CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20667
SPONSOR: Upjohn
Kalamazoo MI
DRUG: Pramipexole (0.125, 0.25, 1.0, 1.25, and 1.5 mg tablets)
INDICATION: Parkinson's Disease
TYPE OF SUBMISSION: NME
REVIEWER: Robert Harris, Ph.D.

Submission Dates: Dec. 26, 1995
Feb. 9, 1996
March 20, 1996

SYNOPSIS:

Pramipexole is a dopamine receptor agonist used in the treatment of Parkinson's Disease. The sponsor plans on marketing 0.125, 0.25, 1.0, 1.25, and 1.5 mg tablets. The recommended starting dose is 0.125 mg administered tid. Patients are gradually titrated up to the lowest effective dose. The maximum dose described in labeling is 4.5 mg/day. Pramipexole can be administered in monotherapy or in combination therapy with carbidopa/levodopa.

Pramipexole is rapidly absorbed, reaching peak concentrations in approximately 2 hours. Over 90% of an oral dose reaches systemic circulation, indicating that pramipexole is almost completely absorbed and does not undergo first pass metabolism. Food does not affect the extent of pramipexole absorption, although Tmax is increased by about one hour when the drug is taken with a meal.

Pramipexole is extensively distributed, having a volume of distribution of approximately 500 L (cv = 20%). It is only about 15% bound to plasma proteins, binding primarily to albumin. Pramipexole distributes into red blood cells, having an erythrocyte to plasma ratio of approximately 2.

Pramipexole displays linear kinetics over the labeled dosing range. The terminal half life is about 8 h (cv = 20%) in young healthy volunteers and about 12 h (cv = 20%) in elderly volunteers. Steady state concentrations are achieved within 2 days of dosing.

Approximately 90% of a pramipexole dose is recovered in the urine, almost all as unchanged drug. Non renal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in the plasma or urine. The clearance of pramipexole is approximately 400 mL/min (cv = 25%), which is about three times higher than GFR. Thus, pramipexole is probably secreted via the renal organic cation transport system. Pramipexole clearance correlates moderately well with creatinine clearance.

Pramipexole clearance is about 30% lower in women than in men. This gender difference is primarily due to differences in body weight, and is greatly reduced after weight normalization.

Pramipexole clearance is also about 30% lower in the elderly compared to the young, indicating that pramipexole clearance, like creatinine clearance, decreases with age. This age related decline in pramipexole elimination is potentially noteworthy because the majority of Parkinson's patients are elderly. Pramipexole clearance also appears to be additionally reduced, by about 30%, in Parkinson's patients compared to healthy elderly volunteers. The reason for this is unknown, but may be related to the generally poorer overall health of Parkinson's patients. The effect of race on pramipexole elimination is unknown. Because the dosage of pramipexole is titrated up from a low starting dose, no specific alterations in pramipexole dosing based on gender, age, or the presence of Parkinson's disease are necessary.

Pramipexole clearance is reduced in renally impaired patients. The clearance of pramipexole was about 75% lower in patients with severe renal impairment (Clcr ≈ 20 mL/min) and about 60% lower in patients with moderate impairment (CLcr ≈ mL/min) compared to healthy volunteers. There is a good correlation between creatinine clearance and pramipexole clearance in patients with decreased renal function. Thus, creatinine clearance can be used as a predictor of the degree of impairment of pramipexole clearance. Because of the decreased pramipexole clearance in patients with renal disease, lower daily doses should be administered. In addition, because of the increase in pramipexole half-life in these patients, it is possible to administer the drug less frequently. Pramipexole is eliminated extremely slowly in hemodialysis patients, making it virtually impossible to predict plasma concentration versus time profiles in these individuals. Very little pramipexole is eliminated by the dialysis process.

Hepatic impairment would not be expected to have a significant effect on the elimination of pramipexole, although this has not been studied.

Pramipexole clearance is reduced by concomitant administration of drugs that inhibit organic base secretion in the kidneys. Cimetidine, a known inhibitor of basic drug secretion caused a 35% reduction in pramipexole clearance. Probenecid, an agent that primarily inhibits organic acid secretion, but also may slightly inhibit base secretion, caused a 10% decrease in pramipexole clearance. Levodopa, carbidopa, and selegiline did not affect the pharmacokinetics of pramipexole. Pramipexole did not affect the systemic elimination of levodopa or carbidopa, although it did alter the rate of levodopa absorption as indicated by Tmax decreasing from about Drugs that inhibit or induce CYP enzymes would not be expected to alter pramipexole pharmacokinetics. It is possible that pramipexole inhibits CYP enzymes, although this possibility was not investigated by the sponsor.

