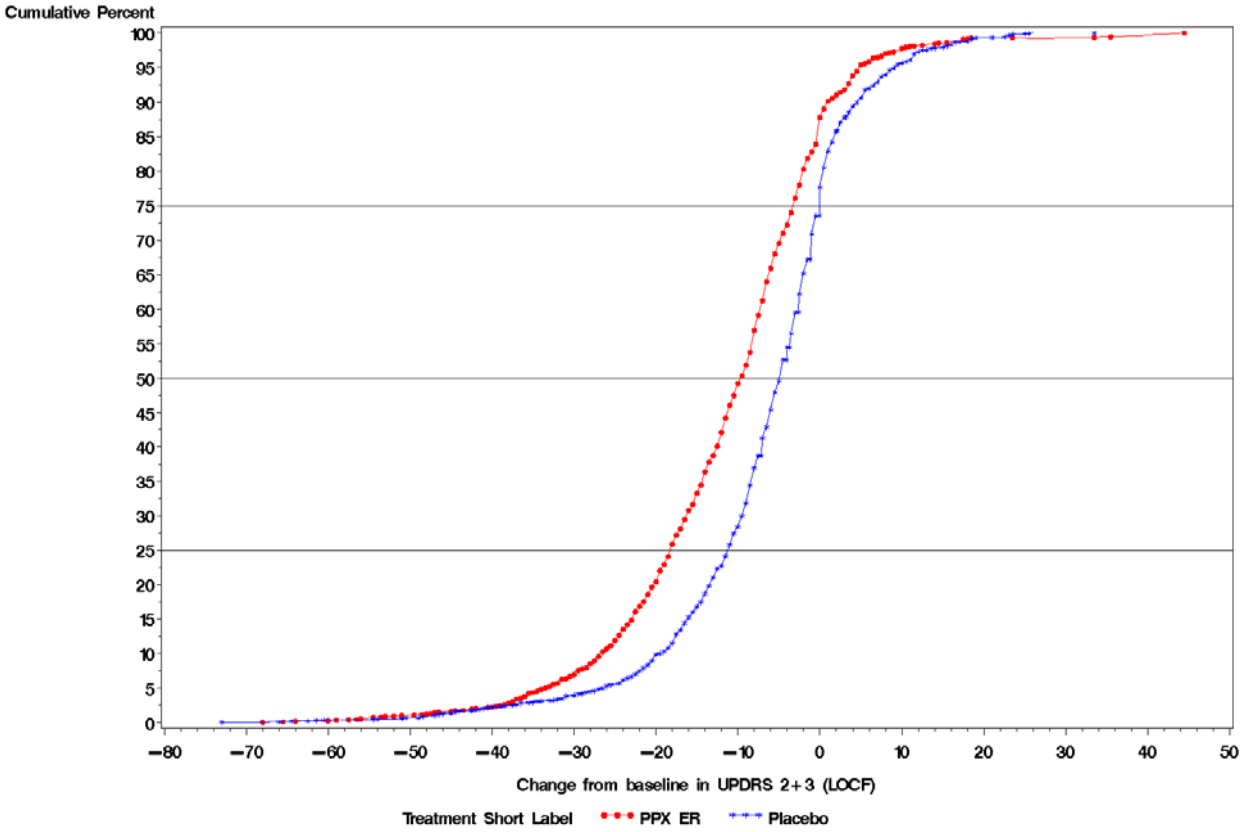
Statistical Reviewer's Analysis

The agency's statistical reviewer, Dr. Luan confirmed the result of the sponsor's analysis of the primary endpoint. In addition, they supported this conclusion by performing a Mixed Model Repeated Measurements (MMRM) analysis including the assessments performed during the maintenance visits ($p<0.0001$ for each of the pramipexole formulations).

Statistical Reviewers Analysis-Cumulative Distribution Function (CDF) for Primary Efficacy Endpoint

The Cumulative Distribution Function (CDF) for the primary endpoint, change from baseline in UPDRS Part II+III at week 18, is presented in Figure 1for Study 248.525. It seems that the CDF for PPX ER group is generally above the CDF for placebo group, indicating that the patients in PPX ER group generally had larger improvement in UPDRS Part II+III score than those in placebo group.

Figure 1: CDF for change from baseline in UPDRS Part II+III at Week 18, FAS1 (LOCF) FDA Statistical Reviewer's Graphic



Secondary Endpoints Analysis

The sponsor chose as their "key secondary endpoint" for the advanced PD trial, the changes in the percentage of daily awake off time. The changed in the percentage of awake off time is frequently chosen as an end point for adjunctive therapy trials in advanced PD trials and it has served as the primary endpoint in some instances. At the Week 18 endpoint, PPX ER improved off-time compared to the placebo group. ER patients reported a mean 12% reduction in awake off time, while the placebo group reported a mean 9% reduction in awake off time (ANCOVA p= 0.0122). However, this effect was statistically weakened and no longer significant by the end of the trial (33Weeks).

