CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-659/S-13
20-680/S-11

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDA:	20,659; Supplement 13
Submission Date:	5/26/98
Drug:	Ritonavir
Sponsor:	Abbott Laboratories Abbott Park, IL
Type of Submission:	Proposed Labeling Change Norvir®™ (ritonavir capsules), (ritonavir oral solution)
OCPB Reviewer:	Joette M. Meyer, Pharm.D.
OCPB Log-in Date:	6/9/98

III. BACKGROUND/RATIONALE

Ritonavir is metabolized by the cytochrome P-450 enzyme system. CYP3A is the major subfamily involved in metabolism, although CYP2D also contributes to formation of the isopropylthiazole metabolite. Ritonavir is also capable of auto-induction of CYP3A, glucuronosyl transferase, CYP1A2, and possibly CYP2C9. In addition to being a substrate and autoinducer, ritonavir is a potent inhibitor of CYP3A, with lesser effects on 2D6.

During the later phases of clinical development of ritonavir, these effects became known after *in vitro* experiments. However, extrapolation of this *in vitro* information to *in vivo* conditions was not reliable. Therefore, when the ritonavir label was originally written it classified all the medications "contraindicated" that had narrow therapeutic indices. These medications were those which could result in serious or life-threatening adverse events if their concentrations became elevated.

In the past two years much new clinical information has been collected regarding the potential for ritonavir to cause drug-drug interactions. In addition, the ability to predict drug-drug interactions has grown. Therefore, in the proposed labeling change, 14 of the 25 contraindicated medications are being removed from the list. In addition, this section has been revised to correspond more closely with the class labeling for protease inhibitors. The sponsor proposes that only medications that are highly dependent on CYP3A for clearance will remain on the contraindicated list. The sponsor has reviewed all ritonavir reports containing mention of any concomitant drug, which was also one of the 14 drugs in question. This was done to assure that deletion of these medications from the contraindicated section of the label would not compromise patient safety.

ketoconazole, indinavir, and methadone. Information regarding the results of these studies has also been added to the text of the "Drug Interactions" section. Also, a statement regarding the dosing of ritonavir and saquinavir in combination has been added to the "Dosage and Administration" section. The sponsor states that the information in this statement was previously discussed with the FDA. Proposed updated data on safety and efficacy was obtained from recently submitted clinical trial study reports.

II. RECOMMENDATION

The proposed labeling changes have been reviewed and found to be acceptable pending some revisions. The comments in Section III have been incorporated into a draft label and forwarded to the sponsor.

III. LABELING COMMENTS

CLINICAL PHARMACOLOGY. Special Populations. Drug-Drug Interactions. Table 2.

1. The table indicates no change in ritonavir AUC or C_{max} when given with ketoconazole.

   Based on data submitted in IND 43,718, Serial No. 400, the AUC and C_{max} of ritonavir increased by 18% and 10%, respectively. The table was modified to reflect these values.

   In addition, the C_{max} information for rifampin [↓ 25% (-5, 46%)] and the AUC information for alprazolam [redacted] was not deleted from the table.

2. Footnote number 1 for the table indicates doses (of indinavir) on Day 15 were administered after a 15% fat breakfast (757 kcal) and 32% fat dinner (815 kcal).

   Based on data submitted in IND 43,718, Serial No. 425, the doses were administered on [redacted] with a 15% fat breakfast and 32% fat dinner. The footnote was modified.

[redacted]

Joette M. Meyer 5/17/99

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Concurrence:

Kellie Schoolar Reynolds 5/17/99

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cc: HFD-530: /NDA 20-659; Supplement 13
/MO/StrubleK
/CSO/LyncheS
HFD-880: /BiopharmTL/ReynoldsK
/Biopharm/MeyerJ
/DPEIII
CDR: /MurphyB

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW
TEAM LEADER ADDENDUM

NDA: 20-659, S-013; and 20-680, S-011
DRUG: Ritonavir (NORVIR®)
FORMULATIONS: oral solution and capsules
APPLICANT: Abbott Laboratories

These supplements were submitted by the applicant to receive full approval for the ritonavir NDAs. In addition to clinical efficacy data, the supplements included a number of labeling changes related to drug interactions. Dr. Joette M. Meyer reviewed four drug interaction study reports, the applicant's rationale for deleting some drugs from the list of contraindications, and the applicant's proposed changes to the drug interaction table included in the PRECAUTIONS section of the label. See Dr. Meyer's review for further details.

