

Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: December 6, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 20-667, Mirapex, [pramipexole]

TO: File NDA 20-667
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my endorsement of the review team's unanimous recommendation that Pharmacia-Upjohn's NDA 20-667 for **Mirapex™** be declared **approvable**.

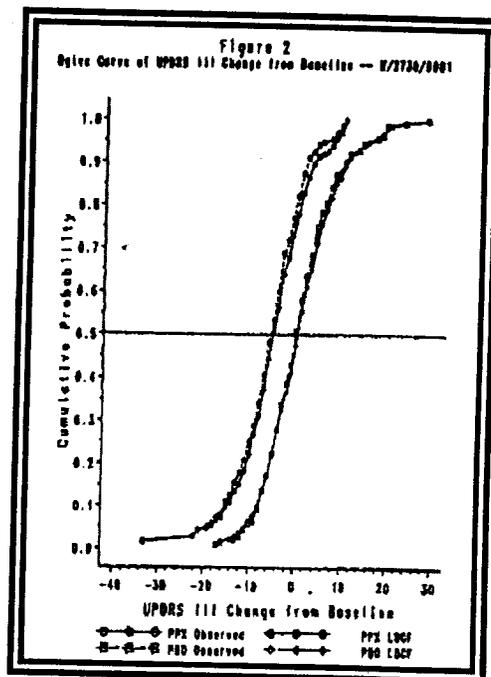
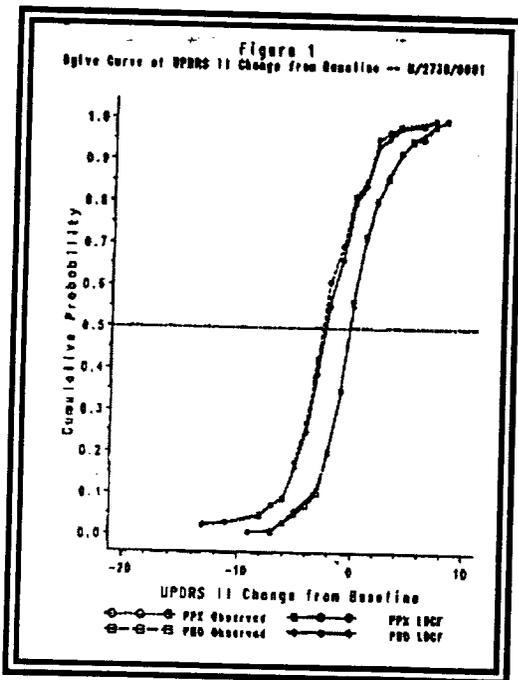
The sponsor's NDA provides results of 8 completed, adequate and well controlled, clinical investigations that speak to pramipexole's capacity to ameliorate the signs and symptoms of Parkinson's Disease. A review of the reports of these studies has led the team to conclude that the sponsor has provided substantial evidence of Mirapex's effectiveness as a treatment of the "signs and symptoms of idiopathic Parkinson's Disease." Specifically, reports to the NDA document the beneficial effects of Mirapex™ in patients with both early Parkinson's Disease (basically, in patients not receiving concomitant treatment with l-dopa and a decarboxylase inhibitor¹) and in those with advanced disease (i.e., those who had once, but were no longer responding satisfactorily, to treatment with maximally tolerable doses of l-dopa/carbidopa²).

¹ Among the 4 clinical trials (#'s 1,4,17 and 21), Studies 1 and 4 are deemed most persuasive and are the primary basis of our affirmative conclusions in this subpopulation.

² Among the 4 completed trials that apply to this subset of the population, Study 10 provides the most compelling results. Studies 19 and 22 are also sources of statistically significant findings supporting the sponsor's claims.

I will not review the effectiveness data here because, as the reviews conducted by Dr. Feeney (9/13/96) and Dr. Hoberman (10/24/96) comprehensively document, the results of the completed trials, including even those that we have not enumerated as sources of substantial evidence, provide robust support for the effectiveness of Mirapex™. The graphics that follow provide a visual insight into the consistency of the evidence of efficacy.

Study 1, Item 2 and 3 on UPDRS



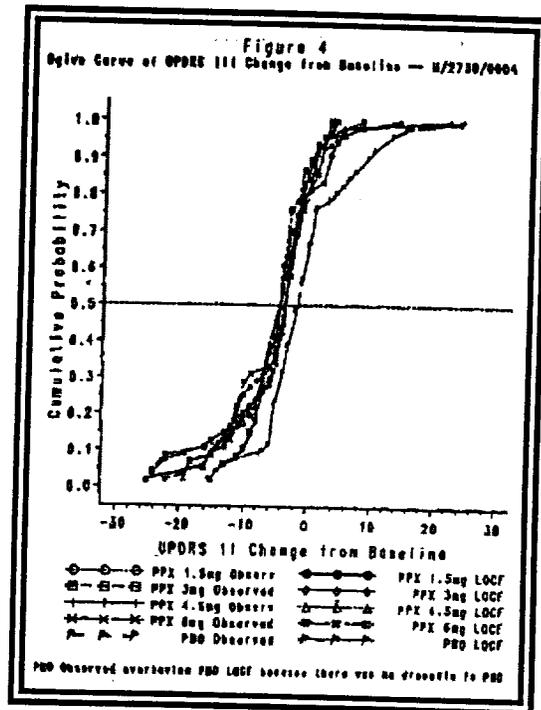
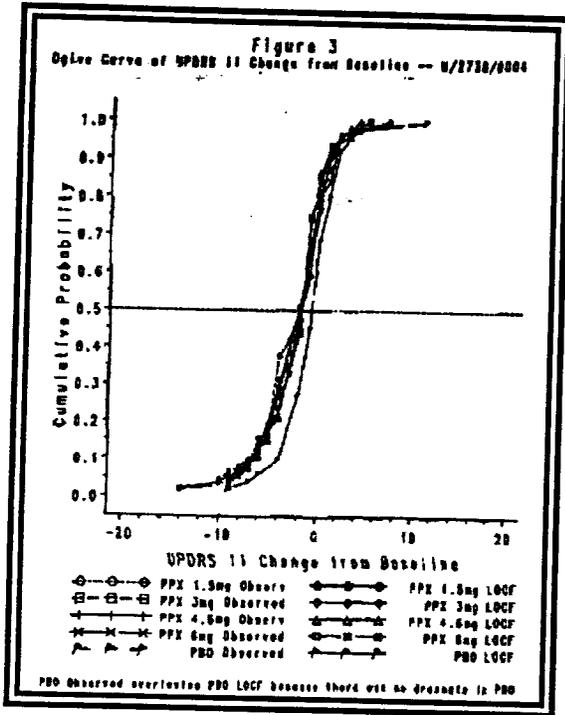
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The left shift of the ogive for improvement on UPDRS virtually says it all³. Exploratory analyses of the effect of age, sex and medication (other than l-dopa/carbidopa) did not find a treatment by concomitant treatment interaction. This is a strong positive study.

