

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-785**

**MEDICAL REVIEW**

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN  
SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**DATE:** 12-08-04

**FROM:** Katherine A. Laessig, M.D.  
Division of Antiviral Drug Products, HFD-530

**TO:** Division File

**SUBJECT:** Group Leader Memo for NDA 21-785 INVIRASE® (saquinavir mesylate) 500 mg Film Coated Tablets

**1.0 Background**

Saquinavir is an HIV protease inhibitor. It is approved as 2 different formulations: INVIRASE 200 mg hard gelatin capsules, which was approved in 1995, and FORTOVASE soft gelatin capsules, which was approved in 1997. Both formulations require tid dosing, for a total of nine capsules a day with INVIRASE, and eighteen capsules a day with FORTOVASE. The applicant, Hoffman La Roche, has submitted this NDA in support of a new formulation for INVIRASE 500 mg film coated tablets. The existing formulation of INVIRASE is available as 200 mg hard gel capsules and is dosed at 1000 mg bid coadministered with another protease inhibitor, ritonavir, at 100 mg bid. The pill burden for this regimen is 6 pills twice a day. FORTOVASE is available as 200 mg soft gel capsules, and may be dosed at 1200 mg tid (6 pills three times daily), or 1000 mg bid coadministered with 100 mg of ritonavir bid (6 pills twice daily). The availability of the 500 mg film coated tablet will permit a significant reduction in pill burden for patients, and potentially an improvement in compliance which is an integral component of the success of an antiretroviral regimen. Because of this significant potential benefit to patients, this application received a priority review.

**2.0 Summary of Study Results**

This submission contains the results of three healthy volunteer studies to show the relative bioavailability and bioequivalence of the INVIRASE 200 mg hard gel capsules to the INVIRASE 500 mg film coated tablets. For extensive discussions of these studies, please refer to the clinical/statistical review of Dr. Yoshihiko Murata and Dr. Susan Zhou, and the clinical pharmacology review of Dr. Jennifer DiGiacinto.

In brief, studies BP 17359 and 17633 demonstrated the bioequivalence and the bioavailability, respectively, of 1000 mg of the film coated tablets coadministered bid with 100 mg of ritonavir to 1000 mg of the hard gel capsules coadministered bid with 100 mg of ritonavir. Study BP 17058 did not demonstrate the bioequivalence of the film coated tablet to the hard gel capsule in the absence of ritonavir boosting, however since the film coated tablet will always be administered with low dose ritonavir, bioequivalence of the 2 individual products is not critical.

There were no efficacy studies reviewed as part of this NDA. However, based on the bioequivalence of the film coated tablets and the hard gel capsules, the film coated tablet formulation is expected to have similar efficacy as the hard gel capsule.

Safety analyses of the bioequivalence and bioavailability studies did not reveal any new and unexpected adverse reactions to saquinavir. However, the applicant did provide data in a limited number of female subjects demonstrating higher exposures of saquinavir compared to male subjects. Despite this finding, the applicant and the review team were not able to demonstrate conclusively that female subjects experienced a higher rate or intensity of adverse events. The applicant will be requested to investigate this potential relationship further in postmarketing commitments.

### **3.0 Recommendations**

The results of studies BP 17359, 17633, and 17058 support the bioequivalence of the film coated tablet INVIRASE formulation to the hard gel capsule INVIRASE formulation when coadministered with low dose ritonavir. Information about the new formulation will be incorporated into the product labeling. I concur with the findings of the medical officer review by Dr. Yoshihiko Murata, and recommend that these supplements be approved.

Katherine Laessig, MD

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/s/

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