CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20658

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-658

Submission Dates:
December 29, 1995
July 16, 1996
September 25, 1996

Generic Name, Strength(s), and Formulation: Ropinirole Hydrochloride (HCl) — 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, and 5.0 mg (As Free Base) Immediate-Release Film-Coated Tablets for Oral Administration.

Brand Name: Requip™

Indication: Parkinson's Disease

Sponsor: SmithKline Beecham Pharmaceuticals
King of Prussia, PA

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: Original NDA

SYNOPSIS

Ropinirole HCL (Requip™) is a novel D_2-dopamine receptor agonist indicated for the treatment of Parkinson's disease. The sponsor is proposing to market the product as 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, and 5.0 mg immediate-release, film-coated tablets. The clinical and to-be-marketed formulations were identical. The recommended starting dose is 0.25 mg administered t.i.d. (0.75 mg/day). Patients are gradually titrated up to 1 mg t.i.d. (3 mg/day). The maximum dose described in labeling is 8 mg t.i.d. (24 mg/day). The sponsor mentions that ropinirole can be administered as monotherapy or in combination therapy with levodopa/carbidopa.

Ropinirole is rapidly absorbed, reaching peak concentrations within 1.5 hours. Absolute bioavailability is and relative bioavailability is Food does not affect the extent of ropinirole absorption, although its Tmax is increased by 2.5 hours when the drug is taken with a meal.

Ropinirole is widely distributed throughout the body with a population apparent volume of distribution value of 525 L (7.5 L/kg; CV= 32 %). Binding of ropinirole to plasma

proteins is 40 % and is independent of drug concentration. Ro
distributed between blood and plasma having a blood-to-plasma
1.1.

Ropinirole is extensively metabolized by the liver (figure 1).

Population oral clearance of ropinirole is 47 L/hr (CV = 45 %). Elimination half-life is 6±2 hours in patients.

Ropinirole displays linear kinetics over 1-8 mg t.i.d. doses and this covers the therapeutic dosing range for the drug. Steady-state is expected to be achieved within 2 days of dosing and accumulation of the drug upon multiple dosing is predictive from single dosing.

Oral clearance of ropinirole was reduced by 30 % in patients over 65 years of age compared to those below 65 years of age.

Population PK analysis showed that gender is not an important factor affecting the oral clearance of ropinirole.

The effect of race on the pharmacokinetics of ropinirole was not evaluated because more than 95% of the patients in the population PK database were Caucasians.

The effect of cigarette smoking on the oral clearance of ropinirole was also not evaluated as only 2% of the population in the PK database were smokers. Smoking is expected to increase the oral clearance of ropinirole since , an isozyme known to be induced by smoking, is involved in the metabolism of ropinirole.

Population PK analysis revealed that the degree of severity of Parkinson's disease (stages 1-4 of Hoehn and Yahr classification), did not cause any change in the oral clearance of ropinirole.

Renal impairment had no effect on the pharmacokinetics of ropinirole in patients with moderate renal function (CLcr=30-50 mL/min) compared to mild to normals (CLcr > 50 mL/min).

The effect of hepatic impairment on the pharmacokinetics of ropinirole has not been studied. It is expected that the elimination of the drug may be reduced in hepatically impaired patients. Doses of ropinirole should be titrated carefully in patients with hepatic disease.

Population PK analysis also revealed that there was no change in the oral clearance of ropinirole in patients with concomitant diseases such as hypertension, depression, osteoporosis/arthritis, and insomnia, compared to patients with Parkinson's disease only.

Administration of domperidone (20 mg) one hour before dosing with ropinirole (0.8 mg) did not alter the pharmacokinetics of ropinirole.

Coadministration of carbidopa+L-dopa (Sinemet®, 10/100 mg b.i.d.) with ropinirole (2.0 mg t.i.d.) had no effect on the steady state pharmacokinetics of ropinirole. Ropinirole in turn increased mean steady-state Cmax of L-dopa by 20 % while its AUC was unaffected.

Coadministration of estrogens (mainly ethinylestradiol) reduced the oral clearance of ropinirole by 35 %.

Commonly prescribed drugs in Parkinson's disease, e.g. selegiline, amantadine, tricyclic antidepreasants, benzodiazepines, ibuprofen, thiazides, and anticholinergics did not affect the oral clearance of ropinirole.