Change in Percentage in Awake Off Time (sponsor's table)

Table 3.2.2.2.1: 1 Percentage off-time, Trial 248.525, 18 weeks treatment / FAS 1 (LOCF)

Key secondary endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
Percentage off-time					
Number of Patients	174	160	171		
Baseline, Mean (SD)	38.7 (15.6)	36.3 (15.8)	37.8 (13.1)		
Week 18, Mean (SD)	29.6 (19.5)	24.1 (17.8)	22.3 (16.4)		
LS Mean Change (SE) – ANCOVA*	-8.8 (1.3)	-13.3 (1.4)	-15.9 (1.3)	0.0122	<0.0001

*ANCOVA with factors treatment and pooled country and covariate baseline

Source data: Appendix 6, Table 3.2.1.2.2.1 and trial 248.525 final report [U09-1270-01], Table 11.4.1. 2.1: 1, Module 5.3.5.1

Table 3.2.2.2.1: 2 Off-time in hours, Trial 248.525, 18 weeks treatment / FAS 1 (LOCF)

Key secondary endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
Off-time (hours)					
Number of Patients	174	160	171		
Baseline, Mean (SD)	6.0 (2.4)	5.8 (2.8)	6.0 (2.2)		
Week 18, Mean (SD)	4.6 (3.2)	3.9 (3.1)	3.5 (2.6)		
LS Mean Change (SE) – ANCOVA*	-1.4 (0.2)	-2.1 (0.2)	-2.5 (0.2)	0.0199	<0.0001

*ANCOVA with factors treatment and pooled country and covariate baseline

Source data: Trial 248.525 final report [U09-1270-01], Appendix 16.1.9.2, Table 6.3.3, Module 5.3.5.1

Patient and Investigator Rated Global Impression Scales (sponsor's table)

Table 3.2.2.3: 1 CGI-I, PGI-I and PGI-I for early morning off-symptoms Responders rates, Trial 248.525, 18 weeks treatment / FAS 1 (LOCF)

Secondary endpoints	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs. placebo	PPX IR vs. placebo
CGI-I Responders					
Number of Patients	171	160	169		
Responders [N (%)]	56 (32.7)	78 (48.8)	88 (52.1)	0.0037	0.0002
% Responders [95% CI]	[25.8, 40.3]	[40.8, 56.8]	[44.3, 59.8]		
PGI-I Responders					
Number of Patients	174	161	172		
Responders [N (%)]	47 (27.0)	60 (37.3)	76 (44.2)	0.0554	0.0005
% Responders [95% CI]	[20.6, 34.3]	[29.8, 45.2]	[36.6, 51.9]		
PGI-I for early morning off-symptoms Responders					
Number of Patients	148	135	146		
Responders [N (%)]	29 (19.6)	47 (34.8)	59 (40.4)	0.0024	<0.0001
% Responders [95% CI]	[13.5, 26.9]	[26.8, 43.5]	[32.4, 48.8]		

CGI-I / PGI-I responders = patients with a score of "1" = very much improved/very much better; or "2" = much improved/much better

Source data: Appendix 6, Table 3.2.1.2.3.1 and trial 248.525 final report [U09-1270-01], Tables 11.4.1.2.2: 6-8, Module 5.3.5.1

In FAS 1 (LOCF) population, the responder rate as assessed by CGI-I at week 18 were 48.8% (p=0.0037) in the pramipexole ER group, 52.1% (p=0.0002) in the pramipexole IR group and 32.7% in the placebo group.

The responder rate as assessed by PGI-I at week 18 were 37.3% (p=0.0554) in the pramipexole ER group, 44.2%(p=0.0005) in the pramipexole IR group and 27.0% in the placebo group. The difference between pramipexole IR and placebo was statistically significant and the difference between pramipexole ER and placebo showed a trend in favor of pramipexole ER.

