

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-417

PHARMACOLOGY REVIEW(S)

PHARMACOLOGIST'S REVIEW

NDA 22-417

Date Submitted: December 19, 2008

Date Assigned: January 2, 2009

Date Completed: March 25, 2009

Assigned Reviewer: Pritam Verma, Ph.D.

DAVP

HFD-530

SPONSOR: Abbott Laboratories

200 Abbott Park Road

Abbott Park, IL 60064

DRUG: Norvir (100 mg ritonavir) Film-Coated Tablets

FORMULATION: Ritonavir, Film-Coated Tablets, 100 mg have been developed by Abbott Laboratories. The dosage form is an (b) (4) film-coated tablet containing 100 mg of ritonavir. The qualitative and quantitative composition of Ritonavir, Film-Coated Tablets, 100 mg, are found in Table 1.

Table 1

Component	Quality Standard	Function	Amount/Unit
	(b) (4)		
Ritonavir	USP	Active	100.0 mg
Copovidone, Compendial (b) (4)	NF	(b) (4)	(b) (4)
Sorbitan Monolaurate Compendial	NF		
Colloidal Silicon Dioxide, Compendial	NF		
	(b) (4)		
Sodium Stearyl Fumarate, Compendial	NF		
Colloidal Silicon Dioxide, Compendial	NF		
Anhydrous Dibasic Calcium Phosphate, Compendial	USP		
(b) (4)	N/A		
	(b) (4)		
	USP		
Total Tablet Weight	N/A		

RELATED INDs and NDAs: 43,718; 20-659; and 20-945.

INDICATION: Norvir tablets are proposed for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

INTRODUCTION

Norvir (ritonavir) soft capsules and oral solution are currently approved in the USA, Europe, Japan and numerous other countries throughout the world. The present application contains information to support registration of Norvir film-coated tablets, a new solid dosage form of Norvir that does not require refrigeration. Norvir tablets are proposed for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The Norvir Tablet dosage form is composed of commonly used pharmaceutical excipients that fall within the specifications, except copovidone. The 100 mg Norvir Tablet contains (b) (4) of copovidone. At the Norvir dose of 200 mg commonly used for boosting, the total daily copovidone exposure would be (b) (4) which is less than previously approved for Kaletra tablets. However, when used at the maximum recommended therapeutic dose of Norvir (1200 mg), daily copovidone exposure is (b) (4) (b) (4) a level that is (b) (4) times higher than from Kaletra tablets. As a result, the sponsor has provided a safety profile of copovidone in animals.

Additionally, a ritonavir degradation product, (b) (4) (b) (4), has been identified in the 100 mg Norvir Tablet dosage form. The daily exposure of (b) (4) in the Norvir tablet dosage form (b) (4) is higher than the capsule (b) (4) or oral solution (b) (4) formulations. The increased level of (b) (4) in Norvir tablets is due to (b) (4) (b) (4)

TOXICOLOGY

The toxicology and safety profile of ritonavir has been previously established and no additional toxicology studies were conducted in support of the ritonavir tablet development program, since the recommended daily dose has not changed.

For detail description of nonclinical studies, please refer to the review of NDAs 20-659 and 20-945.

The sponsor has provided written summaries for copovidone and (b) (4). The issues associated with these two components of the tablet will be discussed in this section.

1. Copovidone

Copovidone has been extensively studied and was well tolerated in acute as well as chronic toxicity studies (Table 2).

Table 2
Toxicology Program for Copovidone

Study Type and Duration	Route of Administration	Doses (mg/kg/day)	Species
<u>Single-dose toxicity</u>	Oral gavage	3200 and 10,000	Mouse
	Intraperitoneal	3200 and 10,000	Mouse
	Oral gavage	10,000	Rat
	Oral gavage	10,000	Dog
	Oral gavage	10,000	Dog
<u>Repeat-dose toxicity</u>			
4-Weeks	Diet	0, 900, 1800, 3600	Dog
13-Weeks	Diet	0, 100, 500, 2500	Dog
26-Weeks	Diet	0, 800, 1600, 3200	Rat
52-Weeks	Diet	0, 500, 1500, 2500	Dog
<u>Genotoxicity</u>			
Bacterial mutagenesis	<i>In vitro</i>	100–5000 µg/plate	<i>Salmonella</i>
Chromosomal aberrations	<i>In vitro</i>	250–10,000 µg/ml	Hamster V79
Chromosomal aberrations	<i>In vitro</i>	5,000–10,000 µg/ml	Human lymphocytes
Chromosomal aberrations	<i>In vitro</i>	5000–10,000	Human lymphocytes
Chromosomal aberrations	Oral by gavage	1,000–4,000	Mouse
<u>Carcinogenicity</u>			
2-Year	Diet	0, 700, 1400, 2800	Rat
<u>Reproduction and developmental toxicity</u>			
Segment II	Oral by gavage	0, 500, 1000, 2000	Rat
Segment II	Oral by gavage	0, 500, 1000, 2000	Rabbit

The NOAELs in the 26-week rat and 52-week dog toxicology studies of copovidone were 3,200 mg/kg/day and 2,500 mg/kg/day, respectively. Copovidone treatment did not produce any embryo toxicity, fetal abnormalities or malformations in studies in rats and rabbits, where the highest dosage tested (2000 mg/kg/day) was the NOAEL. In the battery of genotoxicology assays, copovidone was negative. Copovidone was not tumorigenic when tested in a two-year carcinogenicity study in rats.

