CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-417

SUMMARY REVIEW

Decisional Memorandum to the File

Date	Feb. 4, 2010
From	Jeffrey Murray, M.D., M.P.H.
Subject	Decisional Summary Memorandum
NDA #	22-417
Applicant	Abbott Laboratories
Date of Submission	December 19, 2008 (original submission)
PDUFA Goal Date (resubmission)	Feb. 11, 2010
Proprietary Name / Established (USAN) names	Norvir, ritonavir (RTV)
Dosage forms / Strength	100 mg tablets (NDA 22-417)
Proposed Indication **Dosing Regimen**	Treatment of HIV-1 infection 600 mg twice daily
Recommended:	Approval

1. Introduction/Background/Regulatory History

This memo briefly summarizes the application as originally submitted and the regulatory history following a Complete Response letter to the original application. Please refer to Dr. Kim Struble's Cross Discipline Team Leader Memo dated Sept. 15, 2009 for a thorough summary of the review issues related to the review of this application.

On Dec. 2008, Abbott Laboratories submitted NDA 22-417 under 505(b)(1) to support approval of a 100 mg film-coated tablet of ritonavir. Ritonavir, an HIV-1 protease inhibitor, was first approved in 1996 as 100 mg capsule and oral solution (80 mg/ml) formulations. Due to manufacturing issues, the original 100 mg capsules were discontinued and a new capsule formulation was approved in 1999. Abbott used a melt-extrusion technology to develop the tablet formulation. The tablet is an improvement over the currently available capsule formulation because refrigeration storage is no longer a requirement. The data submitted support stability of the tablet in a wide range of temperature and humidity conditions.

On October 16, 2009, FDA issued a Complete Response (CR) Letter to Abbott because of deficiencies observed during an inspection of the Abbott GmbH facility in Ludswigshafen Germany. With respect to other Chemistry, Manufacturing and Control issues reviewed by the Office of New Drug Quality Assessment and with respect to the Clinical Pharmacology, and Clinical reviews, the application did not have deficiencies precluding approval at the time of the CR action.

Abbott resubmitted the application on 12/11/09 upon reaching resolution of the inspection deficiencies.

2. CMC

There are no new outstanding chemistry, manufacturing or control issues with this NDA for a new tablet formulation of ritonavir that precludes approval of the application.

3. Nonclinical Pharmacology/Toxicology

A review by Dr. Pete Verma was conducted based on the amount of an excipient, copovidone, in the tablet formulation: each Norvir tablet contains (b) (4) of copovidone. According to Dr. Pete Verma's review, a negligible safety risk to patients receiving Norvir tablets is expected based on daily copovidone exposures

4. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions made by Drs. Kimberly, Stanley Au and Kellie Reynolds regarding the interpretation of the bioequivalence and food effect findings and impact of the new tablet formulation on the pharmacokinetics of approved protease inhibitors when co-administered with ritonavir.

Under moderate fat conditions, the tablet formulation is not bioequivalent to the approved capsule formulation. Bioequivalence was met for AUC; however, the mean Cmax was increased by 26%. Because bioequivalence was not met for Cmax, reviewers assessed the impact of increased maximum exposures on the overall safety profile of ritonavir at the approved dose (600 mg twice daily) and the impact of ritonavir tablets (at reduced doses) on the pharmacokinetics other approved protease inhibitors.

In addition, based on the results from two ritonavir tablet trials and previous food effect data with ritonavir capsules, a greater difference in exposure is predicted for ritonavir tablets relative to ritonavir capsules under fasting conditions than under fed conditions. Therefore, at the approved dose of 600 mg twice daily, ritonavir tablet exposures under fasted conditions may exceed those from the original ritonavir phase 2 and 3 trials. As a result the label for ritonavir tablets states that ritonavir should be taken with a meal. This is in contrast to the approved capsule formulation where ritonavir should be given with food if possible.

To assess the impact of higher ritonavir exposures on the pharmacokinetics of other approved protease inhibitors, Abbott submitted information from published literature and abstracts from scientific conferences. For reasons outlined in Dr. Struble's and Dr. Au's reviews, the data Abbott submitted allows one to conclude that there is no safety or efficacy concern following co-administration of the new ritonavir tablets (at doses less than 600 mg twice daily) with other approved protease inhibitors. The potential change in the pharmacokinetics of approved protease inhibitors is not considered clinically significant and does not alter their established safety and efficacy profile

5. Pediatrics

A partial waiver was granted for children less than one month of age. Trials in this age range were deemed not feasible and impractical. The oral solution formulation is available with approved dosing in children greater than one month of age.

6. **Conclusions and Recommendations**

There are no outstanding regulatory issues that preclude approval of this application for this tablet formulation of Norvir.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22417	ORIG-1	ABBOTT LABORATORIES	Ritonavir Tablet

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEFFREY S MURRAY
02/04/2010