³ These are extracted verbatim from pages 22 and 25 of Dr. Feeney's review; the imported text on the figures is too small to read, but the consistent left shift of both the LOCF and OC data for pramipexole assigned patients (greater improvement from baseline for Mirapex™ assigned subjects) on both items of the UPDRS are obvious, a finding reflected in the very small 'p' value for the likelihood of the data given the null being true (no treatment effect).

To be clear, the evidence provided in the NDA is not without limitations. The results of Study 4, provided below, reveal, the sponsor has been unable to find a link between dose the magnitude of Mirapex's therapeutic effects.

Study 4, Fixed Dose comparison of 4 pramipexole vs. placebo (pages 45, 46 of Dr. Feeney's review.



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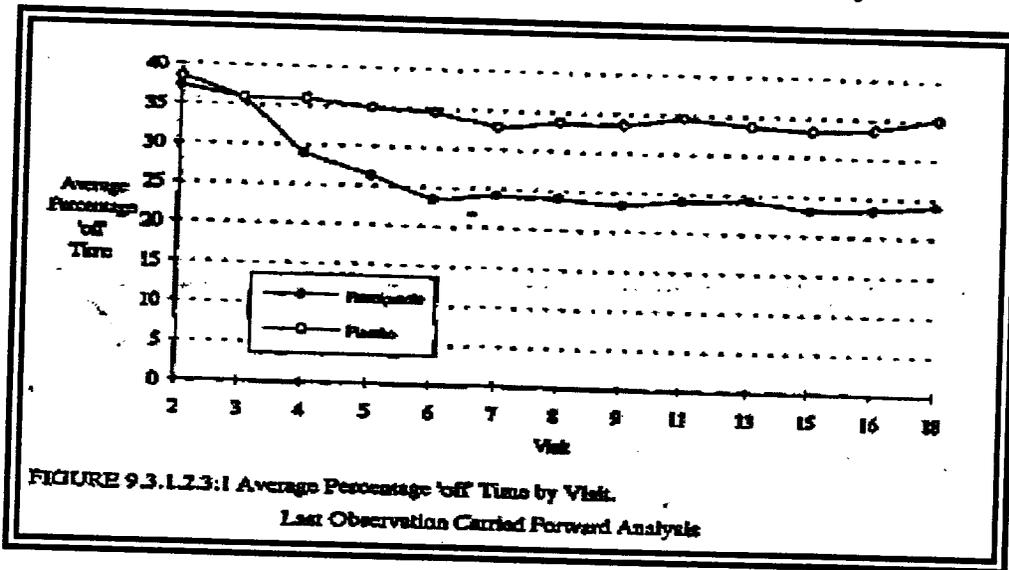
Among the 4 completed trials evaluating Mirapex as an adjunctive treatment, 3 can be deemed to provide support for its efficacy. Among the positive trials (i.e., Studies 10, 19 and 22), **Study 10** is critical to our affirmative conclusions regarding pramipexole's efficacy in this subpopulation.

Study 10

This is a strongly positive study. The graph that follows on the next page illustrates the clinical value of pramipexole in terms of the fraction of time awake that an advanced stage patient, being treated with maximally

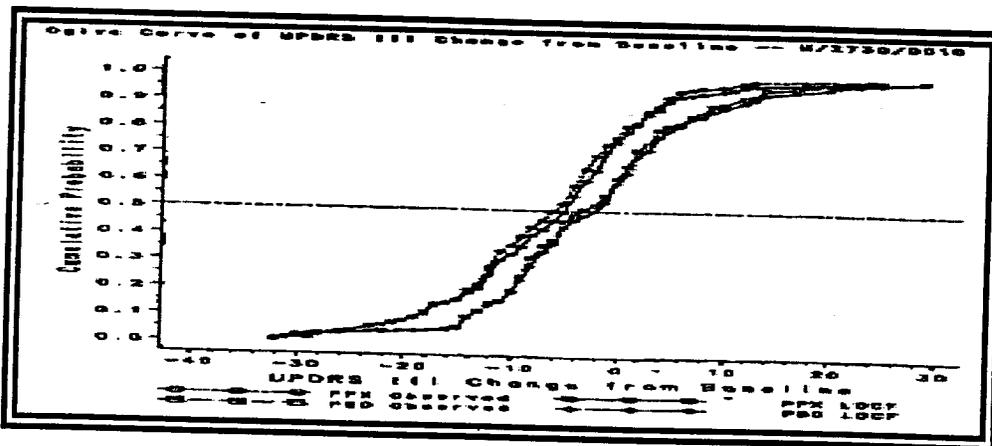
tolerated doses of l-dopa, spends in an 'off⁴' state.

Study 10, Average percent of time off by Visit⁵



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The changes on the UPDRS for both OC and LOCF data sets in this study are consistent as the cdf ogive for changes in its motor component document displayed below documents. (Feeney page 95).



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⁴ The "off" time refers to all time when an awake PD patient is immobilized and/or substantively impaired. Off is contrasted with "on" periods where the patient has some relief from the signs and symptoms of the disease.

⁵ taken from page 83 of Dr. Feeney's review

In sum, the NDA provides robust support for the sponsor's claim that Mirapex is an effective treatment for idiopathic Parkinson's Disease.

Safety in use

The evidence collected and reported to the NDA is sufficient to support a conclusion that Mirapex™ will be "safe for use" under the conditions of use enumerated and recommended in the draft product labeling developed by the Division. This conclusion is accompanied by a number of caveats, however.

