

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-417

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Antiviral Products

Application Number (Drug Name): NDA 22-417
NDA 20-659/S-45

Name of Drug: NORVIR[®] (ritonavir) 100mg tablets
NORVIR[®] (ritonavir) oral solution

Applicant: Abbott Laboratories
Dept. PA76/ Bldg. AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Material Reviewed:

Submission Date: December 19, 2008, January 18, 2010, and January 22, 2010

Receipt Dates: December 19, 2008, January 18, 2010, and January 22, 2010

Submission Dates of Structured Product Labeling (SPL): December 19, 2008

Type of Labeling Reviewed: Word/SPL

The first label submitted on 12/19/08 was compared to the last label submitted on 1/18/10. Included in the annotated label are further agreed revisions submitted on 1/22/10. These were compared to the FDA's November 23, 2009 approved label for NDAs 20-945/S-026 (Norvir Capsule) and 20-659/S-047 (Norvir Solution). Attached annotated label merges all of the above. Please note capsule information was replaced with tablet information accordingly throughout the label.

Background and Summary:

NDA 22-417 is a new drug application providing for the use a 100 mg NORVIR[®] (ritonavir) tablet for the treatment of HIV-1 infection. Information related to the ritonavir tablet for the PEPFAR program was also included in this submission.

NDA 20-659/S-45 is a "Prior Approval" supplemental new drug application already approved for the treatment of HIV-1 infection. This application updates the label with information regarding the new Norvir Tablet formulation. This supplement is the first PLR label format/version.

Norvir Oral Solution will share the same label with Norvir Tablet when the tablet formulation is approved. Abbott submitted the labeling submissions to NDA 22-417 simultaneously referencing these submissions to NDA 20-659/S-45.

Extensive format and content changes and placement were made to the label. Format changes were based on the current SEALD team recommendation. In addition, the Office of Chief Counsel (OCC), the Division of Medication Error and Prevention Analysis (DMEPA), and the Division of Drug Marketing, Advertising, and Communications (DDMAC) were consulted for labeling contents.

Review of the Package Insert:

A. The following was emphasized throughout the label:

NORVIR should be taken with meals.

B. Section 1, Indication and Usage, was updated. The following sentences were deleted:

[Redacted text block] (b) (4)

C. Section 2, Dosage and Administration (D&A):

[Redacted text block] (b) (4)

(D) 64 pages of OtherReviews has been withheld in full immediately following this page as B4 CCI/TS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22417	ORIG-1	ABBOTT LABORATORIES	Ritonavir Tablet
NDA-20659	SUPPL-45	ABBOTT LABORATORIES PHARMACEUTICAL PRODUCTS DIV	NORVIR (RITONAVIR) ORAL SOLUTION

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/s/

AMALIA C HIMAYA
02/01/2010

KAREN D WINESTOCK
02/02/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: September 4, 2009

To: Debra Birnkrant, MD, Director
Division of Anti-Viral Products

Through: Melina Griffis, RPh, Acting Team Leader
Kellie Taylor, PharmD, MPH, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Anne Crandall, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Norvir (Ritonavir) Tablets, 100 mg

Application Type/Number: NDA 22-417

Applicant: Abbott Laboratories

OSE RCM #: 2009-457

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EXECUTIVE SUMMARY

This review was written in response to a request dated March 11, 2009 from the Division of Anti-Viral Products for a medication error assessment of the labels and labeling for the product, Norvir (Ritonavir) tablets (NDA# 22-417). Norvir is currently available as a soft gelatin capsule formulation under NDA # 20-945, which requires refrigeration for storage or, if stored at room temperature, to be used within 30 days. The Applicant submitted a new NDA to provide for a tablet formulation which is always stored at room temperature and will not require refrigeration. Norvir tablets are intended to replace the currently marketed soft gelatin capsules formulation. In addition to having different storage requirements, the tablet and gelatin capsules differ slightly with respect to product administration: Norvir tablets should be taken with food, while Norvir capsules were recommended to be taken with food if possible. However, the tablet and gelatin capsules have the same recommended doses and frequency.

