CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-417

CROSS DISCIPLINE TEAM LEADER REVIEW

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Date	September 15, 2009
From	Kimberly A. Struble, Pharm.D.
Subject	Cross Discipline Team Leader Review
NDA #	22-417 and 20-659 (045)
Applicant	Abbott Laboratories
Date of Submission	December 19, 2009
PDUFA Goal Date	October 19, 2009
Proprietary Name / Established (USAN) names	Norvir, ritonavir (RTV)
Dosage forms / Strength	100 mg tablets (NDA 22-417) and Oral solution 80 mg/mL (NDA 20-659)
Proposed Indication **Dosing Regimen**	Treatment of HIV-1 infection 600 mg twice daily
Recommended:	Complete Response

1. Introduction

This review summarizes the multi-disciplinary evaluation of the information submitted by Abbott Laboratories for a 505(b)(1) new drug application (NDA 22-417) to support approval of a 100 mg film-coated tablet. Ritonavir, an HIV-1 protease inhibitor, was 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. This formulation is a major improvement over the currently available capsule formulation because refrigeration storage is no longer a requirement. Abbott submitted stability data for the tablet in a wide range of temperature and humidity conditions. Therefore, a product which does not require refrigeration is more convenient for patients and may increase overall adherence to therapy.

No new efficacy data were required for this application. The tablet formulation is not bioequivalent to the currently approved capsule formulation. Under moderate fat conditions bioequivalence was met for AUC; however, the mean C_{max} was increased by approximately 26%. Sufficient safety data were provided to support the increased exposures of the tablet formulation. The safety data submitted includes single dose trials with the 100 mg tablets, four previously reviewed multiple dose trials in HIV-1 infected patients, previously reviewed QTc and PR prolongation data and pharmacokinetic modeling data. The basis of approval for the non-bioequivalent tablet formulation for the treatment of HIV-1 infection is summarized in the sections below along with a summary for the use of the new tablet formulation at reduced doses with other approved HIV-1 protease inhibitors.

A partial pediatric waiver was granted for children (b) (4) No post marketing requirements or commitments are needed for this application.

Based on inspection of the Abbott GmbH manufacturing facility in Ludwigshafen, Germany, this application will receive a Complete Response. Significant deficiencies were found at this facility. This facility is the only drug manufacturing facility for the finished ritonavir tablets. The Withhold Recommendation by Compliance precludes approval at this time until Abbott resolves the deficiencies noted by the field investigator.

2. Background

In 1996, ritonavir was approved at 600 mg twice daily for the treatment of HIV-1 infection. Today, ritonavir is predominately used at reduced doses with other approved protease inhibitors and is an essential component of most regimens for treatment-naïve and treatment-experienced patients. Ritonavir is a

strong CYP3A inhibitor and at reduced doses (100 mg once daily to 200 mg twice daily) increases the exposures of other protease inhibitors. The majority of approved HIV-1 protease inhibitors are dependant on coadministration of ritonavir to produce the desired efficacy results. For darunavir, lopinavir, saquinavir, and tipranavir, the approved dosing regimen includes coadministration with ritonavir. These agents can not be administered without ritonavir.

3. CMC

This proposed tablet is a new dosage form of ritonavir that was developed in order to obtain a solid solution formulation using the hot-melt extrusion technology, a process similar to the manufacturing process of Kaletra (lopinavir/ritonavir, 200 mg/50 mg) Tablets (approved via NDA 21-906). (b) (4) (b) (4) (b) (4) Please refer to Dorota Matecka review for further details.

Manufacturing facilities

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Based on inspection of the Abbott GmbH manufacturing facility in Ludwigshafen, Germany, this application will receive a Complete Response. Significant deficiencies were found at this facility. This facility is the only drug manufacturing facility for the finished ritonavir tablets. The Withhold Recommendation by Compliance precludes approval at this time until Abbott resolves the deficiencies noted by the field investigator. Please refer to supporting documentation from Compliance.

4. 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; therefore, for a 600 mg twice daily regimen, the daily copovidone exposure is (b) (4) Additionally, the daily copovidone exposure is (b) (4) times higher than amount in Kaletra tablets. This copovidone daily exposure has an adequate safety margin of 6-16 fold based on NOAELs derived from 26 week rat and 52 week dog studies, respectively. According to Dr. Pete Verma's review, a negligible safety risk to patients receiving Norvir tablets is expected based on daily copovidone exposures.