To begin, a regulatory determination that a drug is "safe for use" is not a finding of fact, but an opinion. The opinion, importantly, is not really about safety, *per se*, but about the balance of risks and benefits associated with the use of the drug. Thus, when a regulator concludes that a drug has been shown to be safe for use, he is asserting only that the risks known to be associated with the use of the drug are, in his professional opinion, reasonably outweighed by the expected benefits of its use.

It should also be recognized that the basis for the opinion offered rests on imperfect knowledge. The measures of treatment effect obtained in clinical experiments that assess treatment effects on rating scales are, for example, not easily understood in terms of meaningful clinical benefit. Moreover, the risks associated with the use of a drug at the time a decision is made about its "safety for use," are invariably fewer than its actual risks because 1) too few patients are ordinarily exposed to a drug during its commercial development to capture adverse drug induced phenomena that occur at low incidence and 2) the typical clinical cohort in which a new drug is tested is not likely to be as vulnerable to the adverse effects/actions of the drug as is the population of patients for which the drug will be prescribed once marketed.

Both of these limitations affect our assessment of Mirapex's safety for use.

First, the total number of patients treated with pramipexole is small; as of the safety cutoff date (January 1995), only 1231 PD patients in toto

had been exposed to pramipexole. Among these, only 520 or so have been exposed to the maximum recommended dose of 4.5 mg/d for at least 12 weeks. While this number is probably sufficient to identify most of the common adverse events that are likely⁶ to be associated with pramipexole's use, the extent of exposure is clearly marginal insofar as its capacity to detect even one case of events that occur at a crude risk of 5 events/1000 patients exposed or less. While the later crude incidence may be deemed reasonably remote from the perspective of the individual patient, it is rather high from a societal viewpoint, especially if any of the risks not detected are serious ones⁷.

Also tending to undercut the basis for a conclusion that pramipexole is safe for use is the fact that the patients entered into the development cohort were selected so as to be free of the more serious illnesses (e.g., active heart disease) that are common among patients in the age range in which Parkinson's Disease is prevalent. This gives pause because it means that the risk of pramipexole caused events that arise uniquely or at increased incidence among older patients (either because of their age, per se, or the presence of age related co-existing disease or the treatments used to control the latter), have not been reliably assessed.

These limitations of pramipexole's clinical testing are not, under current interpretations of the Act's requirements, sufficient to bar its approval for marketing. Nevertheless, they are important because they do affect the nature of the extrapolations reasonably drawn from the relatively uneventful clinical experience reported during pramipexole's clinical

⁶ Dopamine agonists have been used in the management of PD since the early to mid 1970s. The common acute adverse events reported for the two approved products, bromocriptine and pergolide, are quite similar including hypotension, nausea, and vomiting. Typically, with dose incrementation, hallucinations and dyskinesias appear.

⁷ To illustrate, the use of bromocriptine is believed to be causally related to the occurrence of pleuropulmonary effusion and fibrosis. While I have no reliable basis to estimate the true incidence of this rare complication, which by now is widely attributed to dopamine agonist therapy in general, the incidence is likely to be well below that which would be reliably detected in a drug development cohort of the size used to assess pramipexole.

testing and development. Specifically, given the selected nature of the patients recruited in the Mirapex development cohort, it is prudent to be cautious in regard to inferences concerning the product's capacity to induce orthostatic hypotension (see below).

The limitations enumerated notwithstanding, it is fair to state that in regard to the events that have been reported, Mirapex appears to present no new serious risks of use not already known to be associated with the use of dopamine agonists in the treatment of Parkinson's disease. A review of the causes (hallucinations, dizziness, nausea, somnolence, headache and confusion) for premature discontinuations from studies of pramipexole supports this assertion.

As to more serious morbidities and fatalities associated with the use of pramipexole, clinical experience raises no substantive concerns. I note, however, that a case of rhabdomyolysis following exercise that was associated with CPK elevations has raised some concern among staff about the mean elevation of CPK results seen in the safety database. Given the numerous potential causes for CPK elevation, I see no reason to do more than describe the case (e.g., in the Precautions section) and the CPK findings in labeling.

As to fatalities, only 12 occurred among pramipexole recipients. As a consequence, any estimates of the incidence within subgroups of the sample studied are likely to be unstable. We did, nonetheless, elect to examine fatality rates separately among early and advanced cases of PD because the patients in these two groups were deemed likely to be different in terms of their inherent risk of mortality, an assumption, incidentally, that is not supported by the point estimates of the fatality risk among placebo recipients in these groups. In any case, the rate per 100 patient years is approximately the same among early patients regardless of treatment (0.72 vs 0.9 favoring pramipexole). Among patients with advanced disease, however, the data provide a relative risk estimate of almost 3. (2.52 vs 0.88 deaths per 100 patient years). While unfavorable to Pramipexole, the difference in the estimates is due to a difference of 2 deaths. Accordingly, I am not persuaded the finding represents a signal worthy of pursuit.

Labeling Considerations.

In general, in developing labeling, we sought to maintain some degree of consistency with that of dopamine agonist products already marketed with anti-PD indications (Parlodol[bromocriptine] and Permax [pergolide]). This proved somewhat difficult given the long interval that has elapsed since the initial approval of those products.

We have acted as if certain findings are generalizable to all dopamine agonist treatments. Perhaps the most controversial consequence of this strategy is the warning statement we propose about the risk of hypotension associated with dopamine agonist use. Actually, hypotensive events for Mirapex were not reported to occur at an incidence greater than that seen among placebo patients, a point acknowledged in the warnings statement. As noted earlier, however, we are not fully reassured by the absence of a differential risk because of the highly selected nature of the population. Moreover, we are also concerned that the sponsor's classification system may have obscured the risk (i.e., the sponsor combined dizziness and hypotension, an act that may have caused a differential risk of orthostatic events to be missed).

Dosing

The sponsors fixed dose study failed to establish the shape of pramipexole's dose response surface. Directions for the product's use, therefore, reflect experience gained in the clinical development program.

Conclusions and Recommendations

Mirapex has been shown, within the meaning of the Act, to be effective in use and safe for use under the directions for use provided in the draft labeling developed by the Division. Accordingly, the ~~NDA~~ should be deemed approvable.