DMEPA conducted an AERS search for medication error cases associated with the use of this product and identified medication error cases related to wrong drug administration (all errors associated with Ritonavir and Retrovir confusion), wrong dose administration (many of these errors related to titration problems), wrong frequency administration and drug interactions. Most cases occurred within the first five years of product introduction to the market place and tapered off after 1999 with only a small number of cases occurring after 2000. Based on these postmarketing events we recommend changes to the package insert primarily related to the titration regimen and maximum recommended dose.

DMEPA also evaluated the container labels, carton labeling and insert labeling to identify vulnerabilities that could lead to medication errors. Our findings indicate that the presentation of information in the labels and labeling introduces vulnerability to confusion that could lead to medication errors. We provide recommendations in Section 5 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Anti-Viral Products (DAVP) for a review of the labels and labeling, contained in NDA 22-417 which includes a new tablet formulation of Norvir, for evaluation to identify areas that could lead to medication errors.

This new 100 mg tablet formulation is intended to replace the currently approved soft gelatin 100 mg capsule.

1.2 PRODUCT INFORMATION

Norvir (Ritonavir) is an antiretroviral oral medication utilized in highly active-antiretroviral therapy (HARRT). Ritonavir is classified as a protease inhibitor and is to be used in combination with other antiretroviral agents for the treatment of HIV. Ritonavir was approved in 1996 as an oral capsule and as a highly concentrated oral solution.

Ritonavir is primarily used in HAART as a booster, although the labeling does not include this indication. Due to the inhibitory characteristics that are displayed during metabolism, Ritonavir is employed to decrease the clearance of other HIV medications allowing for decreased doses and frequencies of other HIV medications. Ritonavir, utilized as an antiviral component of HARRT in adults, is started at 300 mg twice daily and titrated up to 600 mg by mouth twice daily. Ritonavir as a booster in HAART is typically dosed 100 mg once daily.

Because Ritonavir is metabolized via the CYP3A, many toxic and in some cases fatal drug interactions can occur. (b) (4)

Currently, Ritonavir is available as a combination product with Lopinavir (Kaletra), a highly concentrated oral solution and gelatin capsules which require refrigeration. Abbott intends to replace the oral capsules with the new tablet formulation. The new tablet formulation will be the exact same dose (100 mg) and frequency as the capsules.

2 METHODS AND MATERIALS REVIEWED

Norvir is currently marketed in two different dosage forms, the oral solution and the capsules. Therefore, the Division of Medication Error Prevention and Analysis searched the Adverse Events Reporting System (AERS) databases to identify medication error reports related to the use of these products and thus relevant to this review. We considered these cases in our review of the labels and labeling.

Because the DMEPA staff analyzes reported misuse of drugs, the staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. We use Failure Mode and Effect Analysis¹ (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

2.1 LABELS AND LABELING

Using FMEA, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton labeling and insert labeling to identify vulnerabilities that could lead to medication errors.

2.2 ADVERSE EVENTS REPORTING SYSTEM (AERS) SEARCHES

The Division of Medication Error Prevention searched FDA Adverse Event Reporting System (AERS) database to identify post-marketing reports of medication errors associated with Norvir. A search was completed on July 24, 2009 and used the product name, “Norvir”. The search was limited by the high level group term (HLGT), “Medication Errors” and product term (PT), “Product Quality Issue”.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effect Analysis. Boston. IHI:2004.

The reports were manually reviewed to determine if a medication error occurred. If an error occurred, the staff reviewed the reports to determine if the root cause could be associated with the labels or labeling of the product, and thus pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors unrelated to labeling such as patient non-adherence, intentional overdose, etc.) were excluded from further analysis. Duplicate reports were combined into cases. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

3 RESULTS

3.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) DATABASE

Our search of the AERS database retrieved a total of 99 cases. Of these cases, 69 cases were excluded from further evaluation for one of the following reasons:

- An adverse event was identified but no medication error was identified (31 cases),
- Errors involving confusion with dosing or calculating of doses of Norvir oral solution (n=9),
- The error occurred with a concomitant medication listed on the report but did not involve Ritonavir (n=1),
- Medication errors such as patient non-adherence which are unrelated to label or labeling (n=9),
- The error involved an intentional overdose with Ritonavir or another medicine (Ritonavir was a concomitant medication) (n=10),
- Accidental repeat of one dose by patient (n=6) or accidental exposure (n=1),
- The medication error involved a computer program which failed to alert practitioners of known drug interactions with Norvir (n=2),

The remaining 30 cases of errors with Ritonavir are described below.