5. Clinical Pharmacology

I concur with the conclusions made by Drs. 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. This section summarizes their conclusions.

Two trials pertaining to the final tablet formulation were submitted for review and include a bioequivalence trial (M10-307) and food effect trial (M10-235). Under moderate fat conditions, the tablet formulation is not bioequivalent to the approved capsule formulation. Bioequivalence was met for AUC; however, the mean C_{max} was increased on average by 26%. Given bioequivalence was not met; two important issues were addressed during the review. The review issues were (1) the impact of the increased Cmax exposures on the overall safety profile of ritonavir at the approved dose (600 mg twice daily) and (2) the impact of ritonavir tablets at reduced doses on the pharmacokinetics other approved protease inhibitors. Please also refer to Section 8 for additional details. Given the increase in mean Cmax exposures, patients may experience more side effects when switching formulations, in particular gastrointestinal effects. This cautionary statement is included in the Dosage and Administration section of the label.

In the food effect trial, the tablets were evaluated under fasting, moderate fat and high fat conditions. Ritonavir exposures decreased with food; AUC and Cmax were 21-23% lower when given with a moderate or high fat meal compared to fasted state. As stated in Drs. Stanley Au and Kellie Reynolds reviews," in contrast to ritonavir tablets, ritonavir capsules have higher bioavailability under fed conditions. Based on the results from two ritonavir tablet trials and previous food effect information for the 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 states take ritonavir 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 approved protease inhibitors, Abbott submitted information from published literature and abstracts from scientific conferences. Additionally, the approved product labeling for protease inhibitors were reviewed. To account for the variability of ritonavir exposures and different food effect between formulations, the review team took a conservative "worst case scenario" review approach and evaluated the impact of doubling the ritonavir dose on approved protease inhibitor exposures. Importantly, switching from ritonavir capsules to tablets does not result in a doubling of ritonavir exposures.

Findings from an article by Mathias et al (Clinical Pharmacology and Therapeutics, 009 an: 85(1):64-70) suggests a dose-related CY3A inhibition by ritonavir in the dose range of 20-100 mg and no further CYP3A inhibition at 200 mg. These data along with the published literature and abstracts led us to conclude administration of the new tablet formulation does not present safety or efficacy concerns for atazanavir, darunavir, fosamprenavir, and saquinavir. Further details are summarized above.

The impact of the new tablet on tipranavir exposures was reviewed in more detail because the interaction of tipranavir and ritonavir is complex and not solely dependant on CYP3A metabolism. Tipranavir is a CYP3A substrate, inhibitor and inducer and a P-gp substrate and inducer; whereas, ritonavir is a CYP3A substrate, inhibitor and inducer and P-gp inhibitor and inducer. Ritonavir concentrations following administration of 200 mg with tipranavir are similar to ritonavir concentrations following administration of 100 mg with most other approved protease inhibitors. Therefore, tipranavir given with ritonavir 100 mg may not provide maximum CYP3A inhibition. One consequence of increased tipranavir exposures is exposure related hepatotoxicity, including Grade 3/4 transaminase elevations and hepatic decompensation. According to Dr. Reynolds' review, the high variability in tipranavir exposures, the lack of increase in tipranavir Cmax, and the 25% increase in tipranavir AUC when ritonavir dose is doubled from 100 mg to 200 mg suggest higher ritonavir exposures from the new tablet formulation will not significantly increase tipranavir exposures. To minimize the potential for tipranavir related hepatotoxicity when coadministered with the new ritonavir tablet formulation the ritonavir label was revised to include following in the Drug Interaction section of the label. This text is consistent with the currently approved tipranavir label.

> "All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with tipranavir/ritonavir, and frequently throughout the duration of treatment. "

Additionally, the ritonavir tablet label instructs patients to take ritonavir with meals. Therefore, the Dosage and Administration section for tipranavir needs revisions from use without regard to meals to take with meals. Boehringer Ingelheim will be contacted after approval of ritonavir tablets to make the required tipranavir label change.

The data summarized below show no safety or efficacy concern following co-administration of the new ritonavir tablets at reduced doses with the approved protease inhibitors. The potential change in the pharmacokinetics of approved protease inhibitors is not considered clinically significant to alter their established safety and efficacy profile.