APPEARS THIS WAY
ON ORIGINAL


Paul Leber, M.D.
December 6, 1996

cc NDA 20-667
HFD 101
Temple
HFD-120
Katz
Feeney
Burkhart
Balian
Knudsen
Steele
Fitzgerald
HFD -710
Hoberman
Grilley
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Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: June 23, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 20-667, Mirapex, [pramipexole]

TO: File NDA 20-667
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my formal recommendation that the NDA for Mirapex be approved. This recommendation reflects the Division's review team's conclusion that the firm has satisfactorily met the requests and conditions upon which final approval of the application was conditioned (see the agency's action letter of 12/23/96).

In memoranda to the file, Dr. Katz (6/16/97) and Dr. Burkhart (5/13/97) summarize the findings and evidence that led them each to recommend that the application be approved. Although I fully concur with their recommendations, I have a number of comments for the administrative file.

Safety Update [SU]

With the submission of the SU, the clinical data base for the Mirapex NDA now includes a total of some 2150 subjects (there were 1400 in the original NDA) who provide approximately 1925 patient-years of exposure experience.

No previously unrecognized risks of use have been identified.

Although Dr. Balian (2/27/97) concludes that the experience reported upon provides no finding that would cause the agency to reverse its conclusion that Mirapex has been shown to be safe for use, it bears note that a

sizeable fraction of the new information presented does not derive from experience gained with pramipexole in patients with PD, but from reports of studies of the drug in patients with depression or schizophrenia.

The relationship between dose and common ADRs has not been characterized

The firm has been unable to develop the information necessary to determine whether or not there is a linkage between ADR incidence and pramipexole dose. The review team is persuaded that their inability to do so is a consequence of 1) the fact that pramipexole dose was advanced by titration (i.e., thus, dose and time are confounded), and, 2) the small numbers of untoward events falling within any of the categories that would be created by an arbitrary partition of the dose and time continuum.

Labeling

The sponsor has persuaded the agency review team that a draft of product labeling differing in a number of ways from the labeling put forth in the approvable action is acceptable. The areas of labeling affected by these changes are identified in Dr. Katz's 6/16/97 memorandum.

Recommendation

The application should be approved.

APPEARS THIS WAY

/S/

Paul Leber, M.D.
June 23, 1997

APPEARS THIS WAY

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cc NDA 20-667
HFD 101
Temple
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ON ORIGINAL

MEMORANDUM

DATE: December 2, 1996

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

TO: File, NDA 20-667

SUBJECT: Supervisory Review of NDA 20-667 for the use of Pramipexole
in patients with Parkinson's Disease

BACKGROUND

NDA 20-667, for the use of pramipexole, a D₂ receptor agonist (with greatest affinity for the D₃ receptor sub-type), in patients with idiopathic Parkinson's Disease (PD), was submitted by Pharmacia and Upjohn on December 28, 1996. The NDA includes reports of 9 controlled trials; 4 of the trials enrolled patients with relatively early PD who were not receiving concomitant dopaminergic therapy. In the remaining 5 trials, patients with later stage PD were enrolled, and these patients were receiving concomitant dopaminergic therapy.

The effectiveness data were reviewed by Dr. John Feeney (and Dr. James Sherry) of the Division, in a review dated 9/13/96, and a detailed statistical review of 3 of the controlled trials was performed by Dr. David Hoberman of Biometrics in a review dated 10/24/96. The safety database was reviewed by Drs. John Balian and James Knudsen of the Division in a review dated 11/13/96. In this memo, I will briefly review the efficacy and safety data, and offer my recommendation for action on the NDA.

EFFECTIVENESS

EARLY PD

As noted above, the sponsor has submitted the results of 4 controlled trials in patients with early PD; Studies 1, 4, 17, and 21. Study 21 was small, and Study 17 was single-blind. They will be discussed very briefly

here, but I will focus on the results of Studies 1 and 4.

Study 1

This was a multi-center, randomized, placebo controlled, parallel group trial in which patients with PD Stage I-III Hoehn and Yahr who were not receiving concomitant L-dopa therapy were enrolled. The Hoehn and Yahr scale is a frequently used PD staging instrument, in which I=minimal unilateral disease and V=confined to bed or wheelchair. Stage III=Mild to moderate bilateral disease with some postural instability but physically independent.

Patients were permitted to have received L-dopa in the past, but not for greater than 6 months and not for at least 60 days prior to randomization. Treatment was to be initiated at 0.125 mg TID (total daily dose of 0.375 mg), and weekly dose increments were to be carried out, to the patient's maximally tolerated dose or a maximum dose of 1.5 mg TID (total daily dose of 4.5 mg). This titration phase could last up to 7 weeks.

After the titration phase, patients entered a 6 month maintenance phase, which was followed by a 1 week dose reduction phase.

The protocol stated primary outcomes were change from baseline in the score of the Unified Parkinson's Disease Rating Scale (UPDRS) for the Activities of Daily Living (ADL) and Motor Score sub-scales.

The UPDRS is a frequently used multi-item scale which is designed to assess various aspects of the severity of PD. It consists of 42 items, grouped into 4 parts: Mentation, ADL, Motor Exam, Complications of Therapy. Part II (ADL) consists of 13 items, and Part III (Motor Exam) consists of 14 items, each of which are rated from 0-Normal to 4-maximum impairment. Scores for Part II can range from 0-Normal to 42 Maximal Disability. Scores for Part III can range from 0-Normal to 46-Maximal Disability. The items constituting the ADL are assessed for the previous week (both during "on" periods-during which the patient is functioning well, and during "off" periods-periods when the patient is relatively immobile), and the items for the Motor Score are assessed by the examiner during a study visit. These latter items consist of, for

example, assessment of tremor, rigidity, facial expression, speech quality, bradykinesia, posture, gait, etc.

A total of 300 patients were planned to be enrolled at 24 U.S. and Canadian centers.

RESULTS

A total of 335 patients were randomized (pramipexole 164, placebo 171) at 26 centers in the U.S. A total of 28 pramipexole and 34 placebo patients did not complete the trial, and 163 pramipexole and 170 placebo patients were included in the intent-to-treat, last observation carried forward (LOCF) analyses.

