

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

FEB 27 1997

Safety Review

Application Information

NDA 20-667

Pharmacia & Upjohn

NDA Safety Update Submission Date: January 10, 1997

Drug Name

Generic: Pramipexole

Proposed Trade Name: Mirapex™

Drug Characteristics

Pharmacological Category: Dopamine agonist

Proposed Indications: 1) Primary symptomatic treatment of Parkinson's disease.
2) Adjunctive treatment of Parkinson's disease.

Dosage Forms: Oral tablets in 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg

Proposed Use:

Pramipexole should be given T.I.D.. Dosages should be increased gradually from a starting dose of 0.375 mg/day and should not be increased any sooner than every 5-7 days. In most studies a 7 week dose escalation scheme was followed: 0.125 T.I.D., 0.25 T.I.D., 0.5 T.I.D., 0.75 T.I.D., 1.0 T.I.D., 1.25 T.I.D., and at the 7th week to the maximum dose of 1.5 T.I.D. Withdrawal should occur gradually over a 7-day period.

Safety Update Reviewer: John D. Balian, M.D.

Date of Review: February 27, 1997

1 Summary of Pramipexole Safety Update Review

The original ISS summarized the safety experience for 1408 patients with about 815 person-years (PYs) of pramipexole use, most of it (800 PYs) coming from the Parkinson's Disease (PD) trials. This safety update brings the total to 2146 patients with 1925 PYs of pramipexole exposure, most of it (1878 PYs) coming from the PD trials. This increased exposure does not change the findings, add new clinically significant adverse events (AEs), or new safety issues to the original review.

In the safety update, there is doubling of the number of deaths (15 new cases) in the pramipexole patients, but this is a reflection of more than doubling of the exposure, as noted above. The reports on serious AEs, dropouts, and common AEs were much of the same when compared to the original review. Since most of the new information comes from open-label uncontrolled trials, and most of the patients are not uniquely exposed, incidence rates are not presented here. There were no AEs clinically consistent or suggestive of hepatic failure or necrosis, urolithiasis, agranulocytosis, or aplastic anemia. No new cases of rhabdomyolysis were reported (there was one case in the original review).

In summary, pramipexole use is not associated with increased risk for deaths, serious AEs, or dropouts in PD patients. While there was a clear increase in CV effects (syncope and OSH) attributable to pramipexole in the phase 1 healthy volunteers, no significant differences from placebo were observed in the phase 2/3 trials.

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2 Background

Following the review of NDA 20-667 (submitted by Pharmacia & Upjohn on Dec 26, 1995), the agency informed the sponsor, with a letter dated Dec 23, 1996, that the application is approvable for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD), upon the submission and favorable review of a safety update. The present submission is the safety update report on pramipexole using 2/29/96 as the cutoff date.

2.1 Overview of the Safety Update

The present submission is a compilation of data from the original submission and data analyzed since that submission. The sponsor's presentation of the information follows the same format as the original submission, unfortunately, there is no separation of the new data from the old, thus making a clear identification of the new data very cumbersome. As in the case of the original Integrated Safety Summary (ISS), the sponsor provides pooled descriptions and analyses of the treatment emergent adverse events (AEs), but upon special request, a supplement with separate tables of early-treatment (ET) and advanced-treatment (AT) PD patients was also submitted.

3 Methods of Safety Update Review

This review will follow the format used in reviewing the original submission: stratification of patients into ET and AT populations with a separate review and analysis of the RCTs in the ET and AT patient populations (3 studies from the ET trials and 5 from the AT trials), and wherever pertinent, mention the findings from the other studies (open-label PD, schizophrenia, and depression).

The majority of the new safety data comes from the uncontrolled ongoing PD trials and newly completed trials in schizophrenia and depression. Since this update does not include any further completed RCTs in ET patients, the comparative information on the ET patients presented in the NDA review has not changed. There is one new completed RCT in the AT patient population and this review will update all pertinent tables in this patient population to reflect the addition of the newly completed RCT.

It is not practical to discuss incidence rates for the overall database, since most of the new information comes from open-label, uncontrolled trials, and most of the patients are not uniquely exposed (they were counted in the original NDA review, and they simply have continued their participation in the uncontrolled trials). For this reason, denominators are left out of most tables to avoid confusion.

3.1 Review of Safety Issues Identified in The Sponsor's Proposed Labeling

The sponsor's most recent updated proposed label, 1/27/97, is a very close approximation of

the division's revised version forwarded to the sponsor with the approvable letter. The sponsor has completed the missing sections requested by the division and has responded to outstanding issues. Besides few language changes (for clarity), the only glaring difference between the division's version and the sponsor's, is the sponsor's deletion of the item pertaining to rhabdomyolysis in the precautions section. The sponsor's rationale is that it brings undue attention to a case that the sponsor considers a "unique circumstance". Of minor consequence, the sponsor has not incorporated the data from the newly completed RCT in AT population in the presentation of the 1% AE table in the adverse events section.

4 Review of Findings

4.1 Description of the Pramipexole Development Program

The original ISS described pramipexole treatment emergent AEs based upon observations from 19 Clinical Pharmacology studies, 16 completed phase II-III clinical trials, and 15 ongoing trials.

Of the 19 clinical pharmacology studies involving 297 (260 PPX and 37 placebo) subjects, 17 were conducted in healthy volunteers, 1 (protocol 60) was conducted in volunteers with impaired renal function, and 1 (n=3) was conducted in APD patients.

Of the 16 completed phase II-III clinical trials (i) 9 (studies---#1, 4, 17, and 21 in ET, and studies---#10, 18, 19, 20, and 22 in AT) were PD studies involving 1253 (702 PPX and 551 placebo) patients; and (ii) 7 were completed studies in schizophrenia involving 322 (177 PPX, 50 comparator, and 95 placebo) patients. There were also 15 ongoing studies: (i) 10 ongoing PD studies (controlled and open label); (ii) 3 schizophrenia studies; and (iii) 2 depression studies.

This Safety Update Report provides additional safety data from (i) one newly completed study in PD (protocol 36); (ii) 2 studies in depression (protocols 37 and 43); (iii) 2 studies in schizophrenia (protocols 7 and 67); and (iv) safety data from the open-label ongoing studies. Data from the unfinished controlled studies are not available due to the blind. A tabulation of an updated patient accountability of the completed studies is detailed in table 4.1.1:

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Table 4.1.1 Patient Accountability (All Completed Studies)				
	Number of Patients			
	Pramipexole	Placebo	Comparator	Total
Phase I (Clinical Pharmacology)	260	37	-	297
Phase II/III				
PD Total	794	633	-	1511
EPD	416	262	-	678
APD	366	371	84	821
Other*	12	-	-	12
Schizophrenia	201	95	50	346
Depression	231	69	-	300
Total	1226	797	134	2157

*Protocol 55, an Italian study was prematurely terminated (Jan. 96), because the investigator was not able to recruit enough patients.

The newly completed study in PD, protocol 36 is a randomized, double-blind, placebo-controlled study in AT involving 247 patients (80 PPX, 83 placebo, and 84 bomocriptine). This multi-center, Non-US study was similarly designed as the other AT RCTs, except for the addition of an active control arm. No major differences in the findings (exposure, demographics, deaths, serious AEs, dropouts, and other AEs) were noted between this protocol and the others, hence no separate tables of data will be presented here for this study alone, but new data tables will be presented that incorporate this study.

4.2 Description of the Population

The updated demographic information of the RCTs is not different from the demographics tables of the original review. There were no statistically significant differences between the pramipexole and placebo groups with respect to age, sex, or race. The demographic characteristics of the ET and AT population were generally representative of the expected demographics of PD patients.