Coadministration of ropinirole (2.0 mg t.i.d) with digoxin (0.125-0.25 mg QD) did not alter the steady-state pharmacokinetics of digoxin.

At 1-8 mg t.i.d. doses, individual predicted steady-state plasma concentrations of ropinirole were about 2-fold higher in Responders than in Nonresponders.

The following dissolution methodology and specification are recommended for all strengths of Requip™ tablets:

Comments

(To the Medical Reviewer)

1. Pharmacokinetic labeling changes were made in the CLINICAL PHARMACOLOGY/Pharmacokinetics and PRECAUTIONS/Drug Interactions sections (See Appendix A).

(To be sent to the firm)

2. The sponsor is requested to adopt the following dissolution methodology and specification for all strengths of ropinirole HCL tablets:

   Apparatus:
   Speed:
   Medium:
   Volume:
   Specification:

3. The firm is requested to incorporate pharmacokinetic labeling as outlined in Appendix A.

RECOMMENDATION

The NDA # 20-658, that was filed for Ropinirole hydrochloride tablets on December 29, 1995, has been reviewed and has been found to be acceptable for meeting OCPB requirements. The sponsor should adopt dissolution methodology and specification as outlined in Comment 2 and incorporate pharmacokinetic labeling as outlined in Appendix A.

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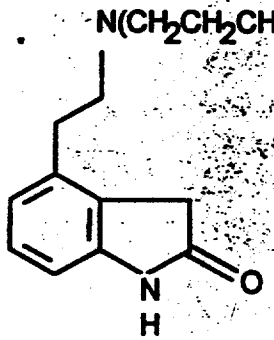
BACKGROUND

Requip™ (ropinirole HCL, SK&F 101468) is a novel D_2-dopamine receptor agonist.

PHYSICO-CHEMICAL PROPERTIES:

Ropinirole HCL is a white to pale greenish yellow powder with a melting range of 243-250° and a solubility of 133 mg/mL in water. The pKa are 9.7 for the protonated tertiary amino group and 12.4 for the indol-2-one group.

STRUCTURAL FORMULA:



Ropinirole hydrochloride

CHEMICAL FORMULA:

Ropinirole is the hydrochloride salt of 4-[2-(Dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one and has the empirical formula of $C_{16}H_{25}N_2OCL$. The molecular weight is 297 (260 as the free base).

INDICATION AND USAGE:

Requip™ is indicated in the symptomatic treatment of Parkinson's disease as primary therapy and as adjunctive treatment to levodopa/carbidopa.

HOW IT IS SUPPLIED:

Requip™ will be available as pentagonal, film-coated, immediate-release tablets containing ropinirole HCL equivalent to ropinirole base, 0.25 mg, 0.5 mg, 1 mg, 2 mg, or 5 mg for oral administration.

RECOMMENDED DOSAGE AND ADMINISTRATION (FIRM'S):

Requip™ should be taken three times daily (t.i.d.). The recommended starting dosage is 0.25 mg t.i.d. (0.75 mg/day). Based on individual patient response, dose should then be titrated with weekly increments of 0.25 mg per dose to 1 mg t.i.d. (3 mg/day) for 4 weeks. After week 4, if necessary, dosage may be increased by 0.5 mg to 1.0 mg per dose on a weekly basis. If sufficient symptomatic control is not achieved or maintained, Requip™ may be further titrated until an acceptable therapeutic response is established, may be up to 8 mg t.i.d. (24 mg/day). It is recommended that ropinirole be taken with meals to improve the patient's gastrointestinal tolerance by minimizing the risk of nausea and vomiting.

MANUFACTURER AND MANUFACTURING SITE:

Ropinirole HCL tablets will be manufactured, packaged, tested for release and for stability at SmithKline Beecham Pharmaceuticals in the United Kingdom.

SUMMARY OF BIOAVAILABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS

Except for the absolute/relative bioavailability study and the domperidone interaction study which were conducted in healthy volunteers, all other studies were conducted in patients with Parkinson's disease.

I. ABSORPTION/BIOAVAILABILITY

Ropinirole is rapidly absorbed reaching peak plasma concentrations within 1.5 hours after dosing (Study # CPMS-063).

Absolute Bioavailability: In healthy volunteers, the absolute bioavailability of ropinirole was % (Study # CPMS-061).