Primary Endpoint Analysis at 33 Weeks (End of Trial)

Table 5.2: 1 Maintenance of effect in UPDRS II+III total score at Week 18 and Week 33, Trial 248.525, FAS 2 (OC)

Primary efficacy endpoint UPDRS Part II+III	**Placebo**	**Pramipexole ER**	**Pramipexole IR**
Number of Patients	100	94	114
Baseline, Mean (SD)	41.3 (18.5)	42.3 (18.9)	41.3 (17.9)
Week 18, Mean (SD)	32.0 (15.9)	27.3 (17.6)	26.4 (17.0)
Change from baseline, Mean (SD)	-9.2 (15.0)	-15.0 (13.2)	-14.9 (12.0)
Week 33, Mean (SD)	31.0 (16.2)	28.1 (19.2)	27.9 (19.1)
Change from baseline, Mean (SD)	-10.3 (14.9)	-14.2 (15.3)	-13.4 (15.8)

Source data: Appendix 6, Table 5.2.1 and trial 248.525 final report [U09-1270-01], Table 11.4.1.1.4: 1, Module 5.3.5.1

Analysis of Subgroups

The statistical reviewer performed a subgroup analyses by country and concluded that there were no meaningful difference between countries in change from baseline in UPDRS Part II+III total score.

Demographic Subgroup Analysis

The statistical reviewer's analysis of subgroups found there were "no important effect of analysis of the following subpopulations: age, race, gender or country. The effect of this drug on an African American population has not been studied".

CDTL Comment

The trial design and conduct were adequate. There were no factors discovered during the review of the clinical trials results or findings of the DSI inspections to question the results of the single pivotal efficacy trial in advanced PD. The results of the primary endpoint analysis (UPDRS parts II + III) are statistically significant in favor of Mirapex ER compared to placebo. The findings reported for important secondary endpoints including the sponsor's Key Secondary endpoint (change in % of awake off time) demonstrate a statistically significant treatment effect or persuasive trend favoring Mirapex ER over placebo. The immediate release Mirapex was numerically superior to the ER preparation in almost all primary and secondary outcome measures. This trial was not designed or powered to detect a statistically

meaningful difference between Mirapex ER and IR. The primary clinical reviewer, the statistical review staff and this CDTL reviewer all reached the same independent conclusion that Mirapex ER has demonstrated effectiveness based on the clinical trials data reviewed in this application. The application is supported by the agency's confirmation of the effectiveness and safety of Mirapex ER in patients with early PD. There were no unresolved differences of opinion between the review disciplines regarding the finding of effectiveness for Mirapex ER in advance PD.

7. Laboratory Findings

Hematology

Descriptive analysis, analysis of shift tables and outlier data did not find a trend indicating an abnormal change from baseline hematology values associated with treatment with Mirapex ER.

Serum Chemistry

Descriptive analysis, analysis of shift tables, outlier data and postmarketing data did not find evidence of a trend indicating a serum chemistry abnormality associated with Mirapex ER or Mirapex. There was a single case of a patient enrolled in a phase I study with chemistry abnormalities fulfilling criteria for Hy's Law. This patient's clinical status, liver enzymes and bilirubin were followed beyond the patient's scheduled trial participation. Eventually, the sponsor concluded the patient's abnormal liver functions were caused by obstructive gallbladder disease.

Vital Signs

There were no remarkable changes in mean systolic and diastolic BP compared to baseline for the groups treated with Mirapex ER or Mirapex IR. A more detailed evaluation of orthostatic hypotension is presented under the section of adverse events of special interest section of this review.

ECG

Analysis of central tendencies by visit in the supine and standing position did not reveal a significant change from baseline for patients enrolled in any of the Mirapex ER, IR or the placebo group.

The primary reviewer examined ECG related adverse event reports for patients enrolled in the advanced PD trials and found there were no significant difference between the Mirapex ER or IR groups compared to patients assigned to the placebo group.

8. Safety

The primary clinical reviewer conducted in-depth reviews of the pooled safety data from all phase 3 clinical trials and the combined 33 week, Early and Advanced Mirapex ER clinical trials datasets. Overall, the pooled 33 week data from the combined Parkinson's disease datasets did not change the safety and adverse events information regarding Mirapex ER. The incidence of treatment emergent impulse control disorders were reported more frequently in the early PD study compared to the advanced PD trial. Treatment emergent asymptomatic orthostatic hypotension was more frequent in advanced PD patients but this adverse effect is described in the approved product label. Somnolence is more common in patients with advanced PD but there was no significant difference between the Placebo and Mirapex ER treated groups.