3.1.1 Wrong Drug (n=22)

The primary type of errors in the AERS cases involved the administration of the wrong drug (Ritonavir vs. Retrovir). The name confusion associated with Ritonavir and Retrovir is well known to this Division and other organizations that monitor drug safety including ISMP and USP. The majority of the errors occurred between 1996 and 1999 when Ritonavir was first introduced into the market.

Twenty-two cases (n=22) involved a wrong drug medication error in which Ritonavir was confused or had the potential to be confused with Retrovir. Retrovir 100 mg capsules and solutions have been marketed since the late 1980s, and Ritonavir 100 mg capsules and 80 mg/mL solution were approved March 1, 1996. The majority of the errors occurred around the time Ritonavir was introduced, and the cause of the errors related to the similarity of the names and overlapping product characteristics (100 mg capsules, similar treatment indications and patient populations). Most reports poorly documented

outcomes and did not describe adverse events, however some of the reports documented the following adverse events: severe vomiting, leukopenia/neutropenia, “feeling poorly” and emerging resistance to anti-viral therapy. Name confusion was explicitly stated as the cause of the errors in some of the cases and a review of the product labels of the currently marketed product does not indicate that label and labeling similarity was a contributing factor (Appendix B).

Since 1999 errors have declined and only one report of wrong drug confusion between this pair was retrieved after 2003. DMEPA continues to monitor this known name pair confusion but does not recommend further action at this time.

3.1.2 Errors associated with Norvir Titration (n=4)

Four cases (n=4) involved inappropriate titration.

- The patient was told to titrate Norvir up to 600 mg twice daily, but the patient started at 600 mg twice daily.
- The patient titrated dose from 200 mg twice daily to 1800 mg daily instead of 1200 mg daily. Causality unknown and vomiting discontinued upon dose decrease.
- There was an error in transcription and as a result the patient started the titration at 600 mg twice daily and titrated up to 1200 mg twice daily rather than titrating up to the maximum dose of 600 mg twice daily.
- The patient took Norvir three times daily during the titration period rather than twice daily. The outcome and causality were unknown.

3.1.3 Monitoring Error/Drug Interaction (n=3)

Three cases (n=3) involved known drug-drug interactions that resulted in an adverse event. Of note, all interactions are appropriately labeled in the insert labeling, including a black box warning for Ergot products.

- One case involved the adverse events that occurred due to the drug-drug interaction between Tegretol and Ritonavir. The patient recovered from the adverse events.
- One case involved an increase in INR due to warfarin and Ritonavir interactions. The outcome was unknown.
- One case involved Cafergot and Norvir. The patient took three Cafergot pills while on Norvir therapy and experienced adverse events due to the interaction and eventually lapsed into a coma. The patient expired 7 days later.

Since the approval of Ritonavir, the package insert has undergone numerous revisions to improve the products labeling. Ritonavir was also given a black box warning to caution practitioners about the use of Ritonavir with certain medications. The package insert is exhaustive in its inclusion of all drug interactions and has comprehensively covered known interactions, including the ones identified in our AERS search. New labels, submitted in 2007, now include an alert to practitioners to find out about medicines that should not be taken with Norvir.

3.1.4 Improper Storage (n=1)

The patient stored his capsules in his car. As a result the soft capsules smelled funny. The patient placed the capsules back in the refrigerator and resumed therapy with the capsules and subsequently experienced adverse events, including big welts on skin, fever, shortness of breath and sweating. It is unclear if these adverse events were a result of the error, however the events reversed after the patient refilled his prescription with properly stored Ritonavir.