The following results were obtained for the primary analysis of UPDRS Parts II and III:

	Change From Baseline	P-value
Pramipexole (N=163)	-1.9	
Placebo (N=170)	+0.4	<0.0001

Similar P-values were obtained for between treatment differences at weeks 0, 4, 8, 12, and 16 (week 0 is the end of titration). The magnitude of the between treatment differences seen at these times was approximately the same as is displayed. Likewise, an analysis of an Area Under the Curve (AUC) analysis for the entire Maintenance Phase yielded values of -57 and -5 for pramipexole and placebo, respectively, with a corresponding p-value of <0.0001. Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney's review, page 22.

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Part III (Motor Score)

	Change From Baseline	P-value
Pramipexole	- 5	
Placebo	+0.8	<0.0001

Again, similar p-values were obtained at each assessment week during the Maintenance Phase, including at the end of titration, although the magnitude of the between treatment differences were slightly less than for the LOCF analysis displayed above. Further, an AUC analysis yielded values of -127 and -11 for pramipexole and placebo, respectively, a difference that was highly significant ($P < 0.0001$). Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney's review on page 25.

As Dr. Hoberman notes in his review (page 3), on average, the patients the LOCF change from baseline for patients discontinuing pramipexole was better than that of dropouts from placebo. Finally, a time to failure analysis yielded a p-value (logrank test) of 0.0015 in favor of pramipexole.

Study 4

This was a multi-center, randomized, double-blind, parallel group study in which patients with idiopathic PD (Hoehn and Yahr I-III) were randomized to one of 3 fixed doses of pramipexole or placebo. Patients were not permitted to have received l-dopa within 3 months prior to the study.

Patients were titrated to their fixed dose over a maximum of 6 weeks. The maximum doses to be achieved were either 0.5 mg TID (1.5 mg/day), 1.5 mg TID (total daily dose of 4.5 mg), 2.0 mg TID (6.0 mg/day), or placebo. Patients not tolerating a given dose could be dropped back to their previous dose, and were not to receive higher doses. After the dose titration, patients entered a 4 week Maintenance Phase, followed by a 1 week Dose Reduction Phase.

Patients were seen every 2 weeks after randomization, at which time the

UPDRS, Parts I-III were assessed. At the final visit, Hoehn and Yahr staging was performed and several quality of life questionnaires were administered.

The primary outcome in this study was change from baseline of the sum of UPDRS Parts I-III. Analyses examining the dose to which patients were randomized as well as the dose actually received were planned.

RESULTS

A total of 264 patients were randomized at 20 centers in the U.S. and Canada. The following table displays the disposition of patients:

	Pr 1.5	Pr 3.0	Pr 4.5	Pr 6.0	Pbo
Randomized	54	50	54	55	51
Completed	44	48	50	46	50

The following table displays the results of analyses of the primary outcome for the doses to which patients were randomized.

	Pr 1.5	Pr 3.0	Pr 4.5	Pr 6.0	Pbo
Baseline	28.5	28.3	27.3	32.9	28.7
Mean Change	-6.1	-5.8	-6.6	-7.1	-1.2

All individual dose-placebo pairwise contrasts yielded p-values of <0.006 , (significant in the face of Bonferroni correction) with an overall p-value of 0.0022. Similar changes were seen when the results were analyzed according to the dose actually achieved (in this latter analysis, it is not clear in which group patients not achieving the dose to which they were randomized were counted, although it is true that most of the steps in the titration algorithms would yield one of the 4 "goal" doses).

The sponsor acknowledges that there was no dose response seen, although with placebo included in a regression analysis, a linear dose response was seen (P-value 0.03) for the analysis in which patients were counted in the

group to which they were randomized.

Although between treatment differences of about 1.5 were seen for the individual dose-placebo contrasts for UPDRS Part II (Motor Scale), the overall p-value was 0.06, while the overall p-value for Part III (ADL) was 0.005.

In general, results of the Quality of Life questionnaires did not achieve statistical significance.

Study 17

This was a single blind, randomized, placebo controlled, parallel group trial in PD patients who had not received l-dopa within 3 months. A total of 48 patients were to be enrolled. The trial had a 7 week titration phase, with a maximum dose of 4.5 mg/day. Following titration, there was a 3 week Maintenance Phase, followed by a 1 week dose reduction phase. The primary outcome was mean change from baseline on Parts II and III of the UPDRS.

RESULTS

A total of 56 patients were randomized, with 55 included in the ITT population analyzed. Analysis of observed cases performed by the sponsor yielded a p-value of 0.002 for the pramipexole (N=28)-placebo (N=24) contrast for UPDRS Part II, and a p-value of 0.10 for the between treatment contrast for UPDRS III.

Study 21

This was a double-blind, placebo controlled, randomized, parallel group study of patients with PD who had received no more than 1 week of l-dopa in the past. Patients were to be titrated to a maximally tolerated dose, up to 4.5 mg/day; the titration phase was to last a maximum of 9 weeks, after which they were to enter a 2 week maintenance phase, followed by a 1 week dose reduction phase. A total of 72 patients were to be randomized, to yield 52 completers.

The primary outcome was to be change from baseline in UPDRS, Part III.

RESULTS

Only 24 patients were enrolled. The sponsor performed an analysis excluding 2 of these patients, which they assert yielded a p-value of 0.02.

LATE PD

Study 10

This was a multi-center, randomized, parallel group, placebo controlled trial in which patients with idiopathic PD (Hoehn and Yahr Stages II-IV) who are not adequately controlled on maximally tolerated l-dopa (as well as other anti-PD medications) were randomized to receive adjunctive pramipexole or placebo.

Patients initially entered a titration phase, beginning with a dose of 0.25 mg TID (total daily dose of 0.375 mg) to be followed by weekly dosing increments to a maximum dose of 1.5 mg TID (to be achieved in 7 weeks) or to a lower maximally tolerated dose.

After titration, patients entered a 6 month maintenance phase, and then a 1 week dose reduction phase. During this maintenance phase, the dose of l-dopa could be reduced for control of dopaminergic adverse events. The l-dopa dose could then be increased, but was not to exceed the baseline dose. Other anti-PD medications were to be held constant during the study.