The sponsor has adequately linked the to be marketed tablets to the tablets used in the clinical trials. The to be marketed tablets are manufactured in Puerto Rico. The dissolution methodology and specification submitted by the sponsor are acceptable.

COMMENTS:

1. Pramipexole elimination is so slow in patients with very severe renal impairment (creatinine CL < 10 mL/min) and in those undergoing hemodialysis that it is virtually impossible to predict the plasma levels upon multiple dosing to these patients. Thus, when writing labeling, the Medical Officer may want to put strong warnings about the use of pramipexole in renally impaired subjects. Please see review of Study 3060, starting on p. A30, for a detailed analysis of renal impairment data.

2. A maximal dose of 1.5 mg/TID was given to patients in the clinical efficacy studies. The table provided in the Renal Impairment subsection of the Dosage and Administration section of labeling (p.11 of this review) assumes that the Agency will decide to limit dosing to this amount within labeling. The third column of this table can be removed if it is decided that a maximum dose will not be given in labeling. Alternatively, the table could be replaced with a sentence instructing BID administration to patients with moderate renal impairment and QD administration to patients with severe renal impairment.

3. In the future, in addition to presenting separate gender analyses for phase I/II studies, the sponsor should also present mean data.

4. Pramipexole may inhibit certain cytochrome P-450 enzymes despite the fact it is not metabolized by these enzymes in vivo. The sponsor is requested to utilize in vitro methodologies to determine whether pramipexole inhibits any of the major P-450 enzymes.

5. The sponsor should analyze their population PK database to determine whether race affects pramipexole pharmacokinetics. In addition, if possible, they should examine whether the population PK database can provide any additional information regarding drug interactions.

RECOMMENDATION: The submission (NDA 20,667) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and has been found to be acceptable. Please convey Comments 1-2 to the Medical Officer, and Comments 3-7 to the firm.

TABLE OF CONTENTS

ABSORPTION

Rate: After administration of pramipexole, the time to reach maximal plasma concentration is approximately 2 hours (0065, 0069).

Extent: Over 90% of a pramipexole dose is absorbed from the GI tract (0030). Over 90% of the absorbed dose reaches systemic circulation (0030). Thus, pramipexole is almost completely bioavailable.

Food effect: Food does not affect the extent of pramipexole absorption, although Tmax is increased by about one hour when the drug is taken with food (0065).

DISTRIBUTION

Volume of distribution: The volume of distribution is about 500 L (cv = 20%), indicating that pramipexole distributes into tissues (0065, 0069, 0047).

Protein and red blood cell binding: Pramipexole is only about 15% bound to plasma proteins, binding primarily to albumin (0030). Pramipexole distributes into red blood cells, having an erythrocyte to plasma ratio of approximately 2 (0030).

METABOLISM AND ELIMINATION

Route: About 90% of a pramipexole dose is excreted in the urine as unchanged drug (0030). About 5% of a dose may be excreted in the urine as metabolites (0030), although no specific metabolites have been identified in the urine or plasma. In some pharmacokinetic studies submitted in the NDA (e.g. 0069, 0047), there appears to be a significant amount of nonrenal clearance (contributing up to 1/3 of the total clearance in study 0069). However, this may be largely due to fact that renal clearance was computed as CLpo multiplied by the fraction of the dose that was not recovered as unchanged drug in the urine. Thus, any drug that was not recovered unchanged in the urine, including drug that was not absorbed from the GI tract, was considered to be eliminated by nonrenal routes. Because it is often technically very difficult to recover 100% of a dose, a majority of what is called nonrenal clearance may simply be due to experimental limitations in accurately quantifying renally excreted drug. This concept is supported by the observation that the calculated nonrenal clearance of pramipexole decreases with renal impairment (0060, see discussion of renal impairment below).