3.2 LABEL AND LABELING

3.2.1 Container Label

The net quantity is in close proximity to the strength.

3.2.2 Package Insert

The titration regimen is not discussed in the Patient Information section of the Package Insert.

4 DISCUSSION

The Applicant's proposal to switch the formulation of Ritonavir from a capsule (requiring refrigeration) to a tablet that is to be stored at room temperature will ease storage requirements for both patients and practitioners. Of note, the new tablet formulation will have the same strength and dosing recommendation as the capsule formulation. The tablet and gelatin capsules differ with respect to time of administration. The new Norvir tablets should be taken with food, while the current Norvir capsule formulation is recommended to be taken with food if possible.

Although the Applicant intends to remove the capsules from the market and replace them with the tablets, we have some concern that medication errors may occur when the tablets are introduced in the marketplace since these two formulations will have different storage requirements and can be administered differently with respect to food.

These concerns are based on a review we have in progress evaluating medication errors reported with another HIV-drug, Kaletra (OSE Review 2009-1002). In 2005, Kaletra tablets were approved for marketing. This product was an addition to Kaletra product line, which had been marketed as a capsule formulation since September 2000. Similar to Norvir, the capsule formulation required refrigeration while the tablet formulation is stored at room temperature. Unlike Norvir, Kaletra capsules had a different dose than the Kaletra tablets. Soon after the introduction of the Kaletra tablets, medication errors occurred with these products because practitioners were not aware of the product differences. We considered this possibility in review of the Norvir labels because of the differences in administration between the Norvir capsules and tablets, and noted that the principal display panel of the container label does not highlight the new formulation (tablets) or storage requirements. Given the confusion that arose with the introduction of Kaletra, we would recommend that the Applicant consider additional labeling for a 6 month time period post-approval of the tablet strategies and outreach strategies to educate health care providers and patients of the difference in the product formulations.

4.1 NORVIR MEDICATION ERRORS

4.1.1 Improper Dose

The improper dose cases identified, particularly in the setting of titrations or conversion to and from the oral solution have posed significant challenges in the proper dosing of Ritonavir. The titration regimen is stated in the Dosage & Administration, however this section of labeling doesn't explicitly state the titration should stop at 600 mg twice daily. Additionally, in the Patient Information section of the insert, there is no mention of the titration regimen and the usual schedule of how titrations occur (as it is stated in the Dosage & Administration section). Revisions to labeling as recommended in Section 5.1 could help mitigate the risk of incorrect titration.

4.1.2 Wrong Frequency of Administration

The wrong frequency errors retrieved in our search indicate that there is some confusion among patients in the correct schedule for administering Ritonavir. Most cases occurred in the late 1990's and coincided with the product introduction to the market. The insert labeling is clear on the subject of the approved dose and frequency with the exception of the maximum titration dose.

4.2 LABELS AND LABELING

Our AERS search did not identify any existing vulnerability that could lead to medication errors with the proposed container labels. However, our assessment of the new container label identified that the net quantity statement is in close proximity to the strength, and is difficult to locate. Since the net quantity (30 tablets) is significantly less than the usual months supply (360 tablets) and Norvir will only be available in 30 count bottles (as opposed to 30 and 120 count bottles of the capsule formulation) we feel that it is important to more prominently display the net quantity away from the strength so that the proper number of bottles (up to 12) may be dispensed to patients.

5 CONCLUSIONS AND RECOMMENDATIONS

The Applicant's proposed container label and labeling that will accompany the new tablet formulation of Norvir contain all the pertinent information in a readable and accessible manner with some notable exceptions. These exceptions include, revising language in the insert labeling related to the recommended titration regimen to avoid errors seen previously with the capsule formulation.

We also provide recommendations in Section 5.2 below that aim at increasing awareness of differences between the capsule and tablet formulation.

We are willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Twanda Scales, Regulatory Safety Project Manager, at 301-796-5056.

5.1 COMMENTS TO THE DIVISION

A. General Information

DMEPA recommends that the Applicant implement an outreach program to inform patients and practitioners about the introduction of the new Norvir tablet formulation. The communications developed should focus on three pertinent factors; the change in storage requirements, the change from capsule to tablet, and the differences in administration with respect to food.