Extrapolation of Copovidone Data from Animals to Humans

On the basis of the NOAELs in rats (3200 mg/kg/day) and dogs (2500 mg/kg/day), safety margins for copovidone are provided in Table 3.

Table 3
Safety Margins for Copovidone Relative to Animal NOAELs

Norvir Tablet Dose ^a (mg)	Copovidone Exposure ^b (70 kg Human)			Safety Margin vs. NOAEL ^c			
				Body Weight (mg/kg)		Body Surface Area (mg/m ²)	
	Mg/day	Mg/kg	Mg/m ²	Rat	Dog	Rat	Dog
200	(b) (4)			262x	205x	42x	110x
1200	(b) (4)			38x	29x	6x	16x

a. Ritonavir dose

(b) (4)

c. NOAELs: Rat = 3200 mg/kg/day or 18,880 mg/m²; Dog = 2500 mg/kg/day or 50,000 mg/m²

The maximum recommended therapeutic dose of Norvir (1200 mg), daily copovidone exposure (b) (4) has a safety margin of 6- to 16-fold based on the NOAELs derived from the 26- week rat and 52-week dog toxicology studies, respectively.

(b) (4)

The (b) (4) of ritonavir is the only degradant that is present at a higher level in the ritonavir tablet formulation than in the currently approved ritonavir soft gel capsule (SGC) or oral solution (OS) formulations. The increased level of (b) (4) in ritonavir tablets is due to the melt extrusion manufacturing process. (b) (4) does not change significantly over the shelf-life of the tablet. The limit of (b) (4) in the currently approved ritonavir SGC and ritonavir OS is (b) (4) and (b) (4), respectively.

For the ritonavir tablet, a release limit of (b) (4) and an acceptance limit of (b) (4) are proposed by the sponsor. While (b) (4) in ritonavir tablets is increased in comparison to previous formulations, the safety of the higher level of (b) (4) was established in a three-month oral toxicity study in dogs.

Three-month oral toxicity study in dogs

In this study, exposure to (b) (4) in the lot used in the toxicology study) equaled or exceeded the maximum human exposure proposed at the recommended ritonavir dosage regimens (Table 4). At a ritonavir dose of 200 mg/day that is commonly used for boosting with other protease inhibitors, safety margins for (b) (4) from the dog toxicity study range from five to eight times the (b) (4) exposure in humans. At the maximum recommended ritonavir dose (1200 mg/day) for single agent therapy, the projected exposure in humans is equivalent to the daily exposure in dogs on a body weight (mg/kg) adjusted basis and nearly equivalent on a surface area (mg/m²) adjusted basis in the three-month toxicity using ritonavir containing (b) (4)

Table 3

(b) (4) Safety Margins Based on 3 – Month Toxicity Study in Dogs vs. Human Ritonavir Doses

	Ritonavir Dose	(b) (4) in API or Tablet	(b) (4)		Safety Margin		
			Daily Dose, mg	Dosage, mg/kg/day	HED ^a (mg)	mg/kg	HED
Dogs	25 mg/kg/day	(b) (4)	7.5	0.75	25	-	-
Humans	200 mg/day	(b) (4)	5.2	0.09	-	8x	5x
Humans	1200 mg/day	(b) (4)	31.2	0.5	-	1.5x	0.8x

- a. HED, human equivalent dose, based on body surface area adjustment and 60 kg human body weight.
- b. The concentration was (b) (4) at the beginning of the study and (b) (4) at the end of the three-month treatment period; (b) (4) was selected as the number to use for calculating safety margins.

On the basis of the safety demonstrated in dogs and clinical experience with other ritonavir dosage forms, the presence of (b) (4) at a level of (b) (4) in ritonavir tablets represents no new or additional safety risk for humans.

Discussion and Conclusions

The safety of ritonavir tablets has been demonstrated in previous submissions and has not been reviewed in this NDA. For ritonavir tablets, drug product impurities are within levels previously qualified for other ritonavir formulations and do not present a safety risk to patients. The inactive ingredients are within compendial specifications and do not represent a safety hazard to patients. On the basis of these attributes, the safety considerations for ritonavir tablets have been well characterized and found to be consistent with other ritonavir dosage forms.

Conclusions

There are no nonclinical pharmacology and toxicology issues which would preclude the approval of this NDA.

Reviewer signature: _____

Supervisor signature: _____

Concurrences:

HFD-530/HGhantous
HFD-530/PVerma

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/s/

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