Rate: The clearance and terminal half-life of pramipexole in healthy volunteers are about 400 (cv = 25%) mL/min and 8 h respectively (cv = 20%; 0061, 0065, 0069). These parameters are altered in certain special populations (see below). Pramipexole displays linear kinetics over the labeled dosing range (0047, 0017, 0062). The renal clearance of pramipexole is about three

...s higher than creatinine clearance (130 mL/min), suggesting that pramipexole is extensively secreted via the renal organic cation transport system (0061).

SPECIAL POPULATIONS

General note: Pramipexole displays a moderate amount of intersubject variability (cv= 30% from population analysis). Certain factors such as age and gender account for a portion of this variability (see below), although most of this variability is unpredictable (see graphs from population analysis). Because the dose of pramipexole is titrated up from a low dose for each patient, the effects of covariates such as weight, age and gender should not affect the dosing of the drug. An exception is with patients who have moderate to severe renal impairment because pramipexole clearance is greatly reduced in these individuals. In these patients, a lower starting dose and less frequent dosing may be necessary (see below).

Gender: Pramipexole clearance is about 25% higher in men than in women (0064, 0063, 0047, 0069, population analysis). This gender difference is primarily due to differences in body weight, and is greatly reduced when data is weight normalized.

Age: Pramipexole clearance decreases with age (0069, population analysis). The half-life and clearance are about 40% longer and 30% lower respectively in the elderly (0069). Consistent with this result, creatinine clearance is also know to decrease with age.

Parkinson's Disease patients: Parkinson's disease patients are usually elderly, so they would be expected to eliminate pramipexole more slowly than did the young subjects studied in the phase I/II studies. In addition, a comparison of population pharmacokinetic data (patients) to data obtained in healthy elderly volunteers suggests that the clearance of pramipexole is further reduced, by about 30%, in Parkinson's patients compared to healthy elderly individuals (300 mL/min vs 425 mL/min). The reason for this additional decrease in clearance is unknown, but may be related to the poorer general health of Parkinson's patients. Because the clinical studies were performed in Parkinson's patients, and because doses are titrated for each patient, no dosage adjustments on account of Parkinson's disease are necessary.

Renal impairment: Pramipexole clearance is reduced in renally impaired patients. The clearance of pramipexole was about 75% lower in patients with severe renal impairment (Clcr ≈ 20 mL/min) and about 60% lower in patients with moderate impairment (CLcr ≈ 40 mL/min) compared to healthy volunteers. In patients with varying degrees of renal impairment, pramipexole clearance correlates very well with creatinine clearance (0060). Thus, creatinine clearance can be used as a predictor of the degree of impairment of pramipexole clearance. For example, if creatinine clearance is ½ normal then pramipexole clearance would be expected to be ½ normal. Because of the decrease in clearance in renally impaired patients, a lower or less frequent initial dose is necessary, and the maximal allowable doses must also be adjusted (see review of Study 0060 on page A30 and the OCPB labeling / Dosing and Administration section). Pramipexole is removed extremely slowly in patients who are undergoing dialysis, and it is very

[illegible] to predict plasma drug concentrations in these patients. Very little pramipexole is removed by the dialysis process.

Hepatic impairment: The effect of hepatic impairment on pramipexole pharmacokinetics has not been investigated. Because the drug is predominantly renally excreted, hepatic impairment would not be expected to have a notable effect on pramipexole elimination.

Race: The effect of race on pramipexole kinetics is unknown. The population pk database may contain information about this topic although the sponsor has not yet organized this information. Again, because the dose is titrated, racial differences in pramipexole kinetics, if present, are not likely to be clinically important.

DRUG INTERACTIONS

Effects of drugs on pramipexole renal elimination: Drugs that affect renal filtration or secretion would be expected to affect pramipexole elimination.

Cimetidine (300 mg, Q 6 h), a well characterized inhibitor of the renal organic cation transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (0061).

Probenecid, a drug that primarily inhibits organic anion transport, caused a 10% increase in pramipexole AUC, and half-life was not affected (0061). The small increase in AUC could be due to the fact that probenecid may weakly inhibit cation secretion.