B. Package Insert

1. The Dosage and Administration and Patient Counseling Section (Sections 2.1 and 17) should clarify the titration regimen by explicitly stating the maximum dose of 600 mg twice daily should not be exceeded upon completion of the titration.
2. The Dosage and Administration (subsection 2.1 and subsection 2.2) should be revised to emphasize that Norvir tablets should be taken twice daily with food.

C. Container Size

We note that the Applicant proposed a 30 tablet container. Given the dosage and administration of this product, the container size does not support the upper dose of this product. The capsules are available in both a 30 and 120 count container. Consider requesting the Applicant to provide a larger size bottle as an option.

5.2 COMMENTS TO THE APPLICANT

Container Label

1. Relocate the net quantity away from the product strength to ensure that that the net quantity statement can be readily identified when dispensing the products.
2. Revise the labels to include an alert on the principle display panel. This alert should notify practitioners and patients of the new storage requirement and new dosing with respect to food in order to avoid confusion with the introduction of the new tablets. We recommend this alert be implemented for the first six months of new product marketing.

REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

APPENDICES

Appendix A Norvir Labels

Approved Norvir Container Label ; 30 capsules, 120 capsules

The image shows the container label for Norvir 120 Capsules. On the left, there is a vertical barcode with the number 02-89-48-2/R1 printed vertically. The main label area is purple and white. At the top, it reads "NDC 0074-6633-96 120 Capsules". Below this, the product name "NORVIR® (RITONAVIR CAPSULES) SOFT GELATIN 100 mg" is prominently displayed. A red-bordered box contains the text "ALERT Find out about medicines that should NOT be taken with NORVIR." Below the alert, it says "For Third Party Study Use Only Not for Commercial Resale or Reimbursement". At the bottom left of the label, there is a small icon and the text "Enclosure is provided with tear-off patient information. Rx only". To the right of the label, there is a column of text providing instructions: "Do not accept if seal over bottle opening is broken or missing. Dispense in original container. Each capsule contains: 100 mg ritonavir. Each capsule is manufactured with up to 12% ethanol in the capsule fill. Store in refrigerator between 36°-46°F (2°-8°C). Protect from light. Avoid exposure to excessive heat. Refrigeration by patient is recommended but not required if used within 30 days and stored below 77°F (25°C). See enclosure for prescribing information. Abbott Laboratories North Chicago, IL 60064, U.S.A."

The image shows the container label for Norvir 30 Capsules. On the left, there is a vertical barcode with the number 0074663330 printed vertically. The main label area is purple and white. At the top, it reads "NDC 0074-6633-30 30 Capsules". Below this, the product name "NORVIR® (RITONAVIR CAPSULES) SOFT GELATIN 100 mg" is prominently displayed. A red-bordered box contains the text "ALERT Find out about medicines that should NOT be taken with NORVIR." Below the alert, it says "Note to Pharmacist: Do not cover ALERT box with pharmacy label. Enclosure is provided with tear-off patient information." At the bottom right of the label, there is a small icon and the text "Rx only". To the right of the label, there is a column of text providing instructions: "Do not accept if seal over bottle opening is broken or missing. Dispense in original container. Each capsule contains: 100 mg ritonavir. Each capsule is manufactured with up to 12% ethanol in the capsule fill. Store in refrigerator between 36°-46°F (2°-8°C). Protect from light. Avoid exposure to excessive heat. Refrigeration by patient is recommended but not required if used within 30 days and stored below 77°F (25°C). See enclosure for prescribing information. Product of Italy Abbott Laboratories North Chicago, IL 60064, U.S.A."

