

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-417**

**MICROBIOLOGY REVIEW(S)**

# VIROLOGY FILING CHECKLIST FOR NDA or Supplement

**NDA Number: 22-417**

**Applicant: Abbott Laboratories**

**Stamp Date: 12/19/2008**

**Drug Name: Norvir®**

**NDA Type: Original**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?			This is bioequivalence study between the proposed tablet and the approved SGC formulations. There is no virology information.
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?			N/A
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?			N/A
4	On its face, has the applicant <u>submitted</u> cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?			N/A
5	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			N/A
6	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?			N/A
7	Has the applicant <u>submitted</u> the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?			N/A
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?			N/A
9	Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	yes		
10	Has the applicant <u>submitted</u> annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	yes		
11	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	yes		
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		No	

**IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Microbiologist

Date

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Microbiology Team Leader

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Date

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

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/s/

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NARAYANA BATTULA  
02/01/2010

JULIAN J O'REAR  
02/02/2010

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
MICROBIOLOGY REVIEW**

**NDA#:** N022417 000 and N20659 S-045 addendum

**DATE REVIEWED:** 1/13/10

**REVIEWER:** Julian J. O'Rear, Ph.D.

**Date Submitted:** 12/8/08

**Date Assigned:** 1/13/10

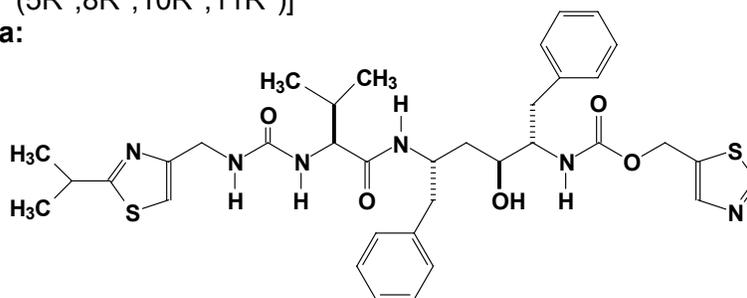
**Date Received:** 12/19/08

**Sponsor:** Abbott Laboratories  
200 Abbott Park Road  
Abbott Park, IL 60064  
Mary Konkowski  
Associate Director, Global Pharmaceutical Regulatory Affairs  
847-938-3063  
847-775-4956 (FAX)  
mary.konkowski@abbott.com

**Product Names:** ritonavir, ABT-538,

**Chemical Name:** 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8.11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R\*,8R\*,10R\*,11R\*)]

**Structural Formula:**



**ABT-538**

**Empirical Formula:** C<sub>37</sub>H<sub>48</sub>N<sub>6</sub>O<sub>5</sub>S<sub>2</sub>

**Molecular Weight:** 720.95

**Drug Category:** Antiviral

**Indication:** Treatment of HIV infection

**Dosage Form/Route of administration:** Tablets /Oral

**Supporting Documents:** IND 43718

**Abbreviations:** AIDS, acquired immunodeficiency syndrome; APV, amprenavir; BID, *bis in die*; d4T, stavudine; HIV-1, human immunodeficiency virus-1; IDV, indinavir; NFV, nelfinavir; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir; 3TC, lamivudine; TID, *tris in die*; WT, wild type;

## BACKGROUND AND SUMMARY

Abbott Laboratories, Inc. has submitted this NDA for a new dosage form of the approved HIV-1 protease inhibitor ritonavir. Ritonavir is currently approved as NORVIR® Capsules and Oral Solution. This submission includes conversion of the current label to PLR format. No efficacy data were presented for review. This review describes additional changes to the Microbiology section of the label in addition to those described in the Microbiology Review of Dr. Battula.

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
MICROBIOLOGY REVIEW**

NDA#: N022417 000 and N20659 S-045 addendum

DATE REVIEWED: 1/13/10

**Microbiology Section of the PLR Label**

**12.1 Mechanism of Action**

Ritonavir is an antiviral drug [See *CLINICAL PHARMACOLOGY* (12.4)].

**12.4 Microbiology**

*Mechanism of Action*

Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor which leads to production of non-infectious immature HIV particles.

*Antiviral Activity in Cell Culture*

The activity of ritonavir was assessed in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes infected with HIV-1. The concentration of drug that inhibits 50% (EC<sub>50</sub>) of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC<sub>50</sub> value for low passage clinical isolates was 22 nM (n = 13). In MT<sub>4</sub> cells, ritonavir demonstrated additive effects against HIV-1 in combination with either zidovudine (ZDV) or didanosine (ddI). Studies which measured cytotoxicity of ritonavir on several cell lines showed that > 20 μM was required to inhibit cellular growth by 50% resulting in a cell culture therapeutic index of at least 1000.