Exposure to Mirapex ER in Patients With Advanced PD

Table 1 Advanced PD Trial: Dose and Duration of Exposure (source: sponsor)

Table 1.2.5.1: 2 Number (%) of patients exposed to pramipexole ER by treatment duration and final dosage level and overall - placebo-controlled Trial 248.525, 18-week analysis / TS 1 (18 weeks treatment)

Treatment exposure	PPX ER 0.375-1.5 mg/day	PPX ER 2.25-3 mg/day	PPX ER 3.75-4.5 mg/day	Total
Number of patients (%)	64 (38.1)	37 (22.6)	63 (38.4)	164 (100.0)
Duration of exposure, in days				
Mean (SD)	106.9 (38.1)	119.4 (20.9)	123.3 (11.0)	116.0 (27.6)
Median	125.0	125.0	125.0	125.0
Exposure in weeks N (%)				
N	64 (100.0)	37 (100.0)	63 (100.0)	164 (100.0)
< 1 week	3 (4.7)	0 (0.0)	0 (0.0)	3 (1.8)
1 - < 4 weeks	3 (4.7)	0 (0.0)	0 (0.0)	3 (1.8)
4 - < 8 weeks	3 (4.7)	2 (5.4)	0 (0.0)	5 (3.0)
8 - <13 weeks	2 (3.1)	1 (2.7)	2 (3.2)	5 (3.0)
13 - <18 weeks	39 (60.9)	18 (48.6)	35 (55.6)	92 (56.1)
18 - <23 weeks	14 (21.9)	16 (43.2)	26 (41.3)	56 (34.1)

Source data: Appendix 7, Table 1.2.4.5

The Number of Patients in Study 248.525 Completing ≥28 Weeks of Mirapex ER

Table 1.2.2.2.2: 2 Duration of patient exposure by treatment - placebo-controlled Phase III Trial 248.525 / TS 2 (33 weeks treatment)

Study: 248.525	Placebo	PPX ER	PPX IR	Total
Number of patients (%)	140 (35.4)	120 (30.4)	135 (34.2)	395 (100.0)
Duration of exposure, in days				
Mean (SD)	203.7 (66.9)	209.8 (64.1)	218.8 (51.2)	210.7 (61.3)
Median	231.0	231.0	231.0	231.0
Exposure in weeks [N (%)]				
N	140 (100.0)	120 (100.0)	135 (100.0)	395 (100.0)
< 1 week	3 (2.1)	2 (1.7)	2 (1.5)	7 (1.8)
1 - < 4 weeks	4 (2.9)	3 (2.5)	2 (1.5)	9 (2.3)
4 - < 8 weeks	4 (2.9)	4 (3.3)	1 (0.7)	9 (2.3)
8 - <13 weeks	5 (3.6)	4 (3.3)	3 (2.2)	12 (3.0)
13 - <18 weeks	3 (2.1)	1 (0.8)	3 (2.2)	7 (1.8)
18 - <23 weeks	5 (3.6)	1 (0.8)	0 (0.0)	6 (1.5)
23 - <28 weeks	2 (1.4)	2 (1.7)	1 (0.7)	5 (1.3)
≥ 28 weeks	114 (81.4)	103 (85.8)	123 (91.1)	340 (86.1)