Relative Bioavailability: Relative bioavailability of ropinirole from a tablet compared to an oral solution was % (Study # CPMS-061).

Food Effect: A multiple dose food study in 12 patients showed that there was no effect of food on the extent of absorption of ropinirole though its mean Tmax was increased by 2.5 hours (Study # CPMS-063).

II. DISTRIBUTION

Volume of Distribution: A population estimate value of 525 L (7.5 L/kg) was obtained for the apparent volume of distribution (Vd/F); interpatient variability (% CV) was 32 % and this could be explained on the basis of differences in weight.

In vitro Protein Binding and Blood-To-Plasma Ratio (Report #: BP004BA): Ropinirole is about 40 % bound to human plasma proteins at concentrations ranging from 9 ng/mL to 3940 ng/mL which covers the therapeutic range for the drug. Ropinirole distributes equally between blood and plasma having a blood-to-plasma partition ratio of approximately 1.1 at concentrations ranging from 14 ng/mL to 6400 ng/mL.

III. METABOLISM

In Vivo: Ropinirole is extensively metabolized by the liver (Figure 1).

In Vitro:

IV. ELIMINATION

Mass Balance: Excretion of radioactivity was essentially complete as 91 % of total radioactivity was recovered over 9 days following oral administration of 0.6 mg (50 μCi) ^{14}C-ropinirole to 4 healthy male volunteers (Study # CPMS-011). Radioactivity was predominantly seen in urine (88±3%) with only 3±1% in feces. Less than 10 % of the administered dose was excreted as unchanged drug in urine. The major metabolite identified in urine was the N-despropyl metabolite of ropinirole which represented about 40 % of the administered dose. The carboxylic acid metabolite and the glucuronide of the hydroxy metabolite each represented about 10 % of the administered dose.

Clearance and Half-Life: A population estimate value of 47 L/hr (0.7 L/hr/kg) was obtained for the oral clearance of ropinirole (CL/F). Interpatient variability (% CV) was 45 % which could be explained on the basis of differences in age and in the use of estrogens by patients. Elimination half-life of ropinirole in patients is 6±2 hours (Study #CPMS-057).

V DOSE PROPORTIONALITY

Ropinirole exhibits linear pharmacokinetics over the single dose range of 0.2-12 mg (Studies # CPMS-018 and CPMS-057). From population PK analysis, it is seen that the drug displays linear kinetics over 1-8 mg t.i.d. doses.

VI MULTIPLE DOSE KINETICS

With an elimination half-life of 6 hours, steady-state levels of ropinirole are expected to be achieved within 2 days of dosing. Accumulation upon multiple dosing is predictive from single dosing.

VII. SPECIAL POPULATIONS

Age: Oral clearance of ropinirole was reduced by 30 % in patients above 65 years of age compared to those below 65 years of age, both groups having been matched for weight (Population PK Analysis). Dosage adjustment is not necessary in the elderly as the dose for ropinirole is individually titrated to clinical response.

Gender: Female patients had comparable oral clearance as male patients (Population PK Analysis).

Race: The effect of race on the pharmacokinetics of ropinirole has not been evaluated. More than 95 % of the patients were Caucasians in the population PK database.

Cigarette Smoking: The effect of smoking on ropinirole clearance has also not been evaluated since only 2 % of the population (i.e 3 patients) in the PK database were smokers. Smoking is expected to increase the oral clearance of ropinirole as CYP1A2, an isozyme known to be induced by smoking, is involved in the metabolism of the drug.

Renal Impairment: Less than 10 % of an administered dose is excreted as unchanged drug in urine. Renal impairment did not affect the oral clearance of ropinirole (Population PK Analysis); 0.60 L/hr/kg in patients with CrCL values > 50 mL/min *versus* 0.63 L/hr/kg in patients with CrCL values 30-50 mL/min. Dosage adjustment is not necessary in patients with renal impairment having CrCL values of 30-50 mL/min.

Hepatic Impairment: The pharmacokinetics of ropinirole have not been studied in hepatic patients. Because the drug is extensively metabolized by the liver (< 10 % excreted unchanged in urine), it is expected that patients with hepatic impairment may have higher plasma levels and lower clearance of ropinirole than patients with normal hepatic function. Since ropinirole dosing is to be titrated to clinical response, dosage adjustment may not be necessary in hepatic patients but the drug should be titrated with caution in these patients.