4.3 Extent of Exposure

4.3.1 Extent of Exposure, Overall and Stratified by Duration of Use

The exposure in the original review was based on 1408 pramipexole patients for a total of 274.4 patient years. This safety update adds 738 pramipexole patients from newly completed and ongoing studies in all treatment groups. Table 4.6.1.1 displays the updated exposure in patient years:

Table 4.6.1.1. Number of Patients and Estimated Person-Years (PYs) in Patients with pramipexole Use up to 2 Years				
	Completed Trials		Completed + Ongoing Trials	
	N	PYs	N*	PYs
Phase I				
Healthy Volunteers+	250	--	276	--
PD Patients (0023)	3	--	3	--
Phase 2/3 (PD, Schizophrenia and Depression)				
All Patients@	1213	351.46	2146**	1924.67**
0-24 Months	1213	351.46	1924	1358.92
>6-24 Months	353	223.71	939	1196.63
>12-24 Months	2	2.84	671	986.54
All PD Patients#	782	305.72	1715	1878.94
0-24 Months	782	305.72	1493	1313.19
>6-24 Months	350	219.93	936	1192.85
>12-24 Months	0	--	669	983.70
ET Patients&	388	134.59	777	867.56
0-24 Months	388	134.59	702	699.28
>6-24 Months	137	84.66	493	662.31
>12-24 Months	0	--	401	588.26
AT Patients&&	340	161.73	884	1001.98
0-24 Months	340	161.73	737	604.50
>6-24 Months	213	135.27	443	530.54
>12-24 Months	0	--	268	395.45
Schizophrenia Patients!	200	17.77	200	17.77
0-24 Months	200	17.77	200	17.77
>6-24 Months	0	--	--	--
>12-24 Months	0	--	--	--
Depression Patients!!	231	27.96	231	27.96
0-24 Months	231	27.96	231	27.96
>6-24 Months	3	3.78	3	3.78
>12-24 Months	2	2.84	2	2.84

* Patients were counted only once

** Includes 147 AT PPX patients with continued use beyond 24 months (total of 105.48 additional PY) and 75 ET PPX patients with continued use beyond 24 months (total of 38.28 additional PY).

+ All completed Studies are 3, 25, 26, 27, 28, 29, 30, 31, 47, 51, 61, 62, 63, 64, 65, 69, and 73; one ongoing study (0060)

@ All completed studies are: 1,4,7, 10, 15, 17, 18, 19, 20, 21, 22, 24, 33, 34, 36, 37, 43, 48, 49, and 67; all open-label ongoing studies are: 2, 6, 11, 13, 14, 16, and 52.
All AT + All ET studies
& All completed ET studies are 1, 4, 17, and 21; all open-label ongoing ET studies are 2, 6, and 16.
&& All completed AT studies are 10, 18, 19, 20, 22, and 36; all open-label ongoing AT studies are 11, 13, 14, and 52.
! All completed schizophrenia studies are 7, 15, 24, 33, 34, 48, 49, and 67.
!! All completed depression studies are 37 and 43.

Overall (including the extension trials that are ongoing), a total of 2146 patients with 1924.67 PYs of pramipexole use are included in the exposure data, most of it (1878.94 PYs) coming from the PD trials.

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4.4 Mortality in Phase 2/3 Studies

4.4.1 Pramipexole Mortality Compared to Placebo

Fifteen additional pramipexole patients and one placebo patient died during study participation between the NDA (cut-off January 31, 1995) and this safety update report (cut-off February 2, 1997). Therefore, the total number of pramipexole patients who died is 29 (14 deaths observed in the original review), and all 29 came from PD patients. Table 4.8.1.1 shows the estimated mortality rates for pramipexole and placebo separately in ET and AT patients, and in Schizophrenia and depression patients:

Table 4.8.1.1. Rate of Mortality Observed					
	Deaths	N	PYs	Rate / 100 PYs	RR** 95% CIs
PD Completed RCTs					
ET Patients (studies 1, 4, 21)					
Pramipexole	1	388	134.60	0.74	0.79 (0.05, 12.5)
Placebo	1	235	106.5	0.90	
AT Patients (studies 10, 19, 20, 22, 36)					
Pramipexole	4	340	161.7	2.5	1.9 (0.36, 10.3)
Placebo	2	347	154.9	1.3	
Schizophrenia (studies 7, 15, 24, 33, 34, 48, 49, 67)					
Pramipexole	0	200	17.8	0	
Placebo	0	95	9.2	0	
Depression (studies 37, 44)					
Pramipexole	0	231	28.0	0.0	
Placebo	0	69	9.5	0.0	
Completed and Open-Label Ongoing Trials					
ET Patients (studies 1, 4, 21, 2, 6, 16)					
Pramipexole	8	777	867.6	0.9	not applicable#
Placebo	1	235	106.5	0.9	
AT Patients (studies 10, 19, 20, 22, 36, 11, 13, 14, 52)					
Pramipexole	18	884	1002.0	1.8	not applicable#
Placebo	2	347	154.9	1.3	

** Rate Ratio (Relative Risk) of Pramipexole is defined as: (Death/100 PYs of PPX) / (Death/100 PYs of Placebo)
 # Because all patients in the ongoing part received pramipexole.

Four patients in study 0012 died but are not included in this table because the randomization codes, # of patients, and drug exposure data were not available. Among these patients, three (#23, 599 and 424) received PPX, one (#118) received placebo.

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The increase in absolute numbers of deaths (29 from 14) is simply a reflection of greatly increased exposure. The pramipexole mortality rate per 100 PYs was 3.5 fold greater in AT compared to ET pramipexole exposed patients, but equivalent in the placebo patients.

There were no deaths reported in the schizophrenia and depression (completed or ongoing) studies. There were no deaths reported in the 19 Phase 1 studies.

4.4.2 Description of Deaths Observed During Pramipexole's Use

The table below presents a summary of deaths reported in the safety update:

Table 4.4.2.1 Patients deaths which occurred between 1/31/95 and 2/29/96			
Study	Patient	Days on study	Cause of death
Pramipexole			
2	2128	406	Myocardial Infarction
	2333	359	Cardiac arrest
	2334	425	Suicide (secobarbital O.D.)
11	1181	396	Pulmonary Carcinoma
	1227	237	Sudden Death
	1296	152	Cardiac failure
	1170	481	Myocardial Infarction
12	599	196	Sudden Death
13	500	62	? (lost to follow-up)
	89	87	Arrythmia/cardiogenic shock
	478	105	pneumonia
16	16128	185	accidental injury (gunshot)
36	229	238	Multi-system failure
52	423	241	Prostate carcinoma
	642	254	Myocardial Infarction
Placebo			
36	430	263	Cerebral Infarct/UTI

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A complete review of the death cases did not reveal any apparent association to the use of PPX.

4.5 All-Cause and AE Dropout Risks

A tabulation of the number of patients that dropped out due to serious AEs reported in the safety update is detailed in table 4.5.2:

	Number of Patients	
	Pramipexole	
PD Total	32	
EPD	13	
APD	19	
Schizophrenia	1	
Depression	2	
Total	35	

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4.5.1 ET Studies

As mentioned earlier, no new ET RCTs were completed and hence there are no changes to the original review.

4.5.2 AT Studies

Table 4.5.2.1 shows the reasons for study dropout in AT patients (completed double-blind, placebo-controlled PD trials including the newly completed study #36) by treatment groups.

Reason For Discontinuation	Number (%) of Patients					
	Pramipexole (N=340)		Placebo (N=347)		Bromocriptine (N=84)	
	N	%	N	%	N	%
Adverse Events	46	13.5	77	22.2	17	20.2
Lack of efficacy	3	0.9	5	1.4	1	1.2
Protocol Violation	2	0.6	1	0.3	0	0.0
Lost to Follow-up	0	0	2	0.6	0	0.0
Other	13	3.8	9	2.6	1	1.2
Total Patients	64	18.8	94	27.1	19	22.6

This reveals no overall changes from the original review.

4.6 Clinical Characteristics of AEs that were Associated with Dropout

4.6.1 Most Common AEs associated with Dropout in ET Patients

No new ET RCTs were completed and hence there are no changes to the original review.