Source data: Appendix 7, Table 1.2.4.2

Exposures from Early PD Trial 248.524

2.7.4 Summary of Clinical Safety

Table 1.2.2.2.1: 1 Duration of patient exposure by treatment Trial 248.524 / TS

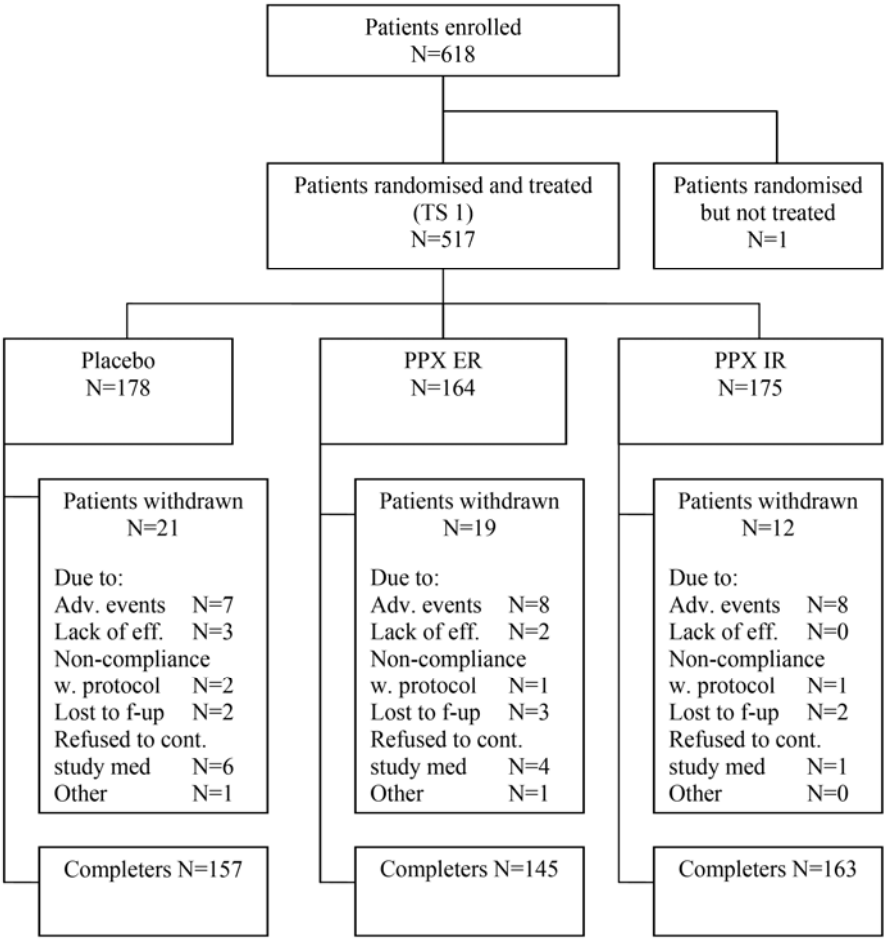
	Placebo	PPX ER	PPX IR	Total
Number of patients (%)	103 (19.1)	223 (41.4)	213 (39.5)	539 (100.0)
Duration of exposure, in days				
Mean (SD)	215.2 (54.8)	199.0 (73.0)	208.2 (65.6)	205.7 (67.1)
Median	231	231	231	231
Exposure in weeks [N (%)]				
N	103 (100.0)	223 (100.0)	213 (100.0)	539 (100.0)
< 1 week	0 (0.0)	8 (3.6)	5 (2.3)	13 (2.4)
1 - < 4 weeks	1 (1.0)	7 (3.1)	4 (1.9)	12 (2.2)
4 - < 8 weeks	4 (3.9)	7 (3.1)	8 (3.8)	19 (3.5)
8 - <13 weeks	3 (2.9)	7 (3.1)	6 (2.8)	16 (3.0)
13 - <18 weeks	2 (1.9)	9 (4.0)	5 (2.3)	16 (3.0)
18 - <23 weeks	1 (1.0)	6 (2.7)	2 (0.9)	9 (1.7)
23 - <28 weeks	1 (1.0)	3 (1.3)	2 (0.9)	6 (1.1)
>=28 weeks	91 (88.3)	176 (78.9)	181 (85.0)	448 (83.1)

Source data: Appendix 7, Table 1.2.4.2

The required minimum number of patient exposed to Mirapex ER for this application was discussed at an End of Phase II Meeting held with the Sponsor on 22 August 2007. The sponsor and the Agency agreed that the interim data analysis will include 6 month data from at least 100 subjects who have completed the trial in order to assess maintenance of efficacy out to 6 months. The sponsor has exceeded the agreed upon number of patient exposures for 6 months for both the Early and Advanced PD populations. Combined, the sponsor had over 279 patients with any stage of PD who were exposed to any dose of Mirapex ER for ≥ 28 weeks.

Patient Disposition

Patient Disposition Trial 248.525 Sponsor's Diagram



The number of patients who withdrew for lack of efficacy was similar in the placebo group and in the Mirapex ER group (3 vs 2) compared to 0 in the Mirapex IR group. Subjects who withdrew because of an adverse event were similar in all 3 groups. The remainder of the reasons patients withdrew from the trial had a similar number of patient in all 3 treatment groups.

Withdrawals for Adverse Events

Summary of The Frequency of Adverse Events and Withdrawals By Study Primary Clinical Reviewer Table

Adverse events and discontinuations	**Placebo**	**PPX ER**	**PPX IR**
248.524 Early PD	103	223	213
Any AE (N, %)	80 (78%)	189 (85%)	172 (81%)
AE of severe intensity	4 (4%)	12 (5%)	11 (5%)
SAE, non fatal	5 (5%)	16 (7%)	14 (7%)
5(5%)	24 (11%)	22 (10%)	
Premature Discontinuation, all reasons	12 (12%)	49 (22%)	37 (17%)
248.525 Advanced PD	178	165	175
Any AE	99 (56%)	90 (55%)	112 (64%)
AE of severe intensity	6 (3%)	10 (6%)	11 (6%)
SAE, non-fatal	15 (8%)	9 (5%)	12 (7%)
Premature Discontinuation due to adverse events	10 (6%)	14 (8%)	11 (6%)
Premature Discontinuation, all reasons	31 (17%)	23 (14%)	13 (7%)
Combined Placebo Controlled Trials:	281	388	388
Any AE	179 (64%)	278 (72%)	284 (73%)
AE of severe intensity	10 (4%)	22 (6%)	22 (6%)
SAE, non-fatal	20 (7%)	25 (6%)	26 (7%)
Premature Discontinuation due to adverse events	15 (5%)	40 (10)%	33 (9%)
Premature Discontinuation, all reasons	43 (15%)	72 (19%)	50 (13%)

The percentage of patients who withdrew prematurely for adverse events was similar for the Placebo, Mirapex ER and IR groups.