*Resistance*

HIV-1 isolates with reduced susceptibility to ritonavir have been selected in cell culture. Genotypic analysis of these isolates showed mutations in the HIV-1 protease gene leading to (b) amino acid substitutions (b) -I84V (b) V82F (b) A71V (b) and M46I (b). Phenotypic (n = 18) and genotypic (n = 44) changes in HIV-1 isolates from selected patients treated with ritonavir were monitored in phase I/II trials over a period of 3 to 32 weeks. Substitutions (b) associated with the HIV-1 viral protease in isolates obtained from 41 patients appeared to occur in a stepwise and ordered fashion; in sequence, these substitutions mutations were position V82A/F (Val to Ala/Phe), I54V (b) A71V/T (b) (b) and I36L (b) followed by combinations of substitutions (b) at an additional 5 specific amino acid positions (Sponsor: Please specify the amino acids). Of 18 patients for whom both phenotypic and genotypic analysis were performed on free virus isolated from plasma, 12 showed reduced susceptibility to ritonavir in cell culture. All 18 patients possessed one or more substitutions (b) in the viral protease gene. The V82A/F substitution (b) appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a ≥ 5-fold decrease in viral sensitivity in cell culture from baseline. (b)

*Cross-Resistance to Other Antiretrovirals*

Among protease inhibitors variable cross-resistance has been recognized. Serial HIV-1 isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility in cell culture but did not demonstrate a concordant decrease in susceptibility to saquinavir in cell culture when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir in cell culture (8-fold). Isolates from 5 patients were also tested for cross-resistance to amprenavir and nelfinavir; isolates from 2 patients had a decrease in susceptibility to nelfinavir (12- to 14-fold), and none to amprenavir. Cross-resistance between ritonavir and reverse transcriptase inhibitors is

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**MICROBIOLOGY REVIEW**

**NDA#:** N022417 000 and N20659 S-045 addendum

**DATE REVIEWED:** 1/13/10

unlikely because of the different enzyme targets involved. One ZDV-resistant HIV-1 isolate tested in cell culture retained full susceptibility to ritonavir.

**CONCLUSIONS**

This NDA is approvable with respect to Clinical Microbiology. The sponsor has agreed to the proposed changes to the Microbiology section of the label.

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**Julian J. O'Rear, Ph.D.**  
**Clinical Microbiology Team Leader**

**CONCURRENCES**

**cc:**  
**HFD-530/Original NDA**  
**HFD-530/Division File**  
**HFD-530/Reviewer Medical/Struble**  
**HFD-530/RPM/Himaya**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22417	ORIG-1	ABBOTT LABORATORIES	RITONAVIR
NDA-22417	TRIAGE-1	ABBOTT LABORATORIES	RITONAVIR

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JULIAN J O'REAR  
01/13/2010

**Microbiology Review**  
**Division of Antiviral Drug Products (HFD-530)**

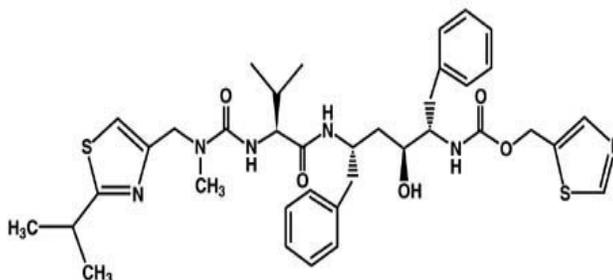
**NDA#:** 22-417      **Serial #:** 000      **Reviewer:** N. Battula, Ph.D.  
**Date submitted:** December 19, 2008      **Date received:** December 20, 2008  
**Date assigned:** December 20, 2008      **Date reviewed:** August 10, 2009

**Sponsor:** Abbott Laboratories  
200 Abbott Park Road  
Abbott Park, IL 60064-6157

**Product name(s):**  
Proprietary: NORVIR<sup>®</sup>  
Non-proprietary: Ritonavir (or ABT-538)

**Chemical:** 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester

**Structural formula:**



Mol. Formula =  $C_{37}H_{48}N_6O_5S_2$       M.Wt = 720.95

**Dosage form/route of administration:** Tablets/ Oral

**Indication:** Treatment of HIV-1 infection in combination with other antiretroviral agents

**Related documents:** NDA 20-945 and 20-659, and IND 43,718

**Background and Summary:** In this NDA the applicant is seeking approval for NORVIR<sup>®</sup> Tablets which is a new dosage form of the currently approved and marketed NORVIR<sup>®</sup> Capsules and NORVIR<sup>®</sup> Oral Solution. Each NORVIR<sup>®</sup> Tablet contains 100 mg of the active ingredient ritonavir. Ritonavir is an inhibitor of HIV-1 protease that has inhibitory activity and is an inducer of CYP3A4. The active ingredient in NORVIR<sup>®</sup> Tablets is unchanged from the material used in approved NORVIR<sup>®</sup> Capsules and NORVIR<sup>®</sup> Oral Solution. NORVIR<sup>®</sup> Tablets are also proposed for the same indication as NORVIR<sup>®</sup> Capsules and NORVIR<sup>®</sup> Oral Solution for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. NORVIR<sup>®</sup> Tablets will be packaged in a 30-tablet count bottle configuration for the U.S. market and in a 60-tablet count bottle configuration for the countries covered under the President's Emergency Plan for AIDS Relief (PEPFAR). The package insert for this NDA is submitted following the conformance criteria for Structured Product Labeling (SPL).