4.6.2 Most Common AEs associated with Dropout in AT Patients

Table 4.6.2.1 is an updated list of AEs, irrespective of severity, that were associated with dropout in more than 1% of AT patients:

Table 4.6.2.1
AT Patients
Adverse Events with PPX Which Caused Study Termination
Occurring with Frequency \geq 1%

Adverse Event	Number (%) of Patients		
	Pramipexole N(%)	Placebo N(%)	Bromocriptine N(%)
Total Patients (N)	340	347	84
CONFUS	8 (2.35)	7 (2.02)	1 (1.2)
DIZZINESS	4 (1.2)	5 (1.4)	0
DYSKINESIA	6 (1.8)	4 (1.2)	0
EXTRAPYR SYND	7 (2.1)	34 (9.8)	7 (8.3)
HALLUCIN	8 (2.4)	3 (0.86)	0
HYPOTENS POST	7 (2.1)	4 (1.2)	0

Studies included M/2730/0010, M/2730/0019, M/2730/0020, M/2730/0022, and M/2730/0036

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Only hallucinations were associated with dropout in more than 1% of pramipexole patients and occurred 2 times more frequently than with placebo.

4.7 Serious AEs Associated with Pramipexole

A tabulation of the number of serious AEs reported in the safety update is detailed in table 4.7.1:

Table 4.7.1 Frequency of serious AEs	
	Number of Serious AEs
	Pramipexole
PD Total	288
EPD	121
APD	167
Schizophrenia	2
Depression	5
Total	583

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A tabulation of the number of patients with serious AEs reported in the safety update is detailed in table 4.7.2:

Table 4.7.2 Number of patients with serious AEs	
	Number of Patients with Serious AEs
	Pramipexole
PD Total	171
EPD	72
APD	99
Schizophrenia	2
Depression	3
Total	176

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As most serious AEs reported come from open-label trials, there is no basis of comparison. A complete review of all serious AEs leading to death or discontinuation did not reveal any apparent association to the use of PPX. There were no serious AEs consistent with liver failure or necrosis, agranulocytosis, aplastic anemia, hemolytic anemia, seizures, or new cases of rhabdomyolysis. There were 2 cases of syncope in the depression trials and 1 case from the PD trials.

4.8 AE Risks Associated with Pramipexole Use Irrespective of Severity

4.8.1 Overall

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4.8.1.1 ET Patients

No new ET RCTs were completed, and hence there are no changes to the original review.

4.8.1.2 AT Patients

Table 4.8.1.2.1 lists the AEs that were reported at $\geq 1\%$ in the PPX arm and twice the rate of placebo in the safety update:

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Table 4.8.1.2.1
AT Patients
Adverse Events Occurring Twice as Frequently as Placebo

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	340	348
Peripheral Edema	7 (2.1)	2 (0.6)
Weight Decrease	4 (1.2)	2 (0.6)
Arthritis	10(2.9)	3(0.9)
Twitching	6 (1.8)	1(0.3)
Bursitis	5 (1.5)	2 (0.6)
Hallucination	55 (16.2)	21(6.0)

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Paranoid Reaction	6 (1.8)	1 (0.3)
Hypesthesia	8(2.4)	5(1.4)
Delusions	4 (1.2)	2 (0.6)
Rhinitis	9 (2.7)	3 (0.9)
Pruritis	4 (1.2)	2(0.6)
Accomodation Abnormality	12 (3.5)	6(1.7)
Vision Abnormality	10 (2.9)	3 (0.9)

Studies included M/2730/0010, M/2730/0019, M/2730/0020, M/2730/0022, and M/2730/0036

Only hallucinations (16.2%) were reported in at least 5% of pramipexole patients and were twice as frequent as with placebo.

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4.9 Changes in Laboratory Parameters Associated with Pramipexole Use

There are no new significant clinical findings or safety concerns in the 8 month safety update.

4.10 Changes in Vital Signs Associated with Pramipexole Use

There are no new significant clinical findings or safety concerns in the 8 month safety update.

4.11 Changes in ECG Parameters Associated with Pramipexole Use

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5 Summary of the Safety Experience in the Pramipexole Development Program

5.1 General Comments

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Overall, there are no new significant clinical findings or safety concerns in the 8 month safety update.

5.2 Cardiovascular System

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Aside from the 3 new cases of syncope (2 from the depression trials and 1 from the PD trials), there are no new significant clinical findings or safety concerns in the 8 month safety update.

5.3 Central Nervous System

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.4 Dermatological

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.5 Gastrointestinal

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.6 Genitourinary/Renal

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.7 Hematologic

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.8 Metabolic Endocrine

There are no new significant clinical findings or safety concerns in the 8 month safety update.
No new cases of rhabdomyolysis are reported.

5.9 Musculoskeletal

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.10 Respiratory

There are no new significant clinical findings or safety concerns in the 8 month safety update.

5.11 Special Senses

There are no new significant clinical findings or safety concerns in the 8 month safety update.

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6 Conclusion

Review of the data in the safety update indicates that pramipexole is relatively safe. There were no occurrences of adverse events that were not reported previously and no general increase in incidence rates from previously reported rates.

In conclusion, when the dose of pramipexole is slowly titrated and individualized to obtain optimum response, pramipexole is a safe treatment for patients with Parkinson's disease.

7 Labeling Recommendations

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Adverse Events section:

(1) The 1% table should be redone to reflect newly available data from the RCT of the AT patient population.

Precautions section:

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(1) The sponsor should note the occurrence of rhabdomyolysis even if the circumstances were unique.

/S/

John D. Balian, M.D.

Date

2/27/97

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Clinical Reviewers, Safety Group
Div. of Neuropharmacologic Drug Products

Orig. NDA 20-667
HFD-120 Div. File

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Safety Team Leader's Review of Clinical Data

NDA: NDA 20-667
Response to Approvable Letter

Date of Submission: January 07, 1997

Sponsor: Pharmacia & Upjohn

Drug: Pramipexole 0.125 mg, 0.25 mg, 0.5 mg,
1.0 mg, 1.25 mg and 1.5 mg
Tablets

Route of Administration: Oral Titration

Proposed Indication: Symptomatic Treatment of Parkinson's Disease

Material Reviewed: January 07 Submission that Responding to the
FDA approvable letter; January 10 Amendment
41; January 13 Amendment 42, and Medical
Officer's Review of the Safety Update in
amendments 41 and 42.

Date of Review: 5/13/97

Summary

Pramipexole's sponsor responded to the approvable letter with a safety update, draft labeling and narrative responses to several queries raised by the agency in the letter and proposed labeling. There were no new safety issues raised by the safety update, and its findings were consistent with those in the NDA safety review. New analyzes conducted to evaluate the effects of dose and duration of use on AE events rates were not helpful because of limited number of events in most dose categories, and confounding of dose with duration of use.

The sponsor changed the pregnancy category from "C" to "B" arguing that the findings from animal reproductive studies were sufficient to conclude that pramipexole had no teratogenic risk in rats or rabbits. The sponsor further argued that its effects on implantation and embryo survival were similar to those with bromocriptine which is labeled pregnancy category "B". The review team, however, considers the reproductive study in rats to have failed because the embryotoxicity markedly limited the number of litters in the high dose group. Thus, until the study is repeated a pregnancy category of "C" is justified as per 201.57.

The sponsor also proposed different language in labeling to describe the retinal toxicity that was observed in albino rats. In my opinion, the effect of that language is to accentuate the uncertainty of the finding's relevance to human users of pramipexole. The FDA proposed language tells the reader not to discount the finding because the potential mechanism of the effect generalizes to humans. Such caution seems justified since there is little data addressing the long-term effects of pramipexole use in humans.

Finally, the precaution that the FDA recommended to describe the one case of rhabdomyolysis was removed from labeling by the sponsor. Since pramipexole's use was associated with slight increase in the mean CPK, the precaution seems justified.

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Background

The FDA issued an approvable letter for pramipexole on December 23, 1996. In that letter, the agency requested a safety update and suggested the conduct of in vitro studies to evaluate potential drug interactions with pramipexole. Also included with the letter was proposed labeling that made several requests of the sponsor, most notably a request to conduct dose-response and time since first exposure analyses of the safety data for events that were numerically more frequent than with pramipexole and occurring in more than 1% of patients. On January 7, the sponsor responded by providing a safety update, new labeling, additional analyses and a discussion of the issues raised in the approvable letter.