Deaths

There were12 deaths that occurred during the Mirapex ER development program up to the cut off date for the safety update. (The Sponsor reported 9, deeming the others to have occurred either before or after receiving drug.) Details of all 12 are summarized below. Upon review, none of these appear to be causally related to PPX.

Non-Fatal Serious Adverse Events

The non-fatal SAEs reported in the advanced PD trial were 9 (5%) for the Mirapex ER group, 12 (7%) among patients treated with Mirapex IR and 15 (8%) in the Placebo group. The narratives of these AEs were reviewed but many reports were incidental significant medical illness. A few cases were adverse events reporting symptoms known to occur with PPX, which rapidly resolved but the patients continued in the trial. There were no unexpected SAEs suggesting a new safety signal reported in the advanced PD NDA.

Non-Serious Adverse Events

Non-Serious Adverse Events (Source:Primary Clinical review)

Body System / Adverse Event	Placebo	MIRAPEX ER	Immediate release MIRAPEX
	(n=178)	(n=165)	(n=175)
	%	%	%
Nervous system disorders			
Dyskinesia	10	17	19
Somnolence	16	15	17
Headache	3	8	5
Dizziness	5	5	11
Dizziness postural	1	3	4
Dementia	1	0	2
Gastrointestinal disorders			
Nausea	11	11	11
Constipation	5	7	6
Diarrhea	1	3	2
Salivary hypersecretion	0	2	1
Abdominal pain upper	1	2	2
Dyspepsia	1	2	2
Vomiting	3	1	6
Psychiatric disorders			
Hallucinations, including visual, auditory and mixed	2	9	11
Insomnia	2	5	5
Sleep disorder	3	4	2
Compulsive sexual behavior	1	2	0
Compulsive shopping	1	2	1

Pathological gambling	0	1	2
Sleep attacks and sudden onset of sleep	1	1	2
Metabolism and nutrition disorders			
Anorexia	2	6	1
Injury, poisoning and procedural complications			
Fall	4	5	4
General disorders and administration site conditions			
Asthenia	2	4	2
Chest pain	0	2	1
Pain	1	2	1
Fatigue	1	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia	2	2	4
Muscle spasms	1	0	2
Osteoarthritis	0	0	2
Vascular disorders			
Orthostatic hypotension	1	2	2
Hypertension	1	1	2
Respiratory, thoracic and mediastinal disorders			
Cough	1	2	2
Eye disorders			
Cataract	3	2	4
Ear and labyrinth disorders			
Vertigo	1	1	2
Investigations			
Weight decreased	1	0	2

Dyskinesia and somnolence were the two most common non-serious adverse events for both Mirapex ER and Mirapex IR. There were only a few adverse events (headache, anorexia and asthenia) that were disproportionately reported in the Mirapex ER group compared to Mirapex IR. Otherwise, there were no adverse events that appeared to be unique to Mirapex ER or appeared to be more severe or significantly more frequent in patients who receiving Mirapex ER.

Adverse Events of Special Interest

Impulse Control Disorders (source: CDTL)

STUDY	PTNO	STUDY DAY	EPTNMDC	EPT	EPTBASDC
0248_0525	6061	160	MMIDI for gambling	1	Not baseline value
0248_0525	6301	0	MMIDI for compulsive buying	1	Baseline value
0248_0525	7200	-1	MMIDI for compulsive buying	1	Baseline value
0248_0525	7201	-1	MMIDI for compulsive buying	1	Baseline value
0248_0525	7228	-1	MMIDI for sexual behaviour	1	Baseline value
0248_0525	7760	0	MMIDI for compulsive buying	1	Baseline value
0248_0525	8002	238	MMIDI for gambling	1	Not baseline value
0248_0525	8004	36	MMIDI for sexual behaviour	1	Not baseline value

0248_0525	8041	90	MMIDI for sexual behaviour	1	Not baseline value
0248_0525	8081	0	MMIDI for gambling	1	Baseline value
0248_0525	8104	231	MMIDI for compulsive buying	1	Not baseline value
0248_0525	8409	28	MMIDI for compulsive buying	1	Not baseline value

The data collected using the modified Minnesota Impulsive Disorders Interview (mMIDI) found 12 patients with positive responses for at least 1 domain of the mMIDI but 6 of the 12 patients has a positive response at baseline. One of the 6 treatment emergent cases of a positive response on the mMIDI was assigned to the placebo group, leaving only 5 patients on Mirapex (ER or IR) with at least 1 positive ICD response on the mMIDI. The AEs reported to found 13 patients reported a total of 17 ICD related AEs using terminology that was related one of five (gambling, eating, shopping, buying or sexual behavior) ICDs covered in the mMIDI. Adverse event data alone may over estimate treatment emergent ICDs since the ICD may not be reported at baseline and it may be reported only after study medication has been dispensed, causing the AE to be falsely counted as a treatment emergent ICD related event.