Interactions with other drugs used in Parkinson's disease: *SINEMET* 25/250 (carbidopa/levodopa) administered as a single dose, did not affect pramipexole kinetics. Pramipexole (1.5 mg tid) did not affect the systemic elimination of carbidopa or levodopa, although it did appear to increase the rate of levodopa absorption (Tmax decreased by about 2 hr and Cmax increased by about 600 ng/mL)(0063). The sponsor speculates that this increase in the rate of absorption is due to a decrease in GI transit time caused by pramipexole binding to dopamine receptors in the GI tract.

Selegiline (5 mg Bid) did not have a significant effect on pramipexole elimination when data from male (n=6) and female (n=5) subjects was combined. If the data was analyzed by gender, selegiline appeared to increase pramipexole clearance in women, and decrease pramipexole clearance in men. Due to the small number of subjects studied, it is inappropriate to make conclusions about gender differences based on this study. The effect of pramipexole on selegiline pharmacokinetics was not examined.

Effects of pramipexole on the elimination of other drugs: Pramipexole could potentially cause increases in the concentrations of drugs that are eliminated via renal secretion such as ranitidine, procainamide and quinidine. In addition, although pramipexole is not significantly metabolized by CYP enzymes in vivo, it could nonetheless inhibit these enzymes. The sponsor has not performed in vitro studies to examine the potential for pramipexole to inhibit CYP mediated drug

metabolism.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Pramipexole is rapidly absorbed reaching peak concentrations in approximately 2 hours. The absolute bioavailability of pramipexole is greater than 90% indicating that it is well absorbed and undergoes little presystemic metabolism. Food does not affect the extent of pramipexole absorption, although Tmax is increased by about one hour when the drug is taken with a meal.

Pramipexole is extensively distributed, having a volume of distribution of about 500 L (cv = 20%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood cells as indicated by an erythrocyte to plasma ratio of approximately 2.

Pramipexole displays linear kinetics over the clinical dosing range. Its terminal half-life is about 8 h in young healthy volunteers and about 12 h in elderly volunteers (see Pharmacokinetics in Special Populations). Steady-state concentrations are achieved within 2 days of dosing.

Metabolism and elimination

Urinary excretion is the major route of pramipexole elimination with 90% of a pramipexole dose recovered in the urine, almost all as unchanged drug. Non renal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in plasma or urine. The clearance of pramipexole is approximately 400 mL/min (cv = 25%), which is about three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system.

Special Populations

Because the pramipexole dose is gradually titrated upward, no dosage adjustments based on gender, weight or age are necessary. However, renal insufficiency, which can cause a large decrease in the ability to eliminate pramipexole, may necessitate dosage adjustment (see Renal Insufficiency) .

Gender: Pramipexole clearance is about 30% lower in women than in men, although most of this difference can be accounted for by differences in body weight. There is no difference in half-life between males and females.

Age: Pramipexole clearance decreases with age as the half-life and clearance are about 40% longer and 30% lower respectively in elderly (ages 65 years or older) compared to young healthy volunteers (ages less than 40 years). This difference is likely due to a reduction in renal function with age.

Parkinson's Disease Patients: A cross-study comparison of data suggests that the clearance of pramipexole may be reduced by about 30% in Parkinson's patients compared to healthy elderly volunteers. The reason for this decrease is unknown, but may be related to the poorer general health of Parkinson's patients. Because the dosing regimen is based on clinical efficacy studies performed in Parkinson's patients, no dosage adjustments are necessary.

Pediatric: The pharmacokinetics of pramipexole in the pediatric population has not been evaluated.

Race: The influence of race on pramipexole pharmacokinetics has not been evaluated.

Hepatic Insufficiency: The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated. However, because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have large effect on pramipexole elimination.

Renal Insufficiency: The clearance of pramipexole was about 75% lower in patients with severe renal impairment (Clcr ≈ 20 mL/min) and about 60% lower in patients with moderate impairment (CLcr ≈ 40 mL/min) compared to healthy volunteers. A less frequent starting dose is recommended in these patients (see Dosage and Administration). In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed in the dialysis process. Caution should be exercised when administering pramipexole to patients with renal disease.

Drug Interactions

Carbidopa/Levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (n=10). Conversely, pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa Cmax by about 40% and a decrease in Tmax from hr.

Selegiline: In healthy volunteers (n=11), selegiline did not influence the pharmacokinetics of pramipexole.

Cimetidine: Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (n=12).