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ANNE CRANDALL
09/04/2009

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09/04/2009

KELLIE A TAYLOR
09/04/2009

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09/04/2009

MEMORANDUM

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

DATE: July 27, 2009

TO: John Lazor, Pharm.D.
Director, Division of Clinical Pharmacology 4
(DCP)

FROM: Xikui Chen, Ph.D.
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yan 7/27/09
Associate Director, Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-417, Norvir®
(Ritonavir) 100 mg Film-Coated Tablets, Sponsored
by Abbott Laboratories

At the request of DCP, the Division of Scientific Investigations audited records of the clinical and analytical portions of the following bioequivalence study:

Study M10-307: Comparison of the Single-Dose Bioavailability of a Ritonavir 100 mg Film-Coated Tablet Relative to a Ritonavir 100 mg Soft Gelatin Capsule in Healthy Adult Subjects

The clinical and analytical portions of this study were conducted at (b) (4) respectively. Following the inspection of (b) (4) (6/9-11/09), there were no significant findings and no FDA Form 483 was issued. Following the inspection of (b) (4) (5/3-9/2009), no FDA Form 483 was issued. However, we discussed a matter for the bioanalytical method entitled "Quantitation of ABT-538 (Ritonavir) and ABT-378 (Lopinavir) in Human Plasma by LC/MS/MS using (b) (4) (b) (4) with the firm. Specifically, this method was validated to analyze both ritonavir and lopinavir simultaneously in the same sample, but it was used to analyze the study plasma samples that contained only ritonavir. We also noticed that the calibrators and

quality control (QC) samples in the analytical runs contained both ritonavir and lopinavir in the same sample. Nevertheless, as the clinical plasma samples of a subject were analyzed in the same analytical run for the test and reference products, the impact of this discussion item would be minimal, if any. The bioanalytical assay results can be considered adequate for review.

Conclusion:

Following the above inspections, DSI recommends that the data from Study M10-307 be accepted for review.

After you have reviewed this memo, please append it to the original NDA submission.

Xikui Chen 7-27-09
Xikui Chen, Ph.D.

Final Classification:

NAI - [REDACTED] (b) (4)
VAI- [REDACTED] (b) (4)

cc:

DSI/Rivera-Lopez/CF

DSI/Viswanathan/Chen/Yau

OND/OAP/DAVP/Rashmi Kalla

OTS/OCP/DCP4/Stanley Au

By e-mail:

HFR-NE3550/Nicholas Mendiola/George C. Amedro

HFR-SW3515/Ismael Olvera

CDER DSI PM TRACK

Draft: XC 7/7/09

Edit: JAO 7/7/09; MKY 7/22/09

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/s/

XIKUI CHEN

07/27/2009

Hard copies available upon request



Internal Consult

Pre-decisional Agency Information

To: Rashmi Kalla
Division of Anti-Viral Products (DAVP)

From: Lynn Panholzer, PharmD
Aline Moukhtara, RN
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Date: July 2, 2009

Re: Norvir (ritonavir) Tablets, NDA 22-417
Labeling Review: Package Insert, Patient Package Insert

Thank you for forwarding this consult request, dated February 13, 2009, to DDMAC. The following comments are based on the draft package insert (PI) and patient package insert (PPI) submitted by Abbott Laboratories on February 5, 2009, available at <\\CDSESUB1\EVSPROD\NDA022417\0004>.

Draft Package Insert

General Comment

- We note multiple references to “HIV” in the proposed label. Other antiretroviral labels specifically refer to “HIV-1.” Should all of the references to “HIV” in the Norvir label be changed to “HIV-1”?

HIGHLIGHTS OF PRESCRIBING INFORMATION

- The presentation of risk information in HIGHLIGHTS is very important promotionally because many companies use HIGHLIGHTS as a guide to determine which risks to include in promotional materials and what specific information about those risks to include. This is particularly important for direct-to-consumer promotion, since HIGHLIGHTS can be used as the Brief Summary attached to ads. In light of this, we have the following comments:
 - The CONTRAINDICATIONS section of HIGHLIGHTS does not appear to address the contraindications to voriconazole or St. Johns Wort. We recommend that language addressing these contraindications be included. We also recommend

that you consider listing the specific drugs that are contraindicated.

