DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20659/S-056
NDA 22417/S-07

SUPPLEMENT APPROVAL

Abbott Laboratories
Attention: Nancy P. Aiello
Associate Director, Regulatory Affairs - PPG
Dept.PA77, Bldg. AP34-3
200 Abbott Park Road
Abbott Park, IL 60064-6188

Dear Ms. Aiello:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received November 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Norvir® (ritonavir) Oral Solution (NDA 20659) and Tablets (NDA 22417).

We acknowledge receipt of your amendment dated December 21, 2011 in response to our General Advice letter dated, December 12, 2011.

We also refer to our letter dated October 19, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

In addition, we refer to non-safety labeling changes in our October 19, 2011 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

These supplemental new drug applications provide for revisions to the labeling for Norvir® (ritonavir) Oral Solution (NDA 20659) and Tablets (NDA 22417), consistent with our October 19 and December 12, 2011 letters, as follows (additions are noted by underline and deletions are noted by ~~strikethrough)~~.

1. The phrase, “Warnings and Precautions, Immune Reconstitution Syndrome (5.8) 11/2011” has been added under the **RECENT MAJOR CHANGES** in the Highlights section of the labeling.

2. The revision date has been changed from 04/2010 to 11/2011 throughout the labeling

3. The **WARNINGS AND PRECAUTIONS/Immune Reconstitution Syndrome** sub-section has been revised as follows:

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including NORVIR. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

4. **Table 5, in DRUG INTERACTIONS/ Established and Other Potentially Significant Drug Interactions** sub-section, has been revised as follows:

Table 5. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: ***Drug Name***	***Effect on*** ***Concentration of Ritonavir or Concomitant***	**Clinical Comment**
HMG-CoA Reductase Inhibitor: atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	~~Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with NORVIR.~~ Titrate atorvastatin and rosuvastatin dose carefully and use the lowest necessary dose. If NORVIR is used with another protease inhibitor, see the complete prescribing information for the concomitant protease inhibitor for details on co-administration with atorvastatin and rosuvastatin.

5. The sixth bulleted paragraph of the **PATIENT COUNSELING INFORMATION/Information For Patients/**General Information sub-section was revised as follows:

- ~~NORVIR is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV-1 disease. The long-term effects of NORVIR are unknown at this time. Patients should be told that~~

~~there are currently no data demonstrating that therapy with NORVIR can reduce the risk of transmitting HIV-1 to others through sexual contact, sharing needles, or being exposed to their blood. For their health and the health of others, it is important that they always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. They should also be advised to never re-use or share needles.~~

NORVIR is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using NORVIR.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if NORVIR can be passed to ~~your~~ the baby ~~in your~~ through breast milk and whether it could harm ~~your~~ the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

6. **Patient Information**:

a. The third paragraph of the "**What is NORVIR?**" section has been revised as follows:

- ~~NORVIR is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV-1 disease. The long-term effects of NORVIR are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with NORVIR can reduce the risk of transmitting HIV-1 to others through sexual contact, sharing needles, or being exposed to their blood. For their health and the health of others, it is important that they always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.~~

  ~~They should also be advised to never re-use or share needles.~~

NORVIR does not cure HIV infection or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using NORVIR.

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.

~~**Does NORVIR Reduce the Risk of Passing HIV to Others?**~~

~~NORVIR does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.~~

b. The sixth bulleted paragraph in the "**What Should I Tell My Doctor Before Taking NORVIR?** section has been revised as follows:

- ~~If you~~ are breastfeeding: **Do not breastfeed.** We do not know if NORVIR can be passed to ~~your~~ the baby ~~in~~ through your breast milk and whether it could harm ~~your~~ the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk. ~~Mothers should not breast-feed if they are taking NORVIR. It is not known whether ritonavir is passed to the baby through breast milk or whether the baby could experience side effects as a result. If you are HIV positive, you may pass HIV onto your baby. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby.~~

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Deputy Director for Safety
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

KENDALL A MARCUS
02/17/2012