Dr. Balian, who was the safety reviewer for the NDA, reviewed the safety update and concluded that the findings were consistent with those in the NDA and that there were no new issues to address. After reviewing the safety update, I concur with Dr. Balian.

Dr. Steele, who was the pharmacology reviewer for the NDA, has reviewed the sponsor's proposed changes to the clinical pharmacology, animal toxicology and pregnancy sections of labeling. His comments and recommendations are considered further below. Dr. Ibrahim reviewed the in vitro studies submitted to address the FDA request for in vitro data to address potential for drug interactions. It is her opinion that these data are sufficient to conclude that pramipexole is unlikely to affect important cytochrome P450 isoenzymes.

Based upon changes to the labeling that were proposed by the sponsor, there are still three issues to consider where there may be some disagreement between the FDA and the sponsor. First, the sponsor has proposed a pregnancy category of "B" while the FDA had concluded that a pregnancy category of "C" is justified based upon the available data. Second, there is some disagreement over the nature of the language to be used to describe the uncertain relevance to humans of the retinal toxicity that was observed in albino rats. Finally, the sponsor removed the precaution that described the one patient with rhabdomyolysis that had been added by the FDA. These issues are discussed further below along with the validity of the dose response and time since first exposure analyses conducted by the sponsor at the FDA's request.

Pregnancy Category

In rabbits, there were no adverse reproductive effects observed at 10 mg/kg/day which the sponsor states is 71 times the AUC in humans. In the animal reproductive studies in rats, three effects were associated with pramipexole exposure: (1) When pramipexole was administered throughout pregnancy at 2.5 mg/kg/day, implantation was impaired. (2) In the organogenesis rat study, significant embryonic loss occurred in the high dose group (1.5 mg/kg). (3) Postnatal growth and development was impaired at doses as low as 0.5 mg/kg/day.

While the effects on implantation, and postnatal growth and development were considered by Dr. Steele to be possibly related to pramipexole's effect on prolactin, which if true may limit the relevance of these findings to humans, the embryotoxicity prevented a complete evaluation of teratogenicity by markedly reducing the number of litters available for observation in the high dose group. While the sponsor states that the AUC resulting from the exposures in the two lower dose groups covered the expected human exposure, Dr. Steele considers the high dose group to have been paramount to evaluating the teratogenic potential of pramipexole because several rare birth defects were observed in the two lower dose groups. Since the findings in the highest dose group were critical in interpreting the study, Dr. Steele considers this organogenesis study to have failed and, in fact, recommended repeating it.

The sponsor argues that the effects observed with pramipexole were the same as those with bromocriptine which is labeled "B". However, the bromocriptine labeling suggests that the number of litters available for review were sufficient in the high dose bromocriptine group. The labeling also describes the birth outcomes from prospective follow-up of maternal exposures which may or may not have contributed to the decision to label it "B".

Thus, it seems that without even considering the relevancy of the findings that may be attributable to prolactin, a consideration that may be complex because of potential difficulties in directly attributing any effects to decreases in prolactin, pramipexole should be labeled "C" at least until the sponsor conducts the appropriate studies.

Retinal Toxicity in Albino Rats

While there is some disagreement about whether the effects (loss of photoreceptor cells, degeneration of retinal pigment epithelium) should be referred to as "retinal degeneration" or "retinotoxicity", the sponsor prefers language that does not mention any link to humans. The FDA, however, used the following wording "The potential significance of this effect in humans has not been established, but cannot be disregarded since retinal disk shedding is a universal vertebrate mechanism." Since no human data has been collected on retinal changes with long-term treatment, the FDA wording seems more prudent since the potential mechanism of the effect may generalize to humans.

Rhabdomyolysis

In the sponsor's discussion about the one case of rhabdomyolysis observed with pramipexole, more history was provided, in that the event occurred after rigorous exercise. Rigorous exercise is generally accepted as being a risk factor for rhabdomyolysis. While I would tend to agree with the sponsor in that one case of any rare event is usually not a justification for a precaution, there is more to the signal in this case.

In Dr. Balian's original review of the NDA, there was a mean increase of about u/L in CPK across several studies, with the difference from placebo having reached statistical significance in two studies. While the evidence of a slight increase in the mean seemed compelling, there was no increase in the percentage of patients who had increases that were of clinical concern. Thus, the slight increase in the mean CPK was, by itself, not considered to be clinically significant. Nevertheless, since there was one accepted case of rhabdomyolysis, a precaution seemed appropriate. In fact, if there had been increases of CPK that were clinically significant, a warning statement could be justified. Thus, a precaution seems consistent with the safety findings.

Effect of Dose and Time Since First Exposure on AE Rates

Based upon the FDA comments contained in the proposed labeling included with the approvable letter, the sponsor has conducted more specific analyses to evaluate dose response. These analyzes were used to clarify the role of dose and time on the risk associated with pramipexole use. However, the analyzes of dose, while confounded with time since the studies allowed titration to clinical endpoints, contained are too few events in dose groups to reach a conclusion about the effect of increasing dose. Thus, I would recommend not mentioning these issues in labeling.

Conclusion and Recommendation

Review of the pramipexole safety update and the sponsor's response to the approvable letter did not identify any new safety issues for consideration. The embryotoxicity observed in the rat reproductive studies justifies a pregnancy category "C". Because the potential mechanism for the retinal toxicity observed in albino rats generalizes to humans, language should clearly articulate this potential risk. A precaution describing the one case of rhabdomyolysis is justified given the slight increase in mean CPK observed in the clinical studies.

/S/

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ON ORIGINAL

Greg Burkhardt, M.D., M.S.
Safety Team Leader, Neuropharmacological Drug Products, HFD-120

cc:HFD-120\Burkhardt\Katz\Leber

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MEMORANDUM

DATE: June 16, 1997

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: Director
Office of Drug Evaluation I/HFD-101

SUBJECT: Review of Sponsor's Response to Approvable Letter for
Pramipexole, NDA 20-667

On December 23, 1996, the Agency sent an Approvable letter to Pharmacia & Upjohn, Inc. for NDA 20-667, Pramipexole in patients with Parkinson's Disease. The letter asked only for the sponsor to accept specific dissolution specifications and methodology as well as submit a safety update. In addition, of course, there were multiple questions embedded in the draft labeling that accompanied the letter.

The sponsor responded to the letter in a submission dated 1/7/97. In that response, the sponsor 1) made a number of changes to the proposed draft labeling, 2) responded to the questions and requests embedded in the draft, 3) submitted a safety update, and 4) agreed to the dissolution specifications and methodology described in the letter.

The sponsor's response has been reviewed by Drs. Balian and Burkhart of this Division, in reviews dated 2/27/97 and 5/13/97, respectively, and by Dr. Baweja of OCPB, in a review dated 4/30/97. No new safety issues emerged. Of note, however, Dr. Burkhart concluded that a reliable analysis of dose response of ADRs could not be performed because 1) dose and time were confounded (due to the fact that the studies used a titration design), and 2) there were too few events of interest in any dose group. This conclusion is important because we asked the sponsor to include in labeling a description of those ADRs, if any, that were dose related. Based on Dr. Burkhart's review, no such statements will be included (see below).

The division reviewed the sponsor's draft labeling, and had a number of areas of disagreement with the firm. The division constructed revised draft labeling, and "faxed" this revised version to the sponsor on 5/28/97. The company informed us of their continued disagreement with some of our proposed language and, as a result, these residual issues were discussed

in a telephone call on 6/10/97.

At this meeting, the Agency and sponsor came to agreement on essentially all issues (minor wording in a few areas was left to the firm to draft). A revised draft of labeling was sent to the Division on 6/12/97. This draft is acceptable with a few minor changes. This most recent draft (again, which we find acceptable) differs from the draft label accompanying the Approvable letter in several important ways:

1) **CLINICAL PHARMACOLOGY:** The sponsor has proposed a sentence at the end of the 1st paragraph that describes relative binding affinities at D₃, D₂, and D₄ receptor sub-types, but that describes (at the Division's urging) the relevance of this binding for Parkinson's Disease as being unknown.

