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RESEARCH**

*APPLICATION NUMBER:*

**21-785**

**PHARMACOLOGY REVIEW**

**PHARMACOLOGY/TOXICOLOGY REVIEW COVER SHEET**

<b>NDA NUMBER:</b>	<b>21-785</b>
<b>NUMBER/DATE/TYPE:</b>	000/1-18-2004
<b>INFORMATION TO SPONSOR</b>	Yes (x) No ( )
<b>SPONSOR</b>	Hoffmann-La Roche Inc., Nutley, New Jersey 07110
<b>DRUG MANUFACTURER</b>	Same as above
<b>DIVISION NAME:</b>	DAVDP
<b>HFD #:</b>	HFD-530
<b>REVIEW COMPLETION</b>	11/25/04
<b>REVIEWER</b>	Kuei-Meng Wu
<b>DRUG TRADE NAME:</b>	INVIRASE Film-Coated Tablet
<b>GENERIC NAME</b>	Saquinavir mesylate
<b>CODE NAME</b>	Ro 31-8959/003 (mesylate salt, CAS# 149845-06-7), Ro 31-8959/000 (free base, CAS# 127779-20-8)
<b>CHEMICAL NAME</b>	cis-N-tert-Butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinoly)carbonyl]-L-asparaginy]amino]butyl](4aS,8aS)-isoquinoline-3(S)-carboxamide methylsulfonate
<b>FORMULA/MW</b>	C <sub>38</sub> H <sub>50</sub> N <sub>6</sub> O <sub>5</sub> .1:1CH <sub>4</sub> O <sub>3</sub> S; MW: 767 (free base = 671)
<b>STRUCTURE</b>	
<b>RELATED INDS</b>	41,099, 43,861, 56,072
<b>DRUG CLASS:</b>	Antiviral
<b>INDICATION:</b>	Monotherapy and Combination Treatment (with HIVID and ZDV) for Patients with Advanced HIV Infections
<b>CLINICAL FORMULATION:</b>	Saquinavir mesylate 500 mg film-coated tablet
<b>ROUTE</b>	Oral
<b>PROPOSED USE:</b>	HIV Infection

**DISCLAIMER:** Tabular and graphical information is from sponsor's submission unless stated otherwise.

## INTRODUCTION

Saquinavir (Ro 31-8959) is an antiviral drug developed for the treatment of HIV infection. The antiviral activity of saquinavir results from inhibition of the HIV protease. This NDA drug product is related to the 500 mg film-coated tablet of saquinavir mesylate. Because the new formulation is to be used with ritonavir 100 mg boosting, the actual human systemic exposures of saquinavir will be based, as proposed by the sponsor, on the study (daily AUC=38170 ng.h/ml, fortovase 1000 mg bid, boosted with ritonavir 100 mg bid). The sponsor has provided AUC comparisons between human and animals that will be used as the reference for labeling changes.

**Table 2 Saquinavir Exposures (AUC<sub>0-24</sub>) Comparisons**

Carcinogenicity Study	Study Number	Dose mg/kg/day	AUC <sub>0-24</sub> (h*ng/mL)	Ratio* (Human/Animal)
Rat	W-9706	0	-	-
n=24		125	798	47.8
12 Males: 12 Females		350	8200	4.65
		1000	10900	3.50
Mice	W-9507	0	-	-
n=96		200	1111	34.4
48 Males: 48 Females		700	11020	3.46
		2500	24870	1.53

\* Ratios are based on exposure seen in patients with Fortovase/ritonavir 1000/100 mg study). i.e. 38170 ng\*h/mL.

Reproductive Toxicity Studies	Dose (mg/kg/day)	AUC (ng.h/mL)	HUMAN (3) AUC (ng.h/mL) Invirase 1000 mg b.i.d. Ritonavir 100 mg b.i.d.	HUMAN (3) AUC (ng.h/mL) Fortovase 1000 mg b.i.d. Ritonavir 100 mg b.i.d.	Ratio* (Human/Animal)
Rat Fertility & General Reproductive Performance (W141885)	125	3870	29214 (GM)	38170 (GM)	9.86
	375	5640			6.77
	1200	9760			3.91
Rat Embryotoxicity & Teratogenicity (B-153194)	200	NM (1)	29214 (GM)	38170 (GM)	-
	600	4260 (1)			8.96
	1600	11000 (1)			3.47
Rabbit Embryotoxicity & Teratogenicity (B-151991)	100	ND (2)	29214 (GM)	38170 (GM)	-
	300	3800 (2)			10.0
	1000	8000 (2)			4.77

\* Ratios are based on exposure seen in patients receiving Fortovase/ritonavir 1000/100 mg.

- (1): AUC data from separate TK study in pregnant rats (report W-141963)  
 (2): AUC data from separate general tolerance and TK study in non-pregnant rabbits (report B-154991)  
 (3) Reference

NM = Not measured  
 ND = Not determined due to insufficient data  
 GM = Geometric Mean

REGULATORY  
COMMENTS

This NDA does not contain pharm/tox data. All preclinical information is cross-referenced to the original saquinavir NDA (20-977). No regulatory comments on pharm/tox are needed, except the following editings/rewrites on pharm/tox portion of the drug's labeling are provided (additions: bold and underlined; deletion: strikethrough).

PHARM/TOX  
LABELING  
CHANGES**Carcinogenesis**

Carcinogenicity studies found no indication of carcinogenic activity in rats and mice administered saquinavir for approximately 2 years. **Because of limited bioavailability of saquinavir in animals**, the plasma exposures (AUC values) in the respective species were — approximately **29% (using rat)** and **65% (using mouse) of** those obtained in humans at the recommended clinical dose boosted with ritonavir.

**Pregnancy**

Teratogenic Effects: Category B

Reproduction studies conducted with saquinavir — have shown no embryotoxicity or teratogenicity **in both rats and rabbits**. **Because of limited bioavailability of saquinavir in animals, the plasma exposures (AUC values) in the respective species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir.**

Clinical experience in pregnant women is limited. Saquinavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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KUEI-MENG WU, PH.D.  
REVIEWING PHARMACOLOGIST  
DAVDP

CC:  
HFD-530 NDA 21-785(000)  
HFD-530/DIVISION FILE

CONCURRENCES: HFD-530/ASSOC DIR/JFARRELY

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/s/

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Kuei Meng Wu  
11/18/04 03:36:30 PM  
PHARMACOLOGIST

James Farrelly  
11/23/04 01:35:37 PM  
PHARMACOLOGIST