Probenecid: Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter did not notably influence pramipexole pharmacokinetics (n=12).

Other drugs eliminated via renal secretion: Drugs that interact with the renal organic cation

transport system including ranitidine, procainamide, and quinidine could potentially inhibit pramipexole elimination. Likewise, pramipexole could potentially inhibit the elimination of these drugs.

CYP Interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo. The ability of pramipexole to inhibit CYP enzymes has not been examined.

Patients with renal impairment:

Pramipexole Dose in the Renally Impaired		
Renal status	Starting Dose (mg)	Maximum Dose (mg) ?
Normal-mild impairment (Creatinine CL > 60 mL/min)	0.125 TID	1.5 TID
Moderate impairment (Creatinine CL = 35-59 mL/min)	0.125 BID	1.5 BID
Severe impairment (Creatinine CL = 15-34 mL/min)	0.125 QD	1.5 QD
Very severe impairment (Creatinine CL < 15 mL/min and hemodialysis patients)	WARNING	

APPEARS THIS WAY
ON ORIGINAL

Biopharm Days June 18, 1996

/S/

Robert Z. Harris, Ph.D.
Division of Pharmaceutical Evaluation I

FT initialed by Raman Baweja, Ph.D. /S/

cc: NDA 20667, HFD-120, HFD-860 (Harris, Baweja, Malinowski), HFD-340 (Viswanathan), Chron, Reviewer, Drug (Clarence Bott HFD-870, PKLN RM. 13B-31). HFD-19 (FOI) .

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-667 Submission Date: August 1, 1996

Name, Strength(s), and Formulation: **Pramipexole 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg Immediate-Release Tablets For Oral Administration.**

Sponsor: The Upjohn Company
Kalamazoo, MI

Indication: Parkinson's Disease

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: Review of Population PK Analysis

REVIEW OF POPULATION PK ANALYSIS

This submission contains an updated study report for the population pharmacokinetic (PK) analysis of sparse plasma data that were obtained from patients who participated in Phase III clinical trials of pramipexole (Protocols M/2730/0001, M/2730/0004, and M/2730/0010).

Method:

(**Attachment 1** presents the detailed population PK method used in the analysis of pramipexole data).

Briefly, data obtained from 484 patients with pramipexole concentrations ranging from ng/mL at doses ranging from mg/day (given TID) were used in the analysis. The patient population in the database ranged in age from years, in weight from kg. Sixty-five percent of the population was male and 35 % female. Ninety-seven percent was white, 1.3 % black, and 1.7 % classified as 'other'. Creatinine clearance values ranged from mL/min. Figure 1 shows the frequency distribution of pramipexole concentrations and sampling times. Figure 2 shows the frequency distribution of age, weight, and creatinine clearance values.

Table 1 shows the number of patients and pramipexole samples for each study for each medication coadministered with pramipexole. The medications included in the analysis were selegiline, trihexyphenidyl, cationic and anionic transport system medications, estrogen, benztropine, levodopa, and amantadine.

Using NONMEM computer program, a 1-compartment open model with first-order absorption and elimination was found to best describe the steady-state plasma concentration/time data of pramipexole. Interindividual variability (% CV in Cl and Ka) variability was modeled using the proportional error model. % CV in Vd could not be estimated due to numerical difficulties within NONMEM. Residual variability was modeled using the proportional error model.

Basic Model:

$$Cl = \Theta_{Cl} \cdot (1 + \eta_j^{Cl})$$
$$Vd = \Theta_{Vd}$$
$$Ka = \Theta_{Ka} \cdot (1 + \eta_j^{ka})$$

Parameter estimates, standard error of the estimates (%SEM), and interindividual and residual variabilities for the basic structural model (no covariates added) are shown in Table 2.

As pramipexole is eliminated almost entirely unchanged by the kidneys, creatinine clearance was added to the basic model as a linear predictor of pramipexole clearance. In order to obtain a more precise and more meaningful estimate for the intercept parameter, Θ_{Cl}, creatinine clearance values were centered by subtracting the minimum CrCl value (25.6 mL/min) for this population from each observation.

Table 3 shows the parameter estimates, % SEM, interindividual variability, and residual variability after accounting for creatinine clearance. Addition of CrCl decreased interindividual variability by 9 % from the basic model.