Parkinson's Disease Stage: Population PK analysis revealed that the degree of severity of Parkinson's disease (stages 1 to 4 of Hoehn and Yahr classification), did not cause any change in the oral clearance of ropinirole.

Other Diseases: No change was observed in the oral clearance of ropinirole in patients with concomitant diseases such as hypertension, depression, osteoporosis/ arthritis, and insomnia, compared to patients with Parkinson's disease only (Population PK Analysis).

IX. DRUG INTERACTIONS

Effect of Other Drugs on Ropinirole:

Domperidone: Administration of domperidone (20 mg) one hour before dosing with ropinirole (0.8 mg) did not alter the pharmacokinetics of ropinirole in 9 healthy volunteers (Study # CPMS-010).

Domperidone is usually taken before ropinirole to block the peripheral dopaminergic effects of the drug (viz. nausea, postural hypotension).

L-Dopa: Coadministration of carbidopa+L-dopa (viz., Sinemet®, 10/100 mg b.i.d.) with ropinirole (2.0 mg t.i.d.) had no effect on the steady state pharmacokinetics of ropinirole (n=28 patients) (Study # CPMS-062).

Estrogens: Coadministration of estrogens (mainly ethinylestradiol; intake 0.6-3 mg over 4-month to 23-year period) reduced the oral clearance of ropinirole by 35 % in 16 patients (Population PK Analysis). Dosage adjustment may not be needed for ropinirole in patients on estrogen therapy but these patients should be carefully titrated with ropinirole.

Commonly prescribed drugs in Parkinson's disease, e.g. selegiline, amantadine, tricyclic antidepressants, benzodiazepines, ibuprofen, thiazides, and anticholinergics did not affect the oral clearance of ropinirole (Population PK Analysis).

Effect of Ropinirole on Other Drugs:

L-Dopa: Ropinirole as 2.0 mg t.i.d. oral administration increased mean steady-state Cmax of L-dopa by 20 % while its AUC was unaffected (n=23 patients) (Study # CPMS-062).

Digoxin: Coadministration of ropinirole (2.0 mg t.i.d.) with digoxin (0.125-0.25 mg QD) did not alter the steady-state pharmacokinetics of digoxin in 10 patients (Study # CPMS-016).

Ongoing Drug Interaction Studies: Two studies are ongoing to examine the

X. CONCENTRATION-EFFECT RELATIONSHIP

At 1-8 mg t.i.d. doses, individual predicted steady-state plasma concentrations of ropinirole were about 2-fold higher in Responders (25 ng/mL) than in Nonresponders (Population PK Analysis).

ANALYTICAL

In the studies submitted, the sponsor utilized a method to measure plasma concentrations of ropinirole. The method was adequately validated.

FORMULATIONS (See APPENDIX II)

There was no change between the clinical formulation and the to-be-marketed formulation, and therefore, no equivalency links were necessary.

DISSOLUTION

Ropinirole hydrochloride is freely and rapidly soluble in water (133 mg/mL). During the development of the dissolution method, water and 0.1N HCL were examined as dissolution media. Water was found to be unsuitable as the rate of dissolution was extremely slow, e.g., dissolved in 30 minutes. This low dissolution in water was thought to be due to a physical interaction between ropinirole and the formulation excipients or due to poor wetting effect. Dissolution in 0.1N HCL was found to be unsatisfactory due to a peak splitting effect during analysis of the solutions by

The sponsor has selected citrate buffer at pH 4.0 as the dissolution medium for ropinirole tablets. Dissolution testing was performed using

Dissolution data were submitted for the 0.25, 1.0 and 5 mg strengths for stability batches (No. 249850, 249910, and 249970) as well as for pivotal clinical batches (No.: 1, 18, 19, 27, and 28). Dissolution from the 0.25, 1.0, and 5 mg tablets was very for individual tablets % of ropinirole HCL had dissolved in 15 minutes (See also APPENDIX III). Similarly, dissolution from the 0.5 mg and 2.0 mg tablets was also very

The dissolution method and specification proposed by the sponsor are as follows:

Apparatus:
Speed:
Medium:
Volume:

Specification:

Based on the individual data submitted which clearly indicate the rapidity with which these tablets go into citrate solution, the following dissolution methodology and specification are recommended by the Agency for all strengths of ropinirole HCL tablets (0.25, 0.5, 1.0, 2, and 5 mg):

Apparatus:
Speed:
Medium:

Specification:

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

ClinPharm/Biopharm Briefing on October 8, 1996

RD/FT initialed by R. Baweja, Ph.D. R. Baweja 10/15/96.

cc: NDA # 20-658 (Orig.), HFD-120, HFD-860 (Ibrahim, Baweja, Malinowski), HFD-340 (Viswanathan), Chron, Drug, and Reviewer Files (Clarence Bott, HFD-870, Parklawn, Rm 13B-31).