- The WARNINGS AND PRECAUTIONS section of HIGHLIGHTS combines 3 risks – diabetes mellitus/hyperglycemia, immune reconstitution syndrome, redistribution/accumulation of body fat – under one bullet point. This presentation minimizes the risk of immune reconstitution syndrome and redistribution/accumulation of body fat because readers may not read past the diabetes mellitus/hyperglycemia risk. If these latter two risks are deemed important enough for HIGHLIGHTS, we recommend that you consider presenting them separately or otherwise present them such that each of the three risks is given similar emphasis.
- The presentation of “Allergic Reactions” in the WARNINGS AND PRECAUTIONS section of HIGHLIGHTS minimizes this risk because it fails to communicate the potential severity of the risk. Specifically, it does not reflect that this risk could be as serious as anaphylaxis, Stevens-Johnson Syndrome, bronchospasm, and angioedema. We recommend that you consider including specific reactions that communicate the potential severity of the risk.
- The presentation of most common adverse reactions occurring at “>5%” may minimize the actual incidences of many of these reactions in clinical trials. For example, asthenia (up to 15.3%), diarrhea (up to 23.3%), nausea (up to 29.8%), and vomiting (up to 17.4%), occurred in a larger percentage of patients taking Norvir alone, and in even higher percentages in patients taking Norvir with ZDV or saquinavir, than is reflected in “>5%.” Would it be appropriate to use a range to communicate incidences?

Additionally, the presentation does not communicate that the reactions listed that occurred at this frequency are the most common adverse reactions **of moderate to severe intensity**. We recommend that this information be included.

FULL PRESCRIBING INFORMATION

(b) (4)



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/s/

Lynn Panholzer
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Aline Moukhtara
7/2/2009 11:23:40 AM
DDMAC CONSUMER REVIEWER

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 22-417 (Norvir [Ritonavir] Tablets) NDA 20-659 (Norvir [Ritonavir] Oral Solution)	Brand Name	Norvir®
OCP Division (I, II, III, IV, V)	IV	Generic Name	Ritonavir
Medical Division	DAVP	Drug Class	Protease inhibitor
OCP Reviewer	Stanley Au	Indication(s)	HIV
OCP Team Leader	Kellie Reynolds	Dosage Form	Tablet/Oral Solution
Pharmacometrics Reviewer		Dosing Regimen	
Date of Submission	December 19, 2008	Route of Administration	Oral
Estimated Due Date of OCP Review (final draft prior to briefing)	July 29, 2009	Sponsor	Abbott
Medical Division Due Date	August 19, 2009	Priority Classification	Standard
PDUFA Due Date	October 19, 2009		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X (Module 5.2: Tabular Listing of All Clinical Studies)			
HPK Summary	X (Module 2.7.2: Summary of Clinical Pharmacology Studies)			
Labeling	X (Module 1.14.1: includes labeling history, annotated draft labeling, and draft labeling)			

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Reference Bioanalytical and Analytical Methods	X (Module 2.7.1: Summary of Bioanalytical Methods and Module 5.3.1.4: Reports of Bioanalytical and Analytical Methods for Human Studies)	4 (these are the bioanalytical reports for M10-307, M10-263, M10-235, M06-842) On 1/28/09, the ritonavir method validation report and the freeze thaw and long term stability reports were submitted.		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X (Module 5.3.1.1 and 5.3.1.2: M06-842, M10-263 and M10-307)	3	1	M10-307 utilized the final commercial RTV tablet, M06-842 and M10-263 did not.
replicate design; single / multi dose:				

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Food-drug interaction studies	X (Module 5.3.1.1: M10-235)	1	1	M10-235 utilized the final commercial RTV tablet
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			The RTV tablet was compared to the RTV soft gel capsules that were originally approved.
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	The dose is based on the approved doses in the original NDA application for the capsule.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		Sponsor has been requested to submit both the actual sampling times and post dose sampling times for the

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					individual ritonavir PK concentration data and the derived individual PK parameters in SAS transport file format.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	A request to waive pediatric studies for this NDA has been submitted.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___Yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

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

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

Stanley Au
2/5/2009 02:49:14 PM
PHARMACOLOGIST

Kellie Reynolds
2/6/2009 08:35:59 AM
BIOPHARMACEUTICS