At monthly intervals, patients were assessed with the following measures:

- 1) UPDRS; the Motor Score was to be assessed during an "on" period.
- 2) Modified Schwab-England Disability Scale; this is an ADL scale.
- 3) Timed Walking Test
- 4) Hoehn and Yahr
- 5) Parkinson's Dyskinesia Scale

Patients were instructed to record a daily diary for at least 2 full days prior to clinic visits. On this diary, patients were to record the total time awake, as well as the total time spent "off", and the severity of the "off" periods (1-4 scale). Part II of the UPDRS, as well as the Schwab-England and Hoehn and Yahr Scales were to be rated for both "on" and "off" periods.

The primary outcomes were to be change from baseline in Parts II and III. The protocol specified that both outcomes would have to reach significance independently in order for the trial to be considered "positive".

A total of 300 patients were to be enrolled at 24 U.S. and Canadian centers.

RESULTS

A total of 360 patients (pramipexole 181, placebo 179) were enrolled at 26 U.S. And Canadian centers. A total of 351 patients (pramipexole 179, placebo 172) were included in the ITT population.

A total of 30/181 (16.6%) of pramipexole patients and 39/179 (22%) of placebo patients discontinued treatment prior to completing the trial.

The following table presents the results for the protocol specified primary outcomes:

Change From Baseline in UPDRS Part II

	LOCF Change	LOCF AUC for Maintenance
Pramipexole (N=179)	-2.7	-57
Placebo (N=171)	-0.5	-18
P-value	<0.0001	<0.0001

Statistically significant differences were seen for the between treatment change from baseline in Part II at all visits during the Maintenance Phase starting at visit 5. (Scores for Part II are averages of scores for "on" and

"off" times). Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney's review, page 90.

Change From Baseline in UPDRS Part III

	LOCF Change	LOCF AUC for Maintenance
Pramipexole (N=179)	-5.6	-114
Placebo (N=171)	-2.8	-64
P-value	0.01	0.01

A total of 7/12 between treatment differences were significant during the Maintenance phase (see Dr. Hoberman's review, Figure 2). Cumulative Distribution Functions for this outcome are reproduced in Dr. Feeney's review, page 95.

As Dr. Hoberman notes, the consistency of the results over time suggest that there was little effect of dropouts on the LOCF analysis.

Dr. Feeney suggests in his review that Percent of Awake Time Spent "off" is a useful measure of effectiveness (this was a protocol specified secondary outcome) because, among other reasons, UPDRS Part II was to be an average of scores during "on" and "off" times, but did not take into account time spent in either of these states (theoretically, scores could have improved, but a patient might have spent more time "off", a clearly undesirable outcome). In addition, Part III was to be assessed during an "on" period, also thereby not taking into account a potential increase in "off" time. Finally, he notes that Parts II and III appear to be independent, whereas total "off" time is, in his view, a more global measure of effectiveness.

The following table displays the results for Average Percent of Awake time spent "Off":

	Baseline	Final	Change	P-value
Pramipexole (N=173)	37.2	24	-13	
Placebo (N=172)	38.3	35	-3	0.0006

The difference between treatments emerged by visit 4, increased until visit 6, then remained essentially constant throughout the Maintenance phase (see Dr. Hoberman's review, Figure 5).

Little difference was seen on the Schwab-England ADL scale or the Hoehn and Yahr scale.

The pramipexole group was able to tolerate a decrease in l-dopa dose of about 25% compared to a 6% reduction in the placebo groups ($P < 0.0001$).

Study 19

This was a 7 center randomized, double blind, placebo controlled, parallel group trial in patients with poorly controlled PD (Hoehn and Yahr II-IV) being treated concomitantly with l-dopa at a maximally tolerated dose. Patients were titrated over a maximum of 7 weeks to a maximum daily dose of 5 mg (presumably 1.25 mg QID), after which they entered a 4 week maintenance phase and then a 1 week dose discontinuation phase.

The primary outcome was change from baseline in total UPDRS score.

RESULTS

A total of 78 (pramipexole 34, placebo 44) were treated. According to the sponsor, the following results for the primary measure were obtained:

	Baseline UPDRS	Final UPDRS	P-value
Pramipexole	53.7	33.6	
Placebo	50.2	44.4	0.0002

Study 22

This trial was essentially identical to Study 19. It was performed at 9 centers in Denmark.

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RESULTS

A total of 69 patients (pramipexole 36, placebo 33) were enrolled. According to the sponsor, the following results were obtained:

	Baseline UPDRS	Final UPDRS	P-value
Pramipexole	51.9	35.0	
Placebo	56.7	47.7	0.018

Study 18

This was a single blind, placebo controlled, parallel group, randomized trial in patients with motor fluctuations on maximally tolerated l-dopa. A total of 48 patients were to be enrolled.

Patients were entered into a 7 week titration phase designed to reach a maximum dose of 4.5 mg/day. Following the titration phase, patients entered a 3 week maintenance phase, followed by a 1 week dose reduction phase.

The primary outcome was Mean Change from Baseline on UPDRS, Part II, and percentage of "off" time; both were to be significant independently in order for the study to be considered to demonstrate effectiveness.

RESULTS

A total of 50 patients (pramipexole 26, placebo 24) were enrolled at 6 U.S. Centers.

According to the sponsor, there were no significant between treatment differences seen in the change from baseline on Part II when examined during "on" and "off" times individually, nor were there significant between treatment differences on the percent of "off" time.

Study 20

This was to be randomized, s=double blind, parallel group, placebo

controlled trial of advanced PD patients. However, only 19 patients were enrolled, and the trial was not analyzable.

SAFETY

A total of 879 unique patients have been exposed to pramipexole in completed Phase 2/3 controlled trials. Of this total, 702 have been patients with Parkinson's Disease (416 have been patients not receiving concomitant l-dopa [early PD] and 286 were receiving concomitant l-dopa [late PD]); the remaining 177 have been patients with schizophrenia. An additional 260 subjects have been enrolled in Phase 1 trials, resulting in a total of 1139 patients/subjects enrolled in completed trials. However, the NDA contains reports of experience in a total of 1408 patients in Phase 2/3 trials and 253 Phase 1 subjects exposed to pramipexole, including those enrolled in extension trials at the time of the NDA cut-off date (1/95). Of these 1408 patients, 1231 were patients with PD.