Drug/Approved Regimen	Comparison	Result	Comment
Darunavir (DRV) Experienced: 600/100 mg twice daily Naïve: 800/100 mg once daily Taken with food	DRV/RTV 600/200 mg once daily and DRV/RTV 400/100 mg once daily	DRV AUC ↑ 30% DRV Cmax ↑ 50%	No further impact on DRV exposures expected Increase DRV exposures resulted from increase in DRV dose with no additional effect from increased RTV dose
Atazanavir (ATV) Naïve and experienced: 300/100 once daily Naïve: 400 mg with no ritonavir Taken with food	ATV/RTV 300/100 mg once daily and ATV/RTV 300/200 mg once daily [*patients with subtherapeutic concentrations with 300/100 mg were increased to 300/200 mg]*	ATV exposures 3 hours post dose were similar before and after RTV dose increase	No further impact on ATV exposures expected
Fosamprenavir (FPV) Naïve: 1400 mg twice daily without ritonavir, 1400/200 once daily, 1400/100 once daily, 700/100 mg twice daily Experienced: 700/100 twice daily Taken without regard to food	FPV/RTV 1400/100 once daily and FPV/RTV 1400/200 mg once daily	No significant change in amprenavir AUC or Cmax. Cmin ↑ 70%	No change in total or maximum amprenavir exposure, no further impact on amprenavir exposures expected; therefore, can still be administered without regard to meals
Saquinavir 9SQV) 1000/100 mg twice daily	SQV/RTV 1200/100 mg once daily and SQV/RTV 1200/200 mg once daily	SQV AUC, Cmax and Cmin ↓ 30-40% with RTV 200 mg	Exposures of SQV given with RTV at approved doses are not expected to result in exposure lower than SQV 1200 mg TID without ritonavir, the dose which established clinical efficacy for SQV

6. Clinical Microbiology

No new clinical virology data were submitted with this application.

7. Clinical/Statistical- Efficacy

No new efficacy data were required to support the new tablet formulation. Bioequivalence was met for AUC and Cmax exposures for the tablet formulation are higher than the approved capsule formulation; therefore, efficacy is not compromised for the approved 600 mg twice daily regimen. As stated above, the

impact of ritonavir tablets at reduced doses on the pharmacokinetics of other approved protease inhibitors is not expected to adversely affect the established efficacy profile of the approved protease inhibitors.

8. Safety

I agree with the assessments made by Dr. Regina Alivisatos in the medical officer review. No new or unexpected safety concerns were seen in the four trials submitted. The impact of the higher Cmax exposures under fed conditions was evaluated and is not likely to significantly affect the overall safety profile. Administration of ritonavir tablets 600 mg twice daily under fasted conditions may exceed the exposures seen in the phase 2 and 3 trials; therefore, ritonavir tablets must be given with a meal. Of note, patients may experience tolerability issues when switching from capsules to tablets, particularly gastrointestinal effects. This cautionary statement is included in the Dosage and Administration section. Additionally, the impact of ritonavir tablets at reduced doses on the pharmacokinetics of other approved protease inhibitors is not expected to adversely affect the established safety profile of the approved protease inhibitors.

9. Advisory Committee Meeting

Not applicable.

10. 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.

11. Other Relevant Regulatory Issues

No other relevant regulatory issues are outstanding for this application; however, given the tablet formulation is not bioequivalent to the capsule formulation changes are needed to the tipranavir label to minimize the potential risk for hepatotoxicity. These actions will occur following approval of this NDA. The Dosage and Administration section needs revisions from take tipranavir/ritonavir without regard to food, to take tipranavir/ritonavir with meals.

12. Labeling

The label was converted to PLR format. The following major revisions were made to the label.

2 DOSAGE AND ADMINISTRATION

This section was updated to state: Take NORVIR with meals. Additionally, the following general dosing guidelines and dose modification subsections were added.

<u>General Dosing Guidelines</u>

Patients who take the 600 mg twice daily soft gel capsule NORVIR dose may experience more gastrointestinal side effects such as nausea, vomiting, abdominal pain or diarrhea when switching from the soft gel capsule to the tablet formulation because of greater maximum plasma concentration (C_{max}) achieved with the tablet formulation relative to the soft gel capsule *[see Clinical Pharmacology (12.3)]*.

Patients should also be aware that these adverse events (gastrointestinal or paresthesias) may diminish as therapy is continued.