Orthostatic Hypotension

Advanced PD Trial: reviewer's tally of BP related AEs(source: Primary Clinical Reviewer)

248.525 Advanced PD Preferred Term	Placebo n=178	PPX ER n=165	PPX IR n=175
Hypotension	1	1	1
Orthostatic hypotension	2	3	3
Dizziness postural	2	5	7
Syncope	0	1	2
Total	5 (3%)	10 (6%)	13 (7%)

There does not appear to be a significant difference in the number of patients reporting TEAEs related to low blood pressure or symptoms of orthostatic hypotension.

Orthostatic Blood Pressure Readings (source: Primary Clinical Reviewer)

Orthostatic Hypotension			
Trial 248.524 Early PD	**PLACEBO**	**PPX ER**	**PPX IR**
	(N=103)	**(N=223)**	**(N=213)**
OH at baseline (AAS / AAN Criteria)	4 (4%)	21 (9%)	19 (9%)
No OH at baseline	99	202	194
OH found during trial: AAS / AAN Criteria*	36 (36%)	70 (35%)	59 (30%)
OH found during trial: Sponsor's criteria*	7 (7%)	18 (9%)	9 (5%)
Trial 248.525 Advanced PD	**PLACEBO**	**PPX ER**	**PPX IR**

	(N=178)	(N=165)	(N=175)
OH at baseline (AAS / AAN Criteria)	17 (9%)	17 (10%)	12 (7%)
No OH at baseline	161	148	163
OH found during trial: AAS / AAN Criteria*	52 (32%)	55 (37%)	72 (44%)
OH found during trial: Sponsor's criteria*	9 (6%)	12 (8%)	17 (10%)
AAS / AAN Criteria: either systolic OH OR diastolic OH present. Sponsor's criteria: both systolic OH AND diastolic OH present. *Percentage calculation uses N in arm without OH at baseline as denominator.			

Orthostatic hypotension by BP parameters regardless if the patient was symptomatic for signs of orthostasis or not, was slightly more common in either Mirapex group, again there did not appear to be a significant difference between the Mirapex ER and IR groups.

Sudden Onset Sleep (source: Primary Clinical Reviewer)

	PLACEBO	PPX ER	PPX IR
248.525 Advanced PD	**(N=178)**	**(N=165)**	**(N=175)**
Hypersomnia	5 (2.81%)	2 (1.21%)	2 (1.14%)
Poor quality sleep	0 (0%)	1 (0.61%)	0 (0%)
Sleep attacks	0 (0%)	0 (0%)	1 (0.57%)
Sleep disorder	5 (2.81%)	7 (4.24%)	3 (1.71%)
Somnolence	29 (16.29%)	24 (14.55%)	30 (17.14%)
Sudden onset of sleep	1 (0.56%)	1 (0.61%)	2 (1.14%)
Total AEs	**40 (22%)**	**35 (21%)**	**38 2(2%)**

Dyskinesia

Advanced PD Trial: Dyskinesia reported as an AE (source: Primary Clinical Reviewer)

Dyskinesia reported as AE	PCB	PPX ER	PPX IR
Trial 248.525 Advanced PD	(N=178)	(N=165)	(N=175)
Dyskinesia	17 (10%)	28 (17%)	34 (19%)
Dyskinesia rated as "severe" AE	0 (0%)	2 (1%)	2 (1%)

Dyskinesia reported as an adverse event was higher in frequency for both Mirapex ER and IR compared with placebo. There was only a slight lower percentage in patients receiving Mirapex ER.

Advanced PD Trial: duration of dyskinesia(source: Primary Clinical Reviewer)

Duration of dyskinesia	PLACEBO	PPX ER	PPX IR
Trial 248.525 Advanced PD	**(N=178)**	**(N=165)**	**(N=175)**
Baseline Duration			
None	103 (58%)	93 (56%)	104 (59%)
1 - 25% of day	42 (24%)	43 (26%)	49 (28%)
26 - 50% of day	22 (12%)	27 (16%)	17 (10%)
51 - 75% of day	10 (6%)	2 (1%)	3 (2%)
76 - 100% of day	1 (0.6%)	0	2 (1%)
Number of subjects reaching this level of duration of dyskinesia at any point through the treatment period.			
None	77 (43)%	65 (39)%	73 (42)%
1 - 25% of day	47 (26)%	40 (24)%	48 (27)%
26 - 50% of day	31 (17)%	39 (24)%	30 (17)%
51 - 75% of day	16 (9)%	15 (9)%	18 (10)%
76 - 100% of day	7 (4)%	6 (4)%	6 (3)%

Overall, dyskinesia appeared to be slightly more frequent in the Mirapex treated groups although this is not consistent for patients in all severity categories measuring the duration of dyskinesia.