Also, they have removed the last sentence of this section, which discussed the effects of pramipexole on neuronal dopamine metabolism in animals.

2) **CLINICAL STUDIES:** The sponsor corrected the number of placebo controlled double blind trials described to 7, not 8, as had been originally (and incorrectly) stated.

3) **WARNINGS:** We asked the sponsor to re-calculate the comparative incidence of objective orthostatic events (we were concerned with misclassification of events that they included as being manifestations of orthostasis). No additional language was added to that proposed in the draft that accompanied the Approvable letter.

4) **PRECAUTIONS:** The language in the sub-section called **Retinotoxicity in Albino Rats** has been changed to be somewhat more detailed and to include a statement about the potential relevance to humans. The sub-section itself has been re-named; it is now called **Retinal pathology in albino rats**.

5) **ADVERSE EVENTS:** In the draft labeling accompanying the Approvable letter, we asked the sponsor to draft statements about the dose relatedness of ADRs for both early and late PD patients. Upon review of this data, we realized that it was impossible to determine which ADRs might be dose related, because the studies all used a titration design, and dose and time were confounded. Hence, we removed any statements designed to list those ADRs which were dose related, and instead included a statement about this confounding after the first paragraph in this section (before the sub-section "**Early**" Parkinson's Disease).

6) **DOSAGE AND ADMINISTRATION:** In this section, we included a table of dosing adjustments necessary for patients with renal impairment. In this table, for the last category of patients (those with severe impairment), we had written WARNING in the space for the proposed dosing. Upon further reflection, we decided that this was cryptic, at best. The revised version now reads "The use of MIRAPEX has not been adequately studied in this group of patients".

In addition to these changes, the sponsor has adequately responded to all the questions we asked in the body of the draft labeling.

RECOMMENDATIONS

The application should be approved and the attached Approval letter should be sent to the sponsor.

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/S/

Russell Katz, M.D.

Cc:

NDA 20-667

HFD-120

HFD-120/Leber/Katz/Burkhart/Feeney/Fitzgerald/Steele/Wheelous

HFD-860/Baweja

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CLINICAL REVIEW AND EVALUATION OF EFFICACY

NDA 20-667

Mirapex (pramipexole)

**APPEARS THIS WAY
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Reviewer: John Feeney, M.D.
James Sherry, M.D., Ph.D. (Studies 19 & 22)
Date: September 13, 1996
Sponsor: Pharmacia & Upjohn
Indication: Parkinson's Disease
NDA Submission Date: December 28, 1995

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Introduction:

Overview of Studies Pertinent to Efficacy

There have been 9 completed controlled trials addressing the efficacy of pramipexole in Parkinson's Disease.

Four of the 9 were conducted in patients with early PD and did not allow concomitant L-dopa therapy: Studies 1,4,17, and 21.

Five of the 9 were conducted in patients with advanced PD, including patients on concomitant L-dopa therapy: Studies 10,18,19,20, and 22.

Early disease was defined as Hoehn and Yahr stages 1-3. Patients in these studies could not be on concomitant L-dopa, but could take some other drugs use to treat symptoms, including amantadine, deprenyl, and anticholinergics. Advanced PD was defined as Hoehn and Yahr stages 2-4, requiring concomitant L-dopa and experiencing some of the adverse events associated with longterm use of L-dopa, including "on-off" periods and dyskinesias.

Studies 1,4, and 10 are the most recent studies (completed around January 1995) and the largest. The sponsor considers these 3 studies the "pivotal" studies. However, **Studies 19 and 22** (both in advanced PD) are not small. Study 19 randomized 78 patients to 2 groups and Study 22 randomized 69 patients to 2 groups. These 2 studies are reviewed by Dr. James Sherry, incorporated into this document.

Study 20 is a very small, double-blind, placebo-controlled trial in advanced PD. It showed no difference between groups, but it really is too small to lead to any generalizations. It stopped enrollment prematurely.

Study 21 is a very small, double-blind, placebo-controlled trial in early PD. It showed a difference in favor of pramipexole. It stopped enrollment prematurely.

Studies 17 and 18 were both single-blind studies, but seem capable by design of demonstrating a difference in favor of the active agent, pramipexole. However, Study 18 in advanced PD showed no difference

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MODIFIED HOEHN AND YAHR SCALE		RATER'S INITIALS (S): _____	
Indicate the patient's Parkinson stage for both 'on' and 'off' periods by checking one box for 'on' and one box for 'off' below.			
STAGE	ON	OFF	
0	<input type="checkbox"/>	<input type="checkbox"/>	No signs of disease
1	<input type="checkbox"/>	<input type="checkbox"/>	Unilateral disease
1.5	<input type="checkbox"/>	<input type="checkbox"/>	Unilateral plus axial involvement
2	<input type="checkbox"/>	<input type="checkbox"/>	Bilateral disease, without impairment of balance
2.5	<input type="checkbox"/>	<input type="checkbox"/>	Mild bilateral disease, with recovery on pull test
3	<input type="checkbox"/>	<input type="checkbox"/>	Mild to moderate bilateral disease; some postural instability; physically independent
4	<input type="checkbox"/>	<input type="checkbox"/>	Severe disability; still able to walk or stand unassisted
5	<input type="checkbox"/>	<input type="checkbox"/>	Wheelchair bound or bedridden unless aided

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Pramipexole			
Study No.	Study Description	Number of Centers	Number of Patients Studied (Pramipexole / Placebo)
Completed Studies in Parkinson's Disease			
Adequate and Well-Controlled Studies			
1	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	26	335 (164 / 171)
4	Multicenter, Dose response, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	20	264 (213 / 51)
10	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	25	360 (181 / 179)
Other Double-Blind Controlled Studies			
19	Multicenter, Ascending dose, Prospective, Randomized, Double-blind, Placebo-controlled Study	9	77 (43 / 34)
20	Randomized, Double-blind, Placebo-controlled, Parallel-group Study	1	19 (9 / 10)
21	Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	6	24 (11 / 13)
22	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	9	69 (36 / 33)
Single-Blind Controlled Studies			
17	Multicenter, Ascending dose, Prospective, Randomized, Single-blind, Placebo-controlled, Parallel-group Study	4	55 (28 / 27)
18	Multicenter, Ascending dose, Prospective, Randomized, Single-blind, Placebo-controlled, Parallel-group Study	6	50 (26 / 24)

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Pramipexole			
Study No.	Study Description	Number of Centers	Number of Patients Studied (Pramipexole / Placebo)
Ongoing Studies in Parkinson's Disease			
Controlled Studies			
M/2730/0005	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	33	176 (1/31/95)
M/2730/0012	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	52	236 (1/31/95)
M/2730/0036	Multicenter, Ascending dose, Randomized, Double-blind, Placebo-controlled, Parallel-group Study	36	124 (1/31/95)
M/2730/0055	Randomized, Double-blind, Placebo-controlled, Parallel-group Study	1	6 (1/31/95)
Uncontrolled Studies			
M/2730/0002	Open-label extension of 1	26	281 (1/31/95)
M/2730/0006	Open-label extension of M/2730/0005	33	41 (1/31/95)
M/2730/0011	Open-label, Ascending-dose Study Extension of 10	25	305 (1/31/95)
M/2730/0013	Open-label, Ascending-dose Study Extension of M/2730/0012	52	88 (1/31/95)
M/2730/0014	Open-label, long-term, safety Study Extension of 19, 20, 22	19	89 (1/31/95)
M/2730/0016	Multi-center, Open-labeled, Non-comparative, Safety Study	19	22 (1/31/95)

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between drug and placebo, despite a reasonable enrollment. Study 17 in early PD did demonstrate a difference in favor of pramipexole.

The sponsor maintains that all 4 studies conducted in early PD showed a difference between pramipexole and placebo. Study 4, a dose-comparison trial, showed no benefit of doses greater than 1.5 mg/day.