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-658

Submission Date: March 28, 1997

Generic Name, Strength(s), and Formulation: **Ropinirole Hydrochloride (HCl) – 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, and 5.0 mg (As Free Base) Immediate-Release Film-Coated Tablets for Oral Administration.**

Brand Name: **Requip™**

Indication: Parkinson's Disease

Sponsor: SmithKline Beecham Pharmaceuticals
King of Prussia, PA

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: (1) Review of Response to Approvable Letter
(2) Review of Two Drug Interaction Studies

This submission is in response to the approvable letter of January 2, 1997 for Requip™ tablets.

Attachment 1 is the **updated** version of OCPB's pharmacokinetic labeling for Requip™ tablets based on responses received from the sponsor.

In addition, the sponsor has submitted two study reports to investigate the potential for drug interactions between theophylline and ropinirole, and between ciprofloxacin and ropinirole:

Theophylline/Ropinirole: Coadministration of theophylline as 300 mg BID oral doses with ropinirole (2 mg TID), did not alter the steady state pharmacokinetics of ropinirole in 12 patients with parkinson's disease. In turn, ropinirole (2 mg TID) did not alter the single-dose kinetics of theophylline infused as 5 mg/kg over 30 minutes. This indicates that theophylline and ropinirole, both of which are substrates of CYP1A2, do not compete for this isozyme. Details of the study protocol are shown in Attachment 2.

Ciprofloxacin/Ropinirole: Ciprofloxacin (500 mg BID) increased the mean AUC and Cmax of ropinirole (2 mg TID) by 90 % and 60 %, respectively (n=12 patients). This indicates that ciprofloxacin, a known inhibitor of , inhibits the metabolism of ropinirole, a substrate for this isozyme. Details of the study protocol are shown in Attachment 3. Effect of ropinirole on the pharmacokinetics of ciprofloxacin has not been

studied.

Attachment 4 is the firm's response to FDA proposed dissolution methodology and specification.

In the review of October 15, 1996, it was recommended that the sponsor adopt the following dissolution methodology and specification for all strengths of ropinirole HCL tablets (0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, and 5.0 mg):

Apparatus:
Speed:
Medium:
Volume:
Specification:

The sponsor proposes to retain (See Also Attachment 4):

(1) The original NDA dissolution medium volumes of 500 mL for tablet strengths below 0.1 mg and 900 mL for tablet strengths of 1.0 mg and above until sufficient data are generated to support the use of 500 mL as the dissolution medium for all tablet strengths.

(2) The original NDA dissolution specification of % in 30 minutes as all samples were tested for release at this time point.

Based on the dissolution data submitted in the original NDA for stability batches and biobatches which showed a very rapid and complete dissolution of ropinirole HCl tablets in 15 minutes and on the fact that ropinirole is freely and rapidly soluble in water (133 mg/mL), the following dissolution methodology and specification are recommended for all strengths of ropinirole HCL tablets:

Apparatus:
Speed:
Medium:
Volume:
Specification:

COMMENTS:

1. The sponsor is requested to adopt the following dissolution methodology and specification for all strengths of ropinirole HCL tablets:

   Apparatus:
   Speed:
   Medium:
   Volume:
   Specification:

2. The sponsor is requested to incorporate OCPB's pharmacokinetic labeling as outlined in Attachment 1 (pages 5-7).

RECOMMENDATION:

Please forward Comments 1 and 2 to the firm.

Safaa Ibrahim

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

RD/FT initialed by R. Baweja, Ph.D. R. Baweja 7/23/97

cc: NDA 20-658 (Suppl.), HFD-120, HFD-860 (Ibrahim, Baweja, Malinowski), and Drug files (Barbara Murphy, Central Documents Room)

Attachment 1

(Updated Version of OCPB's Pharmacokinetic Labeling)