Basic Model with creatinine clearance:

$$Cl = \Theta_{Cl} + \Theta_{Cl}^{CrCl} (CrCl_j - 25.6) \cdot (1 + \eta_j^{Cl})$$
$$Vd = \Theta_{Vd}$$
$$Ka = \Theta_{Ka} \cdot (1 + \eta_j^{ka})$$

Various covariates (demographics and comedications) were then tested in the above model (i.e. basic model with CrCL) to determine their effect on the oral clearance of pramipexole. Age and weight were modeled as linear continous variables. Gender, race, obesity, comedications were modeled as dichotomous variables. The results of this modeling are presented in Tables 4-7. Covariates having significant effect on pramipexole Cl were incorporated in the final model (Table 8).

Results: (See also Attachment 1)

Table 4 shows the effect of demographics (weight, age, gender, race, and obesity) on the oral clearance of pramipexole. Gender, race, and obesity were found to be significant covariates affecting pramipexole Cl. Backward elimination of these covariates from the model (Table 5) showed that only gender and race affects pramipexole Cl.

The effect of concomitant medications on the oral clearance of pramipexole is shown in Tables 6. Initially, amantadine, drugs that are secreted by the cationic transport system (cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine), and drugs that are secreted by the anionic transport system (cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide), were found to be significant covariates affecting pramipexole Cl. Backward elimination of these comedications from the model (Table 7) showed that amantadine and drugs that are secreted by cationic transport system were significant covariates affecting pramipexole Cl.

The **final model** describing the population Pk model of pramipexole is as follows:

$$Cl = \Theta_{Cl} + \Theta_{Cl}^{CrCl} (CrCl_j - 25.6) * (1 + SEX * \Theta_{CL}^{SEX}) * (1 + RACE1 * \Theta_{Cl}^{RACE1}) * (1 + RACE2 * \Theta_{Cl}^{RACE2}) * (1 + X_j * \Theta_{Cl}^{X}) * (1 + \eta_j^{Cl})$$

$$Vd = \Theta_{Vd}$$

$$Ka = \Theta_{Ka} \cdot (1 + \eta_j^{ka})$$

where X_j = concomitant medication in the jth patient.

Final parameter estimates (%SEM), interindividual variability, and residual variability are shown in Table 8 (Attachment 1). Figure 3 shows the scatterplots of predicted versus observed pramipexole concentrations, and weighted residuals versus predicted pramipexole concentration for the final PK model including patients demographics and concomitant medications.

For a white male patient with normal renal function (CrCl=120 mL/min) and not taking any comedication, the oral clearance of pramipexole would be:

$$Cl = 480 \text{ mL/min}$$

which is close to the value obtained in healthy volunteers, 400 mL/min.

In conclusion, population PK modeling of steady state plasma concentration data revealed that the oral clearance of pramipexole increased by 17 % in black patients and by 28 % in patients classified as 'Other' compared to white male patients. Drugs which are secreted by the cationic transport system decreased the oral clearance of pramipexole by 18 %. The effect of these covariates may not be clinically important as the dose of the drug is individually titrated to response.

COMMENTS

Reference is made to the labeling provided for pramipexole in the OCPB review of July 26, 1996:

1. Under **Special Populations/**Race (on Page 10), the statement: "The influence of race on pramipexole pharmacokinetics has not been evaluated" should be written as:

   "Population PK analysis revealed that oral clearance of pramipexole was 17 % higher in black male patients and was 28 % higher in male patients classified as 'Other' than in white male patients"

2. Under **Drug Interactions** on page 10, the following statement should be added:

   "Amantadine: Population PK analysis showed that amantadine does not alter the oral clearance of pramipexole (n=54 patients)."

3. Under **Drug Interactions** on page 10, the statement, "Other drugs eliminated via renal secretion: Drugs that interact with the renal....." should be modified to the following:

   "Other Drugs Eliminated Via Renal Secretion: Population PK analysis revealed that coadministration of drugs that are secreted by the cationic transport system (cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreased the oral clearance of pramipexole by 18 % while those secreted by the anionic transport system (cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) had no effect on the oral clearance of pramipexole.

