DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Miles D. White, MBA
Chairman and Chief Executive Officer
Abbott Laboratories
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, Illinois 60064-6157

Re: NDA 20-659
Norvir® (ritonavir capsules) Soft Gelatin
MACMIS # 12335

WARNING LETTER

Dear Mr. White:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a promotional cost comparison chart[1] (cost chart) (04A-017-B002-1), two brochures (03A-036-6655-2 and 04A-017-B770-2), a pill wall chart (01K-036-1054-1), and updates[2] to a promotional web site (www.norvir.com) for Norvir® (ritonavir capsules) Soft Gelatin disseminated by Abbott Laboratories, Inc. (Abbott). The cost chart is false or misleading in violation of section 502(a) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 352(a)) because it claims that Norvir has the lowest daily cost of all antiretroviral drugs and minimizes the risks of Norvir. In addition, these materials were not submitted to FDA under cover of Form 2253, as required by 21 CFR 314.81(b)(3)(i). Your cost chart raises significant public health and safety concerns because of the violations outlined above and the potential adverse impact these false and misleading messages may have on the HIV community by promoting a subtherapeutic dose and regimen of Norvir.

Background
The Indications and Usage section of the approved product labeling (PI) for Norvir states:

> NORVIR is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on the results from a study in patients with advanced HIV disease that showed a reduction in both mortality and AIDS-defining clinical events for

[1] The cost chart, initially brought to DDMAC's attention in hard copy, was also placed on the web at www.norvir.com.
[2] A code imbedded in www.norvir.com indicates that you updated the site in March 2001, June 2002, and February 2004 (the February 2004 version of this website is what is discussed in this letter).

patients who received NORVIR either alone or in combination with nucleoside analogues. Median duration of follow-up in this study was 13.5 months.

The Dosage and Administration section of the PI states (in pertinent part):

> The recommended dosage of ritonavir is 600 mg twice daily by mouth. Use of a dose titration schedule may help to reduce treatment-emergent adverse events while maintaining appropriate ritonavir plasma levels. Ritonavir should be started at no less than 300 mg twice daily and increased at 2 to 3 day intervals by 100 mg twice daily.

There are serious, potentially fatal risks associated with the use of Norvir. The PI includes a Boxed Warning that states (in pertinent part):

> **CO-ADMINISTRATION OF NORVIR WITH CERTAIN NONSEDATING ANTIHISTAMINES, SEDATIVE HYPNOTICS, ANTIARRHYTHMICS, OR ERGOT ALKALOID PREPARATIONS MAY RESULT IN POTENTIALLY SERIOUS AND/OR LIFE-THREATENING ADVERSE EVENTS DUE TO POSSIBLE EFFECTS OF NORVIR ON THE HEPATIC METABOLISM OF CERTAIN DRUGS.**

As communicated in the Contraindications, Warnings, and Precautions sections of the PI, Norvir has been linked to a number of risks. For example, co-administration of Norvir is contraindicated with amiodarone, bepridil, flecainide, propafenone, quinidine, astemizole, terfenadine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, midazolam, and triazolam. (see Table 4 of the PI). Concomitant therapy with these drugs and Norvir could result in serious and/or life-threatening reactions such as cardiac arrhythmias, prolonged or increased sedation, and respiratory depression.

Likewise, the PI cautions that "Particular caution should be used when prescribing sildenafil in patients receiving NORVIR. Co-administration of NORVIR with sildenafil is expected to substantially increase sildenafil concentrations (11-fold increase in AUC) and may result in an increase in sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection."

The PI also states:

> **Resistance/Cross-resistance.** Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of ritonavir therapy following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors.
>
> **Lipid Disorders.** Treatment with NORVIR therapy alone or in combination with saquinavir has resulted in substantial increases in the concentration of total triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating NORVIR therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate.

Finally, under the heading "Information for Patients," the PI states (in relevant part)

> "Patients should be informed that NORVIR is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIVinfection, including opportunistic infections. Patients should be told that the long-term effects of NORVIR are unknown at this time. They should be informed that NORVIR therapy has not been shown to reduce the risk of transmitting HIV to others through sexual contact or blood contamination."