Of the 5 studies in advanced PD, the sponsor maintains that 3 demonstrate a difference in favor of pramipexole, 1 demonstrates no difference between pramipexole and placebo, and 1 study stopped enrollment so early as to preclude any meaningful interpretation of the results.

Reviews of the individual studies follow.

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Unified Parkinson's Disease Rating Scale (UPDRS)

All the studies in this NDA specified the UPDRS (or components) as primary outcome assessments. Studies 1 and 10 required a dual outcome, a positive effect on Part II and a positive effect on Part III of the UPDRS. Study 4 used the sum of Parts I-III as a primary outcome assessment.

A copy of the scale is attached. Part I rates mentation, mood, and behavior. Part II rates ADLs during the past week. Part III is a motor exam. Part IV rates complications of therapy, including dyskinesias.

Part II has 13 items scored from 0 (best) to 4 (worst) for a worst total score of 52. In advanced Parkinson's Disease where unpredictable shifts from states of good functioning to states of poor functioning occur throughout the day, Part II is scored twice, once for the so-called "on" state and once for the so-called "off" state. The total score on Part II then becomes the average of the "on" score and the "off" score. (This will be discussed in more detail in my review of Study 10.) In early Parkinson's Disease, where the "on-off" phenomenon is not occurring, Part II is scored only once and this averaging technique does not apply.

Part III has 14 items scored from 0-4, but some of the items are scored several times for different body regions (right body vs left body; right arm, left arm, right leg, vs left leg) so that the worst total score is 108. Part III is scored only once in both early and advanced Parkinson's Disease.

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TR No.: 9158-95-023

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 Trial No.: 248.320

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UNIFIED PARKINSON'S DISEASE RATING SCALE Pramipexole 00679A - M2730/0010							
PATIENT INITIALS (3)	DATE OF VISIT (month/day/year)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE	
		2			1001	14	

The same person should conduct a given part of this evaluation throughout the trial. When completing this section, indicate the patient's best level of function during the past week.

PART I. MENTATION, BEHAVIOR AND MOOD

RATER'S INITIALS (3): _____

The worsening of a patient's disease symptom(s) will be recorded on the Adverse Event Report form only if their frequency has increased and/or severity has worsened since baseline or if, in the opinion of the investigator, they do not represent the patient's usual clinical state prior to study entry.

<p>1. Intellectual impairment:</p> <p><input type="checkbox"/> 0 = None</p> <p><input type="checkbox"/> 1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.</p> <p><input type="checkbox"/> 2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.</p> <p><input type="checkbox"/> 3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.</p> <p><input type="checkbox"/> 4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.</p>	<p>2. Thought disorder (DUE TO DEMENTIA OR DRUG INTOXICATION):</p> <p><input type="checkbox"/> 0 = None.</p> <p><input type="checkbox"/> 1 = Vivid dreaming.</p> <p><input type="checkbox"/> 2 = "Benign" hallucinations with insight retained.</p> <p><input type="checkbox"/> 3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.</p> <p><input type="checkbox"/> 4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.</p>
<p>3. Depression:</p> <p><input type="checkbox"/> 0 = Not present.</p> <p><input type="checkbox"/> 1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.</p> <p><input type="checkbox"/> 2 = Sustained depression (1 week or more).</p> <p><input type="checkbox"/> 3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).</p> <p><input type="checkbox"/> 4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.</p>	<p>4. Motivation/Initiative:</p> <p><input type="checkbox"/> 0 = Normal.</p> <p><input type="checkbox"/> 1 = Less assertive than usual; more passive.</p> <p><input type="checkbox"/> 2 = Loss of initiative or disinterest in elective (nonroutine) activities.</p> <p><input type="checkbox"/> 3 = Loss of initiative or disinterest in day-to-day (routine) activities.</p> <p><input type="checkbox"/> 4 = Withdrawn, complete loss of motivation.</p>

PART II. ACTIVITIES OF DAILY LIVING DURING THE PAST WEEK
 (score for both 'on' and 'off' periods)

RATER'S INITIALS (3): _____

<p>5. Speech:</p> <p>ON OFF</p> <p><input type="checkbox"/> <input type="checkbox"/> 0 = Normal.</p> <p><input type="checkbox"/> <input type="checkbox"/> 1 = Mildly affected. No difficulty being understood.</p> <p><input type="checkbox"/> <input type="checkbox"/> 2 = Moderately affected. Sometimes asked to repeat statements.</p> <p><input type="checkbox"/> <input type="checkbox"/> 3 = Severely affected. Frequently asked to repeat statements.</p> <p><input type="checkbox"/> <input type="checkbox"/> 4 = Unintelligible most of the time.</p>	<p>6. Salivation:</p> <p>ON OFF</p> <p><input type="checkbox"/> <input type="checkbox"/> 0 = Normal.</p> <p><input type="checkbox"/> <input type="checkbox"/> 1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.</p> <p><input type="checkbox"/> <input type="checkbox"/> 2 = Moderately excessive saliva; may have minimal drooling.</p> <p><input type="checkbox"/> <input type="checkbox"/> 3 = Marked excess of saliva with some drooling.</p> <p><input type="checkbox"/> <input type="checkbox"/> 4 = Marked drooling, requires constant tissue or handkerchief.</p>
<p>7. Swallowing</p> <p>ON OFF</p> <p><input type="checkbox"/> <input type="checkbox"/> 0 = Normal</p> <p><input type="checkbox"/> <input type="checkbox"/> 1 = Rare choking.</p> <p><input type="checkbox"/> <input type="checkbox"/> 2 = Occasional choking</p> <p><input type="checkbox"/> <input type="checkbox"/> 3 = Requires soft food.</p> <p><input type="checkbox"/> <input type="checkbox"/> 4 = Requires NG tube or gastrostomy feeding.</p>	<p>8. Handwriting:</p> <p>ON OFF</p> <p><input type="checkbox"/> <input type="checkbox"/> 0 = Normal.</p> <p><input type="checkbox"/> <input type="checkbox"/> 1 = Slightly slow and small.</p> <p><input type="checkbox"/> <input type="checkbox"/> 2 = Moderately slow or small; all words are legible.</p> <p><input type="checkbox"/> <input type="checkbox"/> 3 = Severely affected; not all words are legible.</p> <p><input type="checkbox"/> <input type="checkbox"/> 4 = The majority of words are not legible.</p>

(Continued on next page.)