COMMENT (To the Clinical Division):

New additional information from population PK analysis relates to race and drug interactions issues as mentioned in Comments 1-3 above. The technical aspects of the above Comments should be included in the labeling for pramipexole.

APPEARS THIS WAY

/S/

Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT initialed by R. Baweja, Ph.D. /S/ - 10/25/96

cc: NDA # 20-667 (Suppl.), HFD-120, HFD-860 (Ibrahim, Baweja, Malinowski), Chron, Drug, and Reviewer Files (Clarence Bott, HFD-870, Parklawn, Rm 13B-31).

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,667
Pramipexole 0.125, 0.25, 1.0, 1.25 and 1.5 mg Tablets
Submission Dates: January 6, 1997; January 7, 1997;
January 24, 1997; January 27, 1997
Indication: Parkinson's Disease
Reviewer: Raman Baweja, Ph.D.

Pharmacia and Upjohn
Kalamazoo, MI 49001

RETURN
APR 3 0 1997

REVIEW OF RESPONSES TO APPROVABLE LETTER

An Approvable letter was sent to the sponsor on December 23, 1996 for their drug, pramipexole, which is indicated for the treatment of Parkinson's disease. From an OCPB stanpoint the two main items in the letter were labelling and the sponsor's acceptance of the dissolution method and specification. The sponsor has now responded to the approvable letter and the review below will address their responses.

I. Labelling:

(A) Essentially the sponsor has accepted entire portions of OCPB's version of labelling that was sent to them in the approvable letter of December 23, 1996. Current labelling is attached to this review as Appendix I. There are two issues that need to be discussed, viz., Drug Interactions, and Dosing and Administration to the very severely renally impaired group. These follow:

(B) In the Drug Interactions section of labelling the sponsor was requested to expand the subsection on CYP Interactions. More specifically, it had been mentioned in the Agency's labelling that ...."The ability of Pramipexole to inhibit CYP enzymes has not been examined". It should be mentioned that pramipexole is about 90 % recovered in the urine as unchanged drug, and therefore, the issue was not whether it would be a substrate for CYP enzymes; instead the issue was if pramipexole would inhibit CYP enzymes.

The sponsor mentions that Pramipexole does not inhibit enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Further, the drug will not inhibit CYP2D6. All this is correct and can be placed in the labelling. Substantiation for this is provided in Appendix II which shows the percent inhibition of CYP P450 activity by various concentrations of pramipexole. These CYP P450 isoform activities were refractory to inhibition by pramipexole in its concentrations of 1μM and 10 μM (relevant concentrations), and 100 μM (very high and irrelevant concentration).
Appendix II also shows the Dixon plot of pramipexole's inhibition of debrisoquin 4-hydroxylation (CYP 2D6). Inhibition of CYP2D6 was observed with an apparent Ki of 30 μM indicating that pramipexole will not inhibit this enzyme even after administration of the highest recommended clinical dose of 1.5 mg t.i.d.

Overall then, it can be concluded that pramipexole will not inhibit the CYP P450 enzymes and this information can be placed in the labelling.

(C) Dosage and Administration section/Patients with Renal Impairment: A table was made in the labelling for dosing recommendations to this population. The sponsor has accepted these dosing recommendations as they pertain to the normal-mild group (starting dose: 0.125 mg tid), the moderately impaired group (starting dose: 0.125 mg bid), and the severe group (starting dose: 0.125 mg qd). However, it is with regard to the 'very severe impairment group (Creatinine Clearance < 15 ml/min and hemodialysis patients)' where a change has been made by the sponsor. We had written that for this group this be a "Warning"; instead the sponsor has written -- 'the use of Mirapex is not recommended.' The statement from the sponsor appears to be the stronger of the two, and the Medical Officer is requested to look into this.

Comment to the Clinical Division: OCPB accepts the labelling as provided by the sponsor in their latest response. The Medical Officer is requested to note Item I (C) above -- Dosing in the 'very severely renally impaired group'.

/S/

APPEARS THIS WAY
ON ORIGINAL

Raman Baweja, Ph.D. 4/28/97.
Team Leader
DPE I

RD/FT Initialed by M.Mehta, Ph.D. /S/ 4/30/97

cc: NDA 20,667, HFD-120, HFD-860 (Baweja, Mehta, Malinowski), Drug files (Barbara Murphy, Central Documents Room)

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