Misleading Comparative Claim

The cost chart is misleading for two reasons. First, it compares a subtherapeutic dose of Norvir (100 mg once daily) to the labeled dosing regimens of other antiretroviral agents. Second, the chart implies that Norvir may be used other than in combination therapy, when it is not labeled for such use. Given by itself as a subtherapeutic dose, Norvir would likely have no antiviral activity and would place patients at risk for developing protease inhibitor resistance mutations.

Subtherapeutic Dose

The cost chart compares the daily costs (based on wholesale acquisition costs) of common antiretroviral drugs. According to footnote 1, the dosages selected for the compared drugs "reflect commonly prescribed milligrams per day." Norvir appears in the cost chart with a daily cost of $8.57 per day for a dosage of 100 milligrams/day. All the other compared drugs have higher daily costs, ranging from $9.84 to $32.00. The cost chart thus suggests that Norvir, at a dosage of 100 milligrams/day, has the lowest daily cost of all the antiretroviral drugs listed. However, FDA has found Norvir to be safe and effective only at the dosages set forth in the PI (300-600 mg twice daily).

Monotherapy/Combination Therapy

Norvir has been determined to be safe and effective only when used in combination with other antiretroviral agents. However, the cost chart compares the cost of Norvir to other antiretrovirals as monotherapy, and includes a comparison to an antiretroviral that is approved as monotherapy, suggesting that all antiretrovirals can be taken effectively as monotherapy. With the exception of Trizivir®, this has not been demonstrated by substantial evidence or substantial clinical experience. The footnote “Please reference the Prescribing Information for these products for complete dosing instructions” in smaller print at the bottom of the cost chart is not sufficient to correct the overall misleading implication.

Additionally, the claim is accompanied by a citation to the PI for Reyataz™ (atazanavir sulfate), which is another of the antiretroviral drugs listed in the cost chart. According to the PI for Reyataz, that drug can be coadministered with Norvir at a 100mg dose as part of a combination regimen. Therefore, FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Norvir is safe and effective as monotherapy at 100 milligrams/day. Accordingly, the cost chart is false or misleading.

Misleading Presentation of Risk Information

The contraindicated list of drugs provided with the cost chart is incomplete because you excluded ergonovine and methylergonovine. Both drugs are contraindicated with Norvir due to a potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues. In addition, the cost chart fails to disclose that adverse events may occur when Norvir is taken concomitantly with sildenafil and the possibility exists of cross resistance among protease inhibitors and of lipid disorders.

Finally, the cost chart fails to state, as the PI notes, that Norvir is not a cure for HIV infection and that patients taking the drug may continue to acquire illnesses associated with advanced HIV infection. Neither does the cost chart state that the long term effects of Norvir are unknown, and that Norvir has not been shown to reduce the risk of transmitting HIV to others through sexual contact or blood contamination. FDA previously brought similar deficiencies to Abbott's attention in a letter dated April 27, 2001. In a response dated May 18, 2001, Abbott agreed to "revise or destroy" three promotional materials that "d[id] not comply with DDMAC's request" i.e., promotional materials directed to consumers should prominently convey that the drug does not cure HIV infection, does not reduce the transmission of HIV infection, must be taken in combination regimens (if applicable), and refrain from using images not generally representative of patients with HIV infection.

Failure to Submit Under Form 2253

FDA regulations require you to submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling.

You did not submit any of the promotional materials referred to in this letter to FDA under cover of Form 2253 as required by 21 CFR 314.81(b)(3)(i).

Conclusions and Requested Actions

The cost chart misleadingly claims that Norvir has the lowest daily cost of all antiretroviral drugs and minimizes the risks of Norvir, and thus misbrands Norvir under 21 U.S.C. 352(a). In addition, the promotional materials identified above were not submitted to FDA under cover of Form 2253, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that Abbott immediately cease the dissemination of violative promotional materials for Norvir such as those described above. Please submit a written response to this letter on or before June 25, 2004, stating whether you intend to comply with this request, listing all violative promotional materials for Norvir such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this particular matter please refer to the MACMIS ID # 12335 in

addition to the NDA number(s). We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Norvir comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