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UPDRS (CONT.)		Pramipexole 00679A - M2730/0010			
PATIENT INITIALS (S)	VISIT	INVEST NO.	SHEET NO.	PATIENT NO.	PAGE
<input type="checkbox"/> <input type="checkbox"/>	2			1001	15
PART II. - (Continued)					
9. Cutting food and handling utensils: ON OFF <input type="checkbox"/> <input type="checkbox"/> 0 = Normal. <input type="checkbox"/> <input type="checkbox"/> 1 = Somewhat slow and clumsy, but no help needed. <input type="checkbox"/> <input type="checkbox"/> 2 = Can cut most foods, although clumsy and slow, some help needed. <input type="checkbox"/> <input type="checkbox"/> 3 = Food must be cut by someone, but can still feed slowly. <input type="checkbox"/> <input type="checkbox"/> 4 = Needs to be fed.			10. Dressing ON OFF <input type="checkbox"/> <input type="checkbox"/> 0 = Normal. <input type="checkbox"/> <input type="checkbox"/> 1 = Somewhat slow, but no help needed. <input type="checkbox"/> <input type="checkbox"/> 2 = Occasional assistance with buttoning, getting arms in sleeves. <input type="checkbox"/> <input type="checkbox"/> 3 = Considerable help required, but can do some things alone. <input type="checkbox"/> <input type="checkbox"/> 4 = Helpless.		
11. Hygiene: ON OFF <input type="checkbox"/> <input type="checkbox"/> 0 = Normal. <input type="checkbox"/> <input type="checkbox"/> 1 = Somewhat slow, but no help needed. <input type="checkbox"/> <input type="checkbox"/> 2 = Needs help to shower or bathe; or very slow in hygienic care. <input type="checkbox"/> <input type="checkbox"/> 3 = Requires assistance for washing; brushing teeth, combing hair; going to bathroom. <input type="checkbox"/> <input type="checkbox"/> 4 = Foley catheter or other mechanical aids.			12. Turning in bed and adjusting bedclothes. ON OFF <input type="checkbox"/> <input type="checkbox"/> 0 = Normal. <input type="checkbox"/> <input type="checkbox"/> 1 = Somewhat slow and clumsy, but no help needed. <input type="checkbox"/> <input type="checkbox"/> 2 = Can turn alone or adjust sheets, but with great difficulty. <input type="checkbox"/> <input type="checkbox"/> 3 = Can initiate, but not turn or adjust sheets alone. <input type="checkbox"/> <input type="checkbox"/> 4 = Helpless.		
13. Falling (Unrelated to freezing): ON OFF <input type="checkbox"/> <input type="checkbox"/> 0 = None. <input type="checkbox"/> <input type="checkbox"/> 1 = Rare falling. <input type="checkbox"/> <input type="checkbox"/> 2 = Occasionally falls, less than once per day. <input type="checkbox"/> <input type="checkbox"/> 3 = Falls an average of once daily. <input type="checkbox"/> <input type="checkbox"/> 4 = Falls more than once daily.			14. Freezing when walking: ON OFF <input type="checkbox"/> <input type="checkbox"/> 0 = None. <input type="checkbox"/> <input type="checkbox"/> 1 = Rare freezing when walking; may have start-hesitation. <input type="checkbox"/> <input type="checkbox"/> 2 = Occasional freezing when walking. <input type="checkbox"/> <input type="checkbox"/> 3 = Frequent freezing. Occasionally falls from freezing. <input type="checkbox"/> <input type="checkbox"/> 4 = Frequent falls from freezing.		
15. Walking: ON OFF <input type="checkbox"/> <input type="checkbox"/> 0 = Normal. <input type="checkbox"/> <input type="checkbox"/> 1 = Mild difficulty. May not swing arms or may tend to drag leg. <input type="checkbox"/> <input type="checkbox"/> 2 = Moderate difficulty, but requires little or no assistance. <input type="checkbox"/> <input type="checkbox"/> 3 = Severe disturbance of walking, requiring assistance. <input type="checkbox"/> <input type="checkbox"/> 4 = Cannot walk at all, even with assistance.			16. Tremor: ON OFF <input type="checkbox"/> <input type="checkbox"/> 0 = Absent. <input type="checkbox"/> <input type="checkbox"/> 1 = Slight and infrequently present. <input type="checkbox"/> <input type="checkbox"/> 2 = Moderate; bothersome to patient. <input type="checkbox"/> <input type="checkbox"/> 3 = Severe; interferes with many activities. <input type="checkbox"/> <input type="checkbox"/> 4 = Marked; interferes with most activities.		
17. Sensory complaints related to parkinsonism: ON OFF <input type="checkbox"/> <input type="checkbox"/> 0 = None. <input type="checkbox"/> <input type="checkbox"/> 1 = Occasionally has numbness, tingling, or mild aching. <input type="checkbox"/> <input type="checkbox"/> 2 = Frequently has numbness, tingling, or aching, not distressing. <input type="checkbox"/> <input type="checkbox"/> 3 = Frequent painful sensations. <input type="checkbox"/> <input type="checkbox"/> 4 = Excruciating pain.					

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Boehringer Ingelheim Pharmaceuticals, Inc.
 Trial No.: 248.320

UPDRS (CONT.)		Pramipexole 00679A - M2730/0010			
PATIENT INITIALS (3)		VISIT 2	INVEST NO	SHEET NO	PATIENT NO 1001
					PAGE 16

PART III - MOTOR EXAMINATION (This exam **MUST** be completed when the patient is in an 'on' period)
 This examination should be completed approximately two to three hours following a dose of decarboxylase inhibitor / levodopa therapy but prior to the initial dose of trial drug.

TIME OF EXAMINATION: _____ (24-hour clocktime)

RATER'S INITIALS (3): _____

<p>18. Speech:</p> <p><input type="checkbox"/> 0 = Normal.</p> <p><input type="checkbox"/> 1 = Slight loss of expression, diction, and/or volume.</p> <p><input type="checkbox"/> 2 = Monotone, slurred but understandable; moderately impaired.</p> <p><input type="checkbox"/> 3 = Marked impairment, difficult to understand.</p> <p><input type="checkbox"/> 4 = Unintelligible.</p>	<p>19. Facial expression:</p> <p><input type="checkbox"/> 0 = Normal.</p> <p><input type="checkbox"/> 1 = Minimal hypomimia, could be normal "Polar Face".</p> <p><input type="checkbox"/> 2 = Slight but definitely abnormal diminution of facial expression.</p> <p><input type="checkbox"/> 3 = Moderate hypomimia: lips parted some of the time.</p> <p><input type="checkbox"/> 4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.</p>																																													
<p>20. Tremor at rest: (F = Face, LH = Left Hand, RH = Right Hand, LF = Left Foot, RF = Right Foot)</p> <table border="0"> <tr> <td>F</td><td>LH</td><td>RH</td><td>LF</td><td>RF</td> <td><input type="checkbox"/> 0 = Absent.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 1 = Slight and infrequently present.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 2 = Mild in amplitude and persistent, or moderate in amplitude, but only intermittently present.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 3 = Moderate in amplitude and present all the time.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 4 = Marked in amplitude and present most of the time.</td> </tr> </table>	F	LH	RH	LF	RF	<input type="checkbox"/> 0 = Absent.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 = Slight and infrequently present.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 2 = Mild in amplitude and persistent, or moderate in amplitude, but only intermittently present.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 3 = Moderate in amplitude and present all the time.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 4 = Marked in amplitude and present most of the time.	<p>21. Action or postural tremor of hands:</p> <table border="0"> <tr> <td>L</td><td>R</td> <td><input type="checkbox"/> 0 = Absent.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 1 = Slight; present with action.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 2 = Moderate in amplitude, present with action.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 3 = Moderate in amplitude, with posture holding as well as action.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 4 = Marked in amplitude, interferes with feeding.</td> </tr> </table>	L	R	<input type="checkbox"/> 0 = Absent.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 = Slight; present with action.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 2 = Moderate in amplitude, present with action.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 3 = Moderate in amplitude, with posture holding as well as action.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 4 = Marked in amplitude, interferes with feeding.
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<p>22. Rigidity (judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)</p> <p><small>LUE = Left upper extremities, RUE = Right Upper extremities LLE = Left lower extremities, RLE = Right lower extremities</small></p> <table border="0"> <tr> <td>Head</td><td>LUE</td><td>RUE</td><td>LLE</td><td>RLE</td> <td><input type="checkbox"/> 0 = Absent</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 1 = Slight or detectable only when activated by minor or other movements.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 2 = Mild to moderate.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 3 = Marked, but full range of motion easily achieved.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 4 = Severe, range of motion achieved with difficulty.</td> </tr> </table>	Head	LUE	RUE	LLE	RLE	<input type="checkbox"/> 0 = Absent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 = Slight or detectable only when activated by minor or other movements.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 2 = Mild to moderate.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 3 = Marked, but full range of motion easily achieved.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 4 = Severe, range of motion achieved with difficulty.	<p>23. Finger taps (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.):</p> <table border="0"> <tr> <td>L</td><td>R</td> <td><input type="checkbox"/> 0 = Normal.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 1 = Mild slowing and/or reduction in amplitude.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 4 = Can barely perform the task.</td> </tr> </table>	L	R	<input type="checkbox"/> 0 = Normal.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 = Mild slowing and/or reduction in amplitude.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 4 = Can barely perform the task.
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<p>24. Hand movements (Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.):</p> <table border="0"> <tr> <td>L</td><td>R</td> <td><input type="checkbox"/> 0 = Normal.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 1 = Mild slowing and/or reduction in amplitude.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 4 = Can barely perform the task.</td> </tr> </table>	L	R	<input type="checkbox"/> 0 = Normal.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 = Mild slowing and/or reduction in amplitude.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 4 = Can barely perform the task.	<p>25. Rapid alternating movements of hands (Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.):</p> <table border="0"> <tr> <td>L</td><td>R</td> <td><input type="checkbox"/> 0 = Normal.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 1 = Mild slowing and/or reduction in amplitude.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.</td> </tr> <tr> <td><input type="checkbox"/></td><td><input type="checkbox"/></td> <td><input type="checkbox"/> 4 = Can barely perform the task.</td> </tr> </table>	L	R	<input type="checkbox"/> 0 = Normal.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 1 = Mild slowing and/or reduction in amplitude.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> 4 = Can barely perform the task.															
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TR No.: 9158-95-023