Dose Modification for NORVIR

Dose reduction of NORVIR is necessary when used with other protease inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir, saquinavir, and tipranavir. Prescribers should consult the full prescribing information and clinical study information of these protease inhibitors if they are co-administered with a reduced dose of ritonavir *[see Warnings and Precautions (5) and Table 5, Established and Other Potentially Significant Drug Interactions]*.

The CONTRAINDICATIONS section was revised to clarify the rationale for the voriconazole and St. John's Wort contraindication and to update the table with clinical comments for consistency with other antiretroviral package inserts as follows:

4 CONTRAINDICATIONS

- When co-administering NORVIR with other protease inhibitors, see the full prescribing information for that protease inhibitor including contraindication information.
- NORVIR is contraindicated in patients with known hypersensitivity to ritonavir or any of its ingredients.
- Co-administration of NORVIR is contraindicated with the drugs listed in Table 2 because ritonavir mediated CYP3A inhibition can result in serious and/or life-threatening reactions. Voriconazole and St. John's Wort are exceptions in that co-administration of NORVIR with voriconazole results in a significant decrease in plasma concentration of voriconazole, and co-administration of NORVIR with St. John's Wort may result in decreased ritonavir plasma concentrations.

Table 2. Drugs that are Contraindicated with NORVIR

Drug Class	Drugs Within Class That Are Contraindicated With NORVIR	Clinical Comments:
Alpha$_1$-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine	Potential for cardiac arrhythmias.
Antifungal	Voriconazole	Coadministration of voriconazole with ritonavir 400 mg every 12 hours significantly decreases voriconazole plasma concentrations and may lead to loss of antifungal response. Voriconazole is contraindicated with ritonavir doses of 400 mg every 12 hours hours or greater *[see Drug Interactions (7.2)].*
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.
GI Motility Agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St Johns Wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to NORVIR or to the class

		of protease inhibitors.
HMG-CoA Reductase Inhibitors:	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
Sedative/hypnotics	Oral midazolam, triazolam	Prolonged or increased sedation or respiratory depression. *[see Drug Interactions (7.2)]*

The following table in Section 7 was updated for consistency with other package inserts. The updated information is described below.

Table 5. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Ritonavir or Concomitant Drug**	**Clinical Comment**
		HIV-Antiviral Agents
HIV Protease Inhibitor: darunavir	When co-administered with reduced doses of ritonavir ↑ darunavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	See the complete prescribing information for Prezista® (darunavir) for details on co-administration of darunavir 600 mg b.i.d with ritonavir 100 mg b.i.d or darunavir 800 mg q.d. with ritonavir 100 mg q.d.
HIV Protease Inhibitor: fosamprenavir	When co-administered with reduced doses of ritonavir ↑ amprenavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	See the complete prescribing information for Lexiva® (fosamprenavir) for details on co-administration fosamprenavir 700 mg b.i.d with ritonavir 100 mg b.i.d., fosamprenavir 1400 mg q.d. with ritonavir 200 mg q.d., or fosamprenavir 1400 mg q.d. with 100 mg q.d.
HIV Protease Inhibitor: tipranavir	When co-administered with reduced doses of ritonavir ↑ tipranavir (↑ AUC, ↑ C_{max}, ↑ C_{min})	See the complete prescribing information for Aptivus® (tipranavir) for details on co-administration of tipranavir 500 mg b.i.d with ritonavir 200 mg b.i.d. There have been reports of clinical hepatitis and hepatic decompensation including some fatalities. All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with tipranavir/ritonavir, and frequently throughout the duration of treatment.
HIV CCR5 – antagonist: maraviroc	↑ maraviroc	Concurrent administration of maraviroc with ritonavir will increase plasma levels of maraviroc. For specific dosage adjustment recommendations, please refer to the complete prescribing information for Selzentry® (maraviroc).
Other Agents		
Antifungal: ketoconazole itraconazole	↑ ketoconazole ↑ itraconazole	High doses of ketoconazole or itraconazole (> 200 mg/day) are not recommended.

voriconazole	↓ voriconazole	Coadministration of voriconazole and ritonavir doses of 400 mg every 12 hours or greater is contraindicated. Coadministration of voriconazole and ritonavir 100 mg should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
Sedative/hypnotics: Parenteral midazolam	↑ midazolam	Co-administration of oral midazolam with NORVIR is CONTRAINDICATED. Concomitant use of parenteral midazolam with NORVIR may increase plasma concentrations of midazolam. Co-administration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.