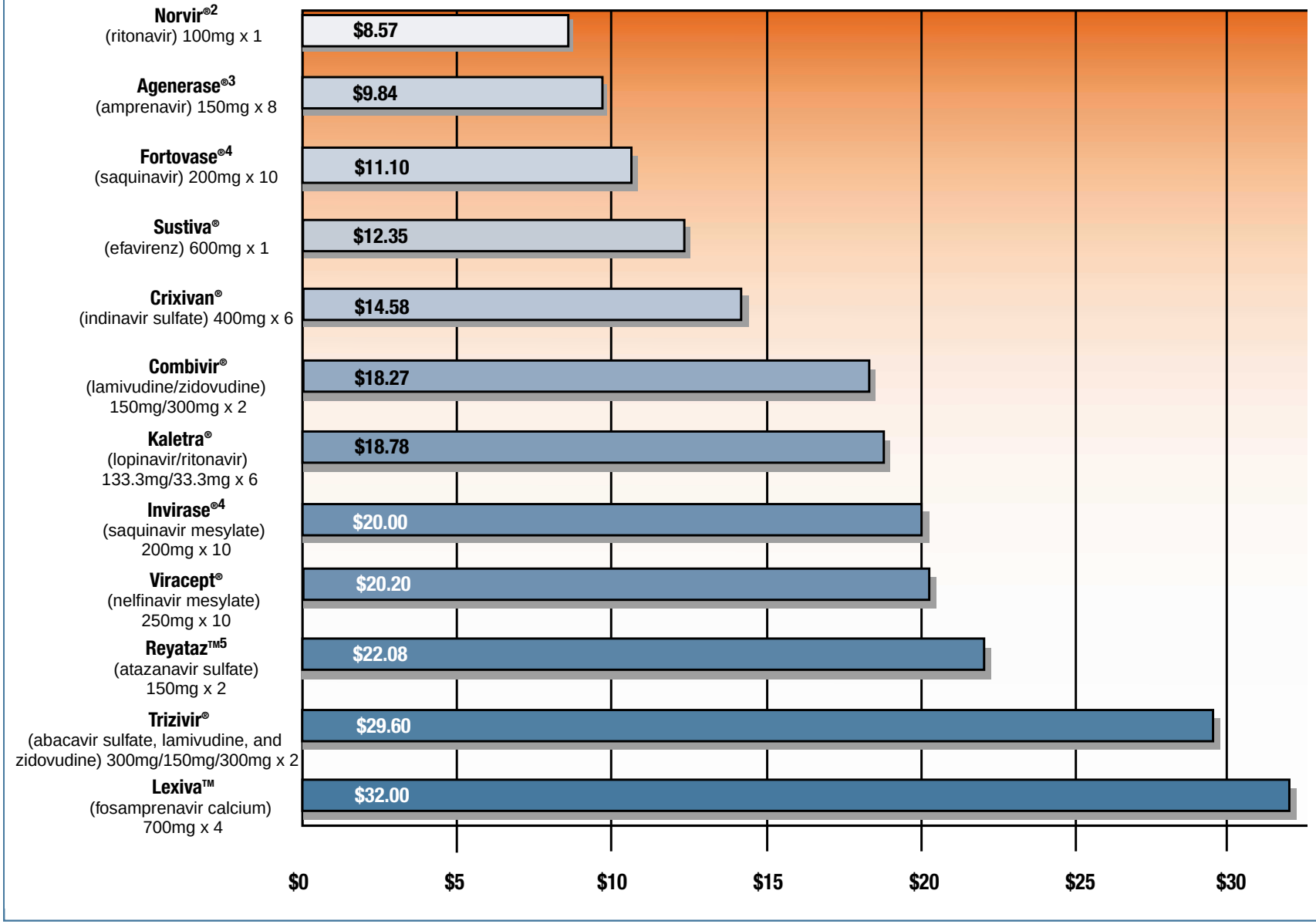
Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Thomas Abrams
6/10/04 10:19:10 AM

Daily Cost of Common ARV Agents[1]



[1]Based on wholesale acquisition cost (WAC), Price Probe, access date, January 8, 2004. WAC may not represent actual price paid by pharmacies or consumers. Price comparisons do not imply comparable effectiveness of products. Dosages reflect commonly prescribed milligrams per day.
[2]Reyataz package insert.
[3]Verispan LLC, HIV Therapy Audit, Q3 2003.
[4]www.fda.gov; December 24, 2003.
[5]IMS Health, Weekly NPA Plus 7 Audit, December 26, 2003.
[6]Kaletra package insert.
[7]Norvir package insert.