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Page: CRF 18

UPDRS (CONT.)		Pramipexole 00679A - M2730/0010																														
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PART III. - (continued)																																
26. Leg agility (Patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 inches.): <table border="0" style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> <table border="0"> <tr> <td style="text-align: center;">L</td> <td style="text-align: center;">R</td> <td></td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>0 = Normal.</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>1 = Mild slowing and/or reduction in amplitude.</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>2 = Moderately impaired. Delays and early fatiguing. May have occasional arrests in movement.</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>4 = Can barely perform the task.</td> </tr> </table> </td> <td style="width: 50%; vertical-align: top;"> 27. Arising from chair (Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.): <table border="0"> <tr> <td><input type="checkbox"/></td> <td>0 = Normal.</td> </tr> <tr> <td><input type="checkbox"/></td> <td>1 = Slow; or may need more than one attempt.</td> </tr> <tr> <td><input type="checkbox"/></td> <td>2 = Pushes self up from arms of seat.</td> </tr> <tr> <td><input type="checkbox"/></td> <td>3 = Tends to fall back and may have to try more than one time, but can get up without help.</td> </tr> <tr> <td><input type="checkbox"/></td> <td>4 = Unable to arise without help.</td> </tr> </table> </td> </tr> </table>			<table border="0"> <tr> <td style="text-align: center;">L</td> <td style="text-align: center;">R</td> <td></td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>0 = Normal.</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>1 = Mild slowing and/or reduction in amplitude.</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>2 = Moderately impaired. Delays and early fatiguing. May have occasional arrests in movement.</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>4 = Can barely perform the task.</td> </tr> </table>	L	R		<input type="checkbox"/>	<input type="checkbox"/>	0 = Normal.	<input type="checkbox"/>	<input type="checkbox"/>	1 = Mild slowing and/or reduction in amplitude.	<input type="checkbox"/>	<input type="checkbox"/>	2 = Moderately impaired. Delays and early fatiguing. May have occasional arrests in movement.	<input type="checkbox"/>	<input type="checkbox"/>	3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.	<input type="checkbox"/>	<input type="checkbox"/>	4 = Can barely perform the task.	27. Arising from chair (Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.): <table border="0"> <tr> <td><input type="checkbox"/></td> <td>0 = Normal.</td> </tr> <tr> <td><input type="checkbox"/></td> <td>1 = Slow; or may need more than one attempt.</td> </tr> <tr> <td><input type="checkbox"/></td> <td>2 = Pushes self up from arms of seat.</td> </tr> <tr> <td><input type="checkbox"/></td> <td>3 = Tends to fall back and may have to try more than one time, but can get up without help.</td> </tr> <tr> <td><input type="checkbox"/></td> <td>4 = Unable to arise without help.</td> </tr> </table>	<input type="checkbox"/>	0 = Normal.	<input type="checkbox"/>	1 = Slow; or may need more than one attempt.	<input type="checkbox"/>	2 = Pushes self up from arms of seat.	<input type="checkbox"/>	3 = Tends to fall back and may have to try more than one time, but can get up without help.	<input type="checkbox"/>	4 = Unable to arise without help.
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 28. Posture: | | | |--------------------------|---| | <input type="checkbox"/> | 0 = Normal erect. | | <input type="checkbox"/> | 1 = Not quite erect, slightly stooped posture; could be normal for older person. | | <input type="checkbox"/> | 2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side. | | <input type="checkbox"/> | 3 = Severely stooped posture with kyphosis; can be moderately leaning to one side. | | <input type="checkbox"/> | 4 = Marked flexion with extreme abnormality of posture. | | | | 29. Gait: | | | |--------------------------|---| | <input type="checkbox"/> | 0 = Normal. | | <input type="checkbox"/> | 1 = Walks slowly, may shuffle with short steps; but no festination or propulsion. | | <input type="checkbox"/> | 2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion. | | <input type="checkbox"/> | 3 = Severe disturbance of gait, requiring assistance. | | <input type="checkbox"/> | 4 = Cannot walk at all, even with assistance. | | | || 30. Postural stability (Response to sudden posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.): | | | |--------------------------|---| | <input type="checkbox"/> | 0 = Normal. | | <input type="checkbox"/> | 1 = Retropulsion, but recovers unaided. | | <input type="checkbox"/> | 2 = Absence of postural response; would fall if not caught by examiner. | | <input type="checkbox"/> | 3 = Very unstable, tends to lose balance spontaneously. | | <input type="checkbox"/> | 4 = Unable to stand without assistance. | | | | 31. Body bradykinesia and hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude and poverty of movement in general.): | | | |--------------------------|---| | <input type="checkbox"/> | 0 = None. | | <input type="checkbox"/> | 1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude. | | <input type="checkbox"/> | 2 = Mid degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude. | | <input type="checkbox"/> | 3 = Moderate slowness, poverty or small amplitude of movement. | | <input type="checkbox"/> | 4 = Marked slowness, poverty or small amplitude of movement. | | | |

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CANARY COPY: INVESTIGATOR

UPDRS (CONT.)		Pramipexole 00679A - M2730/0010			
PATIENT INITIALS (3)		VISIT 2	INVEST NO	SHEET NO	PATIENT NO PAGE 1001 18

PART IV. - COMPLICATIONS OF THERAPY* (during the past week).

A. DYSKINESIAS*

RATER'S INITIALS (3): _____

32. Duration: What proportion of the waking day are dyskinesias present? (historical information):

0 = None.
 1 = 1-25% of day.
 2 = 25-50% of day.
 3 = 51-75% of day.
 4 = 75-100% of day.

34. Painful dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.
 1 = Slight.
 2 = Moderate.
 3 = Severe.
 4 = Marked.

33. Disability: How disabling are dyskinesias? (historical information; may be modified by office examination):

0 = Not disabling.
 1 = Mildly disabling.
 2 = Moderately disabling.
 3 = Severely disabling.
 4 = Completely disabled.

35. Presence of early morning dystonia: (historical information):

0 = No.
 1 = Yes.

B. CLINICAL FLUCTUATIONS

36. Are any 'off' periods predictable as to timing after a dose of medication?

0 = No.
 1 = Yes.

38. Do any of the 'off' periods come on suddenly, e.g., over a few seconds?

0 = No.
 1 = Yes.

37. Are any 'off' periods unpredictable as to timing after a dose of medication?

0 = No.
 1 = Yes.

39. What proportion of the waking day is the patient 'off' on average?

0 = None.
 1 = 1-25% of day.
 2 = 25-50% of day.
 3 = 51-75% of day.
 4 = 75-100% of day.

C. OTHER COMPLICATIONS*

40. Does the patient have anorexia, nausea, or vomiting?

0 = No.
 1 = Yes. If yes, check appropriate box(es) below:
 1 Anorexia 2 Nausea 3 Vomiting

42. Does the patient have symptomatic orthostasis?

0 = No.
 1 = Yes. List symptoms: _____

41. Does the patient have any sleep disturbances, e.g., insomnia?

0 = No.
 1 = Yes. Describe: _____

* The worsening of a patient's disease symptom(s) will be recorded on the Adverse Event Report form only if their frequency has increased and/or severity has worsened since baseline or if, in the opinion of the investigator, they do not represent the patient's usual clinical state prior to study entry.