Of the 1231 PD patients, 178 have been exposed for greater than 1 year (59 for greater than 2 years), and 365 have been exposed for between 6 months and 1 year. A total of 552/1231 (45%) of PD patients have received the maximum proposed dose of 4.5 mg/day for at least 12 weeks, and 981/1231 (80%) have received at least 1 day of this maximum dose. Of the 702 PD patients in controlled trials, 349 (50%) received an average dose of between mg/day. Of this group, 207 received this average dose for between weeks (this included extension trials).

DEATHS

A total of 17 deaths had occurred in the course of pramipexole's development as of 1/95; of these 17, 15 deaths (or the event leading to death) occurred within 30 days of the last dose of study drug. A total of 12 of the deaths occurred in pramipexole treated patients. In the controlled trials, the following comparisons are made:

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	Deaths	Rate/100 patient-years	Relative Risk
Early patients			
Pramipexole (N=416)	1	0.72	0.80
Placebo (N=262)	1	0.90	
Late Patients			
Pramipexole (N=286)	3	2.52	2.87
Placebo (N=289)	1	0.88	

For the entire pramipexole treated PD population, the early patients mortality dropped to 0.11 deaths/100 patient years, while the late patients mortality dropped to 1.83 deaths/100 patient years.

Of the pramipexole deaths, the reviewers considered 8 to be potentially cardiovascular in nature.

Of these 8, there were several documented or presumed MI or heart failures, mostly in patients with past history of severe cardiac disease. One patient had no history of cardiac disease, but had an MI during Study 10 (late PD), presumably sometime towards the middle to late portion of the Maintenance Phase. He died shortly thereafter.

Another patient with no real cardiac history died on day 61 of study 1 (early PD) from a presumed pulmonary embolus. A third patient with a past history of mild cardiac insufficiency and bronchitis suffered multiple episodes of dyspnea and syncope. He died after an episode of syncope, but no autopsy was performed.

DISCONTINUATIONS

Early PD

In controlled trials of early PD patients, the total dropout rate in

pramipexole patients was 14.4%, compared to 16.2% in placebo patients. The rate of dropouts secondary to adverse events was 12% for pramipexole patients, compared to 11% for placebo patients. The rates of discontinuations were variable in these studies, with the largest difference between drug and placebo occurring in Study 4; 12% and 2%, respectively. Most of these dropouts occurred secondary to adverse events at the highest dose (6 mg/day). The most common adverse events associated with discontinuation that were greater than 1% and also greater than the placebo rate were: hallucinations (3%), dizziness, nausea (2%), somnolence (1.55%), headache (1.3%), and confusion (1%).

Of the discontinuations due to adverse events, 8/388 (2.1%) of the pramipexole and 3/235 (1.3%) of the placebo patients had events considered serious. Of the 8 pramipexole patients, 1 died secondary to a cardiovascular event, and the remaining 7 included 1 case each of drowsiness, decreased platelets, abdominal pain, somnolence, paranoid psychosis, sensory hallucinations, and confusion/hallucination.

Late PD

In controlled trials in late PD patients, the overall discontinuation rate was 15.4% in pramipexole patients and 20.4% in placebo patients. In these studies, the dropout rate due to adverse events was 11.5% for pramipexole patients and 15.8% for placebo patients. The most common adverse events associated with discontinuation that were greater than 1% and also greater than the placebo rate were: hallucinations (2.7%), postural hypotension (2.3%), dyskinesia (1.9%), confusion, dizziness (1.2%).

Of the discontinuations due to adverse events, 8/259 (3.1%) of the pramipexole and 6/266 (2.3%) of the placebo patients had adverse events considered serious. Of these 8 pramipexole patients, 2 had cardiovascular events and died.

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Other Serious Adverse Events in Controlled Trials

Early PD

Of the 388 pramipexole treated patients in controlled trials, 20 (5%) had adverse events deemed serious, while 5.5% of placebo patients had such events. Of the 20 serious adverse events in the pramipexole patients, 7 were cardiovascular. One of these was discussed in the section on Deaths, and the other 6 were 2 MIs, 2 angina, and 1 case each of pulmonary embolism, and LV dysfunction.

Of the remaining 13, 7 have been discussed in the section on serious adverse events leading to discontinuation; the other 6 consisted of 2 cases of prostate cancer, and 1 case each of fractured hip, thyroid nodule, basal cell carcinoma, and rectal cancer.

Late PD

Of the 259 pramipexole treated patients in controlled trials, 18 (7%) had serious adverse events, compared to 7.5% of the placebo patients. Of the 18 serious adverse events in pramipexole patients, 3 were cardiovascular; 2 resulted in death, and one had angina. The other 15 consisted of the following: pneumonia, dyskinesia, fractures, somnolence, bladder cancer, paranoia, nausea, neck pain, CPK elevation, increase of periods, back pain, abdominal pain, confusion, and multiple myeloma.

Other serious events

It is difficult to tell from the documents available what the incidence of serious adverse events is in the entire PD database. However, Drs. Balian and Knudsen have highlighted several of the events as being worthy of note.

Cardiovascular

A 72 year old man experienced severe orthostatic hypotension after a single 0.125 mg dose of pramipexole. He was on multiple medications

(including treatment for prostatic CA). One hour after the dose, his supine BP was _____, but on standing his BP was essentially 0. He could not stand for about 3.5 hours after dosing. Apparently, his EKG was normal (time after dosing unknown to me).

Hematologic

A 72 year old man receiving pramipexole 4.5 mg/day (as well as nifedipine for about 260 days) was documented to have a platelet count of _____ mm³ after 40 days of treatment (baseline count was _____). Three days later the platelet count was _____. On day 47, pramipexole was discontinued; at the time, the count was _____. A bone marrow aspiration was not consistent with marrow suppression, and no further information is available.

Respiratory

A 77 year old man with a history of cardiac disease and LV dysfunction experienced dyspnea on day 32 of treatment with pramipexole (at the time his dose was 3 mg/day). Four days later, at a dose of 4.5 mg/day, he was hospitalized for dyspnea and was determined to have LV dysfunction and pulmonary congestion. His treatment was discontinued and underwent cardiac bypass surgery shortly thereafter.

Laboratory abnormalities

A 49 year old man experienced a marked increase in CPK (about _____) after 1 month of treatment. Medication was discontinued, and CPK began to decrease. The patient was admitted to the hospital and treated for rhabdomyolysis.