The applicant did not submit any efficacy studies with the NORVIR<sup>®</sup> Tablet formulation. However the applicant stated that several properties of the tablet formulation suggest that the tablet formulation should have approximately equivalent efficacy compared with the currently approved soft gelatin capsule formulation (for details see the clinical review by Dr. Regina Alivisatos). The applicant referred to bioequivalence studies conducted in healthy subjects comparing the approved NORVIR<sup>®</sup> Capsules with the investigational NORVIR<sup>®</sup> Tablets (for details of bioequivalence evaluation see the clinical pharmacology review by Dr. Stanley Au). Currently marketed NORVIR<sup>®</sup> Soft Gelatin Capsules require storage under refrigerated conditions. The new NORVIR<sup>®</sup> Tablet dosage form has been under development to remove the refrigeration requirement. In support of the stability at different temperature and humidity conditions the applicant provided CMC data (for details see the chemistry review by Dr. Dorota Matecka).

There are no new clinical microbiology data in the submission. However to reflect the current format of package insert the microbiology portion of the package insert is revised for consistency with other microbiology sections of the package inserts in SPL format. The revised microbiology portion of the package insert is included below.

**Conclusions and Recommendations:** Abbott Laboratories in this NDA is seeking approval for NORVIR<sup>®</sup> Tablets a new dosage form of the currently approved and marketed NORVIR<sup>®</sup> Capsules and NORVIR<sup>®</sup> Oral Solution. The applicant is seeking that the new formulation of NORVIR<sup>®</sup> Tablets also be approved for the same indication as NORVIR<sup>®</sup> Capsules and NORVIR<sup>®</sup> Oral Solution which are approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

In support of the new formulation the sponsor submitted CMC and PK data. However there is no efficacy or clinical microbiology data.

The applicant submitted the package insert according to the conformance criteria for Structured Product Labeling (SPL). For consistency the microbiology portion of the package insert is revised in conformity with other microbiology portions of the package inserts in SPL format. There are no microbiology related issues with regard to the new formulation of NORVIR tablets.

## **Microbiology**

### *Mechanism of Action*

Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor which leads to production of non-infectious immature HIV particles.

### *Antiviral Activity In Cell Culture*

The activity of ritonavir was assessed in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes infected with HIV-1. The concentration of drug that inhibits 50% (EC<sub>50</sub>) of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC<sub>50</sub> value for low passage clinical isolates was 22 nM (n = 13). In MT<sub>4</sub> cells, ritonavir demonstrated additive effects against HIV-1 in combination with either zidovudine (ZDV) or didanosine (ddI). Studies which measured cytotoxicity of ritonavir on several cell lines showed that > 20 μM was required to inhibit cellular growth by 50% resulting in a cell culture therapeutic index of at least 1000.

### *Resistance*

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HIV-1 isolates from selected patients treated with ritonavir were monitored in phase I/II trials over a period of 3 to 32 weeks. Substitutions (b) (4) associated with the HIV-1 viral protease in isolates obtained from 41 patients appeared to occur in a stepwise and ordered fashion; in sequence, these substitutions (b) (4) were position V82A/F (Val to Ala/Phe), I54V (b) (4) A71V/T (b) (4), and I36L (b) (4) followed by combinations of substitutions mutations at an additional 5 specific amino acid positions (Sponsor: Please specify the amino acids). Of 18 patients for whom both phenotypic and genotypic analysis were performed on free virus isolated from plasma, 12 showed reduced susceptibility to ritonavir in cell culture. All 18 patients possessed one or more substitutions (b) (4) in the viral protease gene. The V82A/F substitution (b) (4) appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a  $\geq 5$ -fold decrease in viral sensitivity in cell culture from baseline. (b) (4)

(b) (4)

#### *Cross-Resistance to Other Antiretrovirals*

Among protease inhibitors variable cross-resistance has been recognized. Serial HIV-1 isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility in cell culture but did not demonstrate a concordant decrease in susceptibility to saquinavir in cell culture when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir in cell culture (8-fold). Isolates from 5 patients were also tested for cross-resistance to amprenavir and nelfinavir; isolates from 2 patients had a decrease in susceptibility to nelfinavir (12- to 14-fold), and none to amprenavir. Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV-1 isolate tested in cell culture retained full susceptibility to ritonavir.

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Narayana Battula, Ph.D.  
Microbiologist

#### **Concurrence:**

Micro TL, Julian O'Rear \_\_\_\_\_ Date \_\_\_\_\_

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22417	----- ORIG 1	----- ABBOTT LABORATORIES	----- RITONAVIR

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/s/  
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NARAYANA BATTULA  
08/21/2009

JULIAN J O'REAR  
08/24/2009