Section 12.3 Pharmacokinetics was updated to provide information on the tablet formulation as follows:

Absorption

NORVIR tablets are not bioequivalent to NORVIR capsules. Under moderate fat conditions (857 kcal; 31% fat, 13% protein, 56% carbohydrates), when a single 100 mg NORVIR dose was administered as a tablet compared with a capsule, $AUC_{(0-\infty)}$ met equivalence criteria but mean C_{max} was increased by 26% (92.8% confidence intervals: ↑15 -↑39%).

No information is available comparing NORVIR tablets to NORVIR capsules under fasting conditions.

Effect of Food on Oral Absorption

A food effect is observed for NORVIR tablets. Food decreased the bioavailability of the ritonavir tablets when a single 100 mg dose of NORVIR was administered. Under high fat conditions (907 kcal; 52% fat, 15% protein, 33% carbohydrates), a 23% decrease in mean $AUC_{(0-\infty)}$ [90% confidence intervals: ↓30%-↓15%], and a 23% decrease in mean C_{max} [90% confidence intervals: ↓34%-↓11%]) was observed relative to fasting conditions. Under moderate fat conditions, a 21% decrease in mean $AUC_{(0-\infty)}$ [90% confidence intervals: ↓28%-↓13%], and a 22% decrease in mean C_{max} [90% confidence intervals: ↓33%-↓9%]) was observed relative to fasting conditions.

However, the type of meal administered did not change ritonavir tablet bioavailability when high fat was compared to moderate fat meals.

13 Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

From a clinical perspective, the data submitted are sufficient to recommend approval of Norvir 100 mg tablets; however, significant deficiencies were observed at the only drug manufacturing facility for the finished ritonavir tablets (Ludwigshafen, Germany). The Withhold Recommendation

by Compliance precludes approval at this time until Abbott resolves the deficiencies noted by the field investigator. A complete response letter will be issued.

- Risk Benefit Assessment

The risk benefit assessment considered several factors.

- Ritonavir is an essential component for many treatment-naïve and treatment-experienced regimens. The convenience of a stable product not requiring refrigeration is important to patients and may improve adherence to therapy.
- Although the tablet formulation is not bioequivalent to the approved capsule formulation under fed conditions, the increased Cmax does not preclude approval. Sufficient safety data were provided to support the increased exposures of the tablet formulation. 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; therefore, the label states take ritonavir with a meal. Additionally, labeling includes a statement regarding potential for tolerability issues when switching from the capsule to the tablet formulation.
- The higher ritonavir Cmax is not likely to affect the pharmacokinetics of co-administrated protease inhibitors and impact the known safety and efficacy profile. One potential concern was co-administration with tipranavir given the complex drug-drug interaction profile. Exposure related hepatotoxicity was seen in the tipranavir trials; therefore, the impact of a potentially higher ritonavir Cmax on tipranavir exposures was evaluated. The high variability in tipranavir exposures, the lack of increase in tipranavir Cmax, and the 25% increase in tipranavir AUC when ritonavir dose is doubled from 100 mg to 200 mg suggest higher ritonavir exposures from the new tablet formulation will not significantly increase tipranavir exposures. To minimize the potential for tipranavir related hepatotoxicity when co-administered with ritonavir tablets, the ritonavir label was revised to include clinical and laboratory monitoring information, especially in co-infected patients. Additionally, the tipranavir dosing and administration will be revised to state take with meals rather than the currently approved instructions to take without regard to food. This revision is requested because ritonavir tablet exposures under fasted conditions may exceed those from the original ritonavir phase 2 and 3 trials.

As mentioned above, from a clinical perspective, the data submitted are sufficient to recommend approval of Norvir 100 mg tablets; however, a complete response letter will be issued given the significant deficiencies observed at the only drug manufacturing facility for the finished ritonavir tablets (Ludwigshafen, Germany).

- Recommendation for Postmarketing Risk Management Activities

  No postmarketing risk management activities are required for this application.

- Recommendation for other Postmarketing Study Commitments

  No postmarketing study commitments are required for this application

- Recommended Comments to Applicant

No additional comments to convey to the applicant.

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

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KIMBERLY A STRUBLE
10/15/2009