Retinal pathology

Eye examinations for vision and fundoscopy were performed by an ophthalmologist at screening and week 28 in both the early and advanced PD trials. Abnormalities were not a reason for exclusion from the trials. "Clinically significant changes" from baseline were reported as AEs. Analysis of adverse events by MAED Service software yielded no particular pattern of ophthalmological dysfunction.

In looking at the results of fundoscopy or vision examination from screening visit to week 28 in either trial reveals no clear safety signal. What constitutes normal or abnormal for this dichotomized outcome was not clearly specified.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

The sponsor requested a Waver for Pramipexole ER. A waiver has been granted 8/19/09 since PD is considered as an indication that is exempt from the pediatric requirement under BPCA. A pediatric waiver is granted for Mirapex ER in advanced Parkinson's disease.

11. Other Relevant Regulatory Issues

Three foreign sites were selected for inspection by the Division of Scientific Investigations, These three sites were requested on the basis of their high enrollment of 76 sites in this NDA's pivotal efficacy/safety trial. The site chosen in the Philippines represents 20 % of all patients entered in that country. The two clinical sites chosen in Barcelona represent almost half of that country's contribution to the trial. On inspection of these sites by the Division of Scientific Investigations, no actions were indicated for any violation of GCP. Data was considered reliable. There were found to be some irregularities in the recording of data in patient diaries for on-off states – a patient reported outcome. (It is supposed to be completed by the patient or caregiver). In the two Barcelona sites it is not clear how this was implemented. However, this was a minor protocol violation and there was no appearance of a pattern of malfeasance. This finding had no influence on the interpretation of the results of the confirmatory trial.

The Sponsor affirms that all studies in the clinical development program of pramipexole ER in PD were approved by ethics committees or institutional review boards, in line with Good Clinical Practice guidelines, the Sponsor's Standard Operating Procedures (SOPs) and according to the Declaration of Helsinki, version 1996. Written informed consent was obtained from all patients prior to any study related procedure.

The Sponsor certifies that it did not use any debarred investigators.

Financial Disclosures

The Sponsor provided required information regarding financial disclosure. These were reviewed and there were no findings of conflicts of interest among the investigators participating in the confirmatory trial; the consultants receiving funds above the threshold for reporting did not enter patients or act as clinical investigators.

12. Labeling

The proprietary name "Mirapex ER" was approved by the agency prior to approval of the NDA for the early Parkinson's disease indication. The carton and container labeling were also approved with the early PD approval action. The final label is in the final stages of negotiations with Boehringer Ingelheim at the time of this review.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval

Risk Benefit Assessment

There were no new safety concerns discovered during the review of this application. The adverse events associated with Mirapex ER in patients with advance Parkinson's are similar to those reported in the Mirapex IR label. The postmarketing experience with Mirapex IR has caused concern for impulse control disorders (ICD) associated with all drugs that raise dopaminergic tone used to treat patients with PD. The recent data from a prevalence study conducted by this sponsor using Mirapex IR supports the conclusion that ICDs are associated with dopamine agonist use. The data collected in advanced PD trial and the early PD trial using Mirapex ER suggest that ICD may be less frequent in a clinical trials population but there is still evidence to support that ICD is associated with starting Mirapex ER even when the symptoms are not present at baseline and when all other PD medications are continued without changes. This finding supports moving information in the label regarding ICD into the "Warnings and Precautions" section of the Mirapex ER and IR labels.

Mirapex ER has demonstrated effectiveness in an adequately controlled clinical trial in patients with Advance PD. The effectiveness in PD is supported by the results of the Mirapex ER trial in patients with early PD, meeting the requirement of replication in at least two clinical trials in Parkinson's disease. The effect size is statistically significant and the study results demonstrate a high degree of internal consistency with positive outcomes on nearly all of the secondary endpoints. Global ratings indicate the treatment of Mirapex ER is perceived as an improvement by the majority of patients with advanced PD who received this medication.

Recommendation for Postmarketing Risk Management Activities

None

Recommendation for other Postmarketing Study Commitments

None

Recommended Comments to Applicant
None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22514	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	TBD (PRAMIPEXOLE DIHYDROCHLORIDE)ER TABS

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/s/

GERALD D PODSKALNY
03/19/2010