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Other Adverse Events

Early PD

The following adverse events were seen in at least 5% of the 388 pramipexole treated patients in controlled trials and at least twice as frequently as in the placebo patients:

Somnolence-22%

Constipation-14%

Hallucination-9%

Other adverse events seen at a greater incidence than placebo included confusion, anorexia, amnesia, hypesthesia, vision abnormality, dysphagia, weight loss, akathisia, thinking abnormal, decreased libido, myoclonus, and fever.

Late PD

The following adverse events were seen in at least 5% of 260 pramipexole treated patients in controlled trials and at least twice as frequently as in the placebo patients:

Hallucination-16.5%

Dry Mouth-6.5%

Urinary Frequency-5.8%

Other adverse events seen at a greater incidence than placebo included dyskinesia (47% compared to a placebo rate of 32%), chest pain, vision abnormality, rhinitis, twitching, peripheral edema, pneumonia, paranoid reaction, bursitis, CPK increase, myasthenia, delusions, sleep disorder, and diplopia.

Dose Response

Only Study 4 (early PD) was designed as a fixed dose study. In this study, nausea, and somnolence and insomnia were seen to be dose related. In both early and late controlled trials, the greatest risk for several adverse events was observed in the titration phases.

Abnormal Lab Values

In general, pramipexole produced no systematic abnormalities in routine laboratory tests.

However, in the combined controlled trial database (Studies 1, 4, and 10), 19 (3.5%) of the pramipexole treated patients and 9 (2.3%) of the placebo patients had CPK levels exceeding normal limits; this difference was not statistically significant. The number of patients with significant elevations is unclear, although it appears to be a relatively small proportion of the 19.

In other controlled trials, 2/76 (2.6%) of pramipexole treated patients experienced elevated CPK levels, compared to 0/83 (0%) of placebo patients. One of the patients had a CPK at day 48 of IU/L, resulting in discontinuation of treatment. CPK returned to normal after drug discontinuation.

There was one case diagnosed as rhabdomyolysis; this case has been discussed.

LFTs

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In the 3 controlled trials (Studies 1, 4, and 10), a total of 15/553 (2.7%) of pramipexole patients experienced elevations of LFTs (ALT, AST, and/or GGT) greater than 2.5 X ULN. A total of 5/394 (1.3%) of placebo patients had similar elevations. Most of the elevations in the pramipexole patients occurred in Study 10, in which there were 10 such patients (5.7%), compared to 2 (1.2%) placebo patients.

Of the 15 pramipexole treated patients with elevations, 8 had elevations of GGT only; 7 of these 8 had elevations of GGT prior to treatment with pramipexole. Of these 7, 3 had baseline elevations at least 2.5 X ULN; of the remaining 4 with baseline elevations, most had elevations close to X ULN, and the elevations noted on treatment for most of the 7 with baseline elevations were similar in degree to the pre-treatment elevations.

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Most of the other LFT elevations were relatively mild (in most of these patients, the maximum value of either AST or ALT obtained was in the range of _____). 1 patient had one ALT of _____. It is difficult to tell, from the reviews, the ultimate disposition of these patients. However, it appears that, for many of these patients, the elevations either stabilized or returned towards normal with continued treatment (for several other cases, alternative explanations for the elevations were available).

One patient (a 67 year old man) in Study 10 experienced a GGT of _____ U/L (_____ U/L) on day 50 of treatment; this was associated with an ALT of _____. Treatment was discontinued and LFTs returned to normal within 30 days. Throughout, his bilirubin was normal.

Orthostatic Hypotension/Syncope

In animal studies, pramipexole lowers blood pressure and pulse, presumably related to its D2 and α_2 agonism.

In Phase 1 studies, pramipexole was seen to cause dose related orthostatic hypotension, first seen after single doses of 0.2 mg. In some subjects, syncope occurred upon standing. In controlled trials in early PD patients, there were 5 episodes of syncope in pramipexole patients (1.3%), and 2 such episodes in placebo patients (1.0%).

In controlled trials of late PD patients, there were 4 episodes of syncope in pramipexole patients (2.2%), and 7 in placebo patients (3.4%).

In neither population was there a significant difference between drug and placebo patients in the rate of discontinuations for serious or non-serious adverse events.

Regarding orthostatic hypotension, this was reported at a frequency of 7.7% in early PD patients compared to 8.9% in early placebo patients. In late PD patients, 53% of pramipexole and 48% of placebo patients were reported to have experienced at least 1 episode of orthostatic hypotension. Few of these episodes were symptomatic, and a total of 7 pramipexole and 3 placebo patients discontinued from controlled trials

(combined early and late patients) because of orthostatic hypotension.

SUMMARY

The 3 randomized controlled trials (Studies 1, 4, and 10) described in this memo clearly demonstrate the effectiveness of pramipexole as a symptomatic treatment for patients with Parkinson's Disease. This conclusion applies to patients with relatively mild disease not receiving concomitant dopaminergic therapy, as well as to patients with more advanced disease who are receiving concomitant l-dopa.

The safety experience contained in the NDA provides no signal that pramipexole will be unacceptably dangerous when used according to appropriate labelling, although the safety database is not as large as we might hope. For example, we know that 552 patients have received this dose for at least 12 weeks, but we do not know how many have received this dose for longer durations. It would be useful for the sponsor to explicitly display the number of patients who received 4.5 mg/day for specific durations.

The panoply of adverse events seen are typical for D2 agonists, and there is some reassurance that the incidence of syncope/orthostatic hypotension appears not to have been greater than that seen in placebo patients in the controlled trials (again, given the limitations imposed by the relatively small number of patients in controlled trials). It is of some note that the mortality (deaths/100 patient years) in the late PD patients was 2.52 in pramipexole patients compared to 0.88 in placebo patients (relative risk of 2.9). However, this represents, in reality, 3 deaths in the drug treated group compared to 1 death in a placebo patient, with 95% CIs of (0.3, 27). Examination of the causes of death did not reveal any obvious, specific pramipexole relationship.

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RECOMMENDATIONS

For the reasons stated above, I recommend that the attached Approvable letter be sent to the sponsor.

/S/

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Russell Katz, M.D.

Cc:
NDA 20-667
HFD-120
HFD-120/Leber/Katz/Feeney/Sherry
HFD-120/Burkhart/Balian/Knudsen/Griffey
HFD-710/Hoberman

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