Please see accompanying full Prescribing Information for Norvir and Kaletra.

The brands listed are trademarks of their respective owners.

Please reference the Prescribing Information for these products for complete dosing instructions.

Kaletra® (lopinavir/ritonavir) Indication and Safety Information[6]

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV infection. This indication is based on analyses of plasma HIV RNA levels and CD_4 cell counts in controlled studies of KALETRA of 48 weeks duration and in smaller, uncontrolled dose-ranging studies of KALETRA of 72 weeks duration.

KALETRA should not be given to patients who have had an allergic reaction to KALETRA (lopinavir/ritonavir) or any of its ingredients. KALETRA is contraindicated with astemizole, cisapride, dihydroergotamine, ergonovine, ergotamine, flecainide, methylergonovine, midazolam, pimozide, propafenone, terfenadine or triazolam. KALETRA should not be co-administered with lovastatin, simvastatin, St. John's wort (*Hypericum perforatum*) or rifampin.

Concomitant use with sildenafil is expected to substantially increase sildenafil concentrations and may increase sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection.

Pancreatitis, including some fatalities, has been observed in patients receiving KALETRA.

Caution should be exercised when administering KALETRA to patients with hepatic impairment including those with hepatitis B or C or marked elevations in transaminases. There have been reports of hepatic dysfunction, including some fatalities. A causal relationship with KALETRA therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of KALETRA treatment.

Treatment with KALETRA has resulted in large increases in total cholesterol and triglycerides, which should be monitored before and during therapy.

In patients receiving PIs, increased bleeding (in patients with hemophilia), new onset or exacerbation of diabetes mellitus, and hyperglycemia have been reported.

Various degrees of cross-resistance among protease inhibitors have been observed.

Redistribution and accumulation of body fat has been reported in patients receiving ARV therapy. A causal relationship has not been established.

In KALETRA clinical trials, the most common adverse events of moderate to severe intensity reported in ≥2% of patients were abdominal pain, asthenia, diarrhea, headache, nausea, and vomiting.

Norvir® (ritonavir) Indication and Safety Information[7]

NORVIR is indicated in combination with other antiretroviral agents for the treatment of HIV infection. This indication is based on the results from a study in patients with advanced HIV disease that showed a reduction in both mortality and AIDS-defining clinical events for patients who received NORVIR either alone or in combination with nucleoside analogues. Median duration of follow-up in this study was 13.5 months.

NORVIR may not be right for everyone, including people with liver disease, hepatitis, or hemophilia.

Redistribution/accumulation of body fat has been observed in patients receiving protease inhibitors.

Elevated blood sugar levels have been reported in patients taking protease inhibitors.

Allergic reactions ranging from mild to severe have been reported.

Pancreatitis has been observed in patients receiving NORVIR therapy, including those who developed high triglycerides.

The risk of muscle pain, including severe muscle disease, may be increased when NORVIR is used in combination with HMG-CoA reductase inhibitors (statin class of lipid-lowering drugs).

Concomitant use of NORVIR with St. John's wort (Hypericum perforatum) is not recommended. St. John's wort may reduce NORVIR levels, lead to increased viral load and possible resistance to protease inhibitors.

Common adverse reactions include diarrhea, vomiting, asthenia, taste perversion, abdominal pain, anorexia, headache, peripheral paresthesia, circumoral paresthesia, and dizziness.

Coadministration of NORVIR with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations may result in potentially serious and/or life-threatening adverse events.

NORVIR is contraindicated with the drugs listed below:

amiodarone	dihydroergotamine	midazolam	quinidine
astemizole	ergotamine	pimozide	terfenadine
bepridil	flecainide	propafenone	triazolam
cisapride			

Please see accompanying full Prescribing Information for Norvir and Kaletra.

Abbott Laboratories
Abbott Park, IL 60064

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