This addendum includes:

1. Further details regarding the changes to the drug interactions mentioned in the CONTRAINDICATIONS section and PRECAUTIONS section of the label
2. New information regarding the ritonavir-meperidine drug interaction
3. New information regarding the ritonavir-sildenadfil drug interaction

Changes to the drug interactions mentioned in the CONTRAINDICATIONS section and PRECAUTIONS section of the label

Advice was sought, through OCPB team leaders, from the clinical divisions responsible for the drugs that the applicant proposed be removed from the list of contraindications. Based on recommendations from the clinical divisions, the following decisions were made:

1. Retain the following drugs as CONTRAINDICATIONS (Table 3): flecanide, propafenone.
2. Move the following drugs from CONTRAINDICATIONS to Table 4 (mentioned in WARNINGS): The WARNINGS section states that the magnitude of the interactions and therapeutic consequences between ritonavir and the drugs listed in Table 4 cannot be predicted with any certainty. When co-administering ritonavir with any agent listed in Table 4, special attention is warranted.
3. The following drugs do not need to be mentioned in the ritonavir label:
4. Note: Meperidine will not be included in Table 3 due to the results from a drug interaction study that were submitted for review. (See below)

Ritonavir-meperidine drug interaction

The applicant submitted preliminary results from a study evaluating the effect of ritonavir on the pharmacokinetics of meperidine in HIV-negative subjects. This was an open label study. Eight subjects (4 males and 4 females) enrolled and completed the study. Each subject received a single 50 mg dose of meperidine on Day 0 and Day 11. Ritonavir was administered on Days 2 through 14, titrated as 300 mg BID for two days, 400 mg BID for two days, and 500 mg BID thereafter. Meperidine was administered as 50 mg Demerol® tablets; ritonavir was administered as 100 mg Norvir® capsules. Blood samples for meperidine and normeperidine were collected following the Day 1 and Day 11 meperidine doses. Blood samples for ritonavir were collected following the final dose.

Pharmacokinetic Results

Compound	Treatment	Pharmacokinetic Parameters (Arithmetic mean ± SD)		Ratio of means Point estimate (95% confidence interval)	
		*AUC (ng*hr/mL)	Cmax (ng/mL)	*AUC	Cmax
Meperidine (n=8)	Meperidine	621 ± 245	126 ± 47	0.38 (0.35, 0.41)	0.41 (0.28, 0.58)
	Meperidine + ritonavir	235 ± 98	51 ± 21		
Normeperidine (n=6)	Meperidine	246 ± 167	20.6 ± 5.2	1.47 (0.76, 4.45)	1.88 (1.42, 2.47)
	Meperidine + ritonavir	362 ± 165	38.6 ± 9.7		

*AUC = AUC_{∞} for meperidine and AUC_{tau} for normeperidine.

Ritonavir exposure was similar to previous reports following administration of 500 mg BID.

Meperidine AUC is significantly reduced by concomitant ritonavir, so it is not necessary to contraindicate meperidine during treatment with ritonavir. Because normeperidine is pharmacologically active, exhibiting both analgesic activity and CNS stimulant activity (seizures), a dosage increase of meperidine, when coadministered with ritonavir, is not recommended.

The applicant incorporated the results from this study into the following sections of the ritonavir label:

1. CLINICAL PHARMACOLOGY section, Table 2: The changes in meperidine and normeperidine AUC and Cmax are included in the "Effects of ritonavir of co-administered drug AUC and Cmax" section of the table.
2. PRECAUTIONS, Drug Interactions section: The results of this study are summarized, including the fact that a dosage increase of meperidine, when coadministered with ritonavir, is not recommended.

The applicant's statements in the label, regarding the meperidine-ritonavir drug interaction, are acceptable.

Ritonavir-sildenadfil drug interaction

Pfizer conducted a study evaluating the effect of ritonavir on sildenafil. The results of the study are described in the sildenafil (Viagra®) label. Abbott has added the results of the study to the ritonavir label, in the PRECAUTIONS, Drug Interactions section. The section in the ritonavir label indicates that co-administration of sildenafil 100 mg single dose with ritonavir 500 mg BID

[redacted]

In addition to information that the applicant has included regarding the ritonavir-sildenafil interaction, the applicant will be instructed to make the following changes:

1. Add the results of this study to Table 2 in the CLINICAL PHARMACOLOGY section of the label.
2. Add a WARNING regarding the coadministration of sildenafil with ritonavir, similar to the WARNING in the amprenavir (Agenerase) label.

CONCLUSIONS: The majority of the labeling changes mentioned in this review have been incorporated into the label by the applicant. The remaining changes will be communicated to the applicant during final labeling negotiations. The Regulatory Review Officer (Dr. Kim Struble) is recommending some minor wording changes to the drug interaction sections in the label. There are no further clinical pharmacology/biopharmaceutics comments at this time.

Kellie Schoolar Reynolds 5/18/99

Kellie Schoolar Reynolds, Pharm.D.
Pharmacokinetics Team Leader

concurrence: John A. Lazor, Pharm.D.
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cc:

HFD 530	/NDAs 20-659 & 20-680
	/MO/KStruble
	/PM/SLynche
HFD 880	/PKTL/KReynolds
✓HFD 880	/DPE III
✓CDR	/Barbara Murphy

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