DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Mr. Greg Murawski, MBA, RAC
Manager, Regulatory Affairs
Abbott Laboratories
Dept. 491, Bldg. AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Re: NDA #21-226, 21-251
Kaletra® (lopinavir/ritonavir) Capsules
Kaletra® (lopinavir/ritonavir) Oral Suspension
MACMIS ID#: 12810

Dear Mr. Murawski:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed two direct-to-consumer (DTC) promotional pieces for Kaletra® (lopinavir/ ritonavir) Capsules and Oral Suspension disseminated by or on behalf of Abbott Laboratories (Abbott), obtained by DDMAC through routine surveillance. The first is a print advertisement (ad) (04B-036-C233-1) that appeared in the May 2004 issue of POZ magazine, a publication directed toward the HIV community. The second is a restroom poster (04D-036-D455-1) (poster), submitted under cover of Form 2253. These promotional pieces overstate the effectiveness of Kaletra, and omit the indication and material information about the risks associated with Kaletra in the treatment of HIV infection. Therefore, the promotional materials misbrand the drug under Sections 502(a) and (n) of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 352(n)).

Background

According to the FDA-approved labeling (PI), Kaletra is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in Kaletra, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir. According to the indications and usage section of the PI:

> 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 is associated with several potentially life-threatening adverse events. The contraindications section of the PI states (in pertinent part):

> Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

In addition, the warnings section of the PI states that concomitant use of Kaletra with sildenafil, lovastatin, simvastatin, other HMG-CoA reductase inhibitors, or St. John's wort can lead to significant drug-drug interactions. The warnings section of the PI states:

> **Drug Interactions**
> KALETRA is an inhibitor of the P450 isoform CYP3A. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects.
>
> Particular caution should be used when prescribing sildenafil in patients receiving KALETRA. Co-administration of KALETRA with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events including hypotension, syncope, visual changes and prolonged erection (see **PRECAUTIONS: Drug Interactions** and the complete prescribing information for sildenafil.)
>
> Concomitant use of KALETRA with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including KALETRA, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy, including rhabdomyolysis may be increased when HIV protease inhibitors, including KALETRA, are used in combination with these drugs.
>
> Concomitant use of KALETRA and St. John's wort (hypericum perforatum), or products containing St. John's wort, is not recommended. Co-administration of protease inhibitors, including KALETRA, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of lopinavir and lead to loss of virologic response and possible resistance to lopinavir or to the class of protease inhibitors.
>
> **Pancreatitis**
> Pancreatitis has been observed in patients receiving KALETRA therapy, including those who develop marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to KALETRA has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see **PRECAUTIONS – Lipid Elevations**). Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during KALETRA therapy.

> **Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate**.
>
> **Diabetes Mellitus/Hyperglycemia**
> New onset diabetes mellitus, exacerbations of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

Failure to Meet Brief Summary Requirements

The print ad for Kaletra presents five different chronological photographs of a man with captions indicating that the photographs were taken in May 2000, April 2001, October 2002, August 2003, and March 2004. The man appears to be in good health in all five photographs and undergoes no visible changes from one photograph to the next. Below the photographs is the following text: "Where do you see yourself in 5 years? Talk to your doctor about Kaletra." The ad thus implies that that the man shown in the photographs has been healthy over the past several years and that this positive outcome is a direct result of taking Kaletra. Accordingly, the ad implies that patients taking Kaletra can expect to survive and be healthy for at least five years.

Similarly, the poster presents four different photographs of the same man depicted over five years (May 1999, March 2002, April 2004, one undated). The headline of the poster is "Where do you see yourself in 5 years?" and the text below states, "Talk to your doctor about Kaletra." In addition, the poster presents the tagline "Still undetectable. Still in control." beneath the product logo. Like the print ad, the poster suggests that patients taking Kaletra can expect to survive and be healthy for at least five years, and have undetectable HIV RNA levels and their disease under control at the end of that five-year period.

Neither promotional piece contains the information described above in the Background section. Specifically, the promotional pieces fail to provide the indication for Kaletra. They also fail to provide any risk information regarding Kaletra.

As noted, FDA's approval of Kaletra was based on analyses of plasma HIV RNA levels and CD_4 cell counts in controlled studies of 48 weeks duration and in smaller uncontrolled dose-ranging studies of 72 weeks duration. FDA is not aware of substantial evidence or substantial clinical experience to support claims of survival, good health, undetectable HIV RNA levels, and disease control for five years. The poster has a disclaimer indicating that "Individual Results May Vary." This does not correct the misleading impression concerning the effectiveness of Kaletra conveyed by the poster.

Conclusion and Requested Action

For the reasons discussed above, the print ad and poster misbrand Kaletra under Sections 502(a) and (n) of the Act.

DDMAC requests that Abbott immediately cease the dissemination of promotional materials for Kaletra the same or similar to those described above. Please submit a written response to this letter on or before November 15, 2004, describing your intent to comply with this request, listing all promotional materials for Kaletra the same or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at (310) 594-6771. In all future correspondence regarding this matter, please refer to MACMIS #12810, in addition to NDA 21-226, 21-251. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion. 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 Kaletra comply with all applicable requirements of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Jennifer C. Murphy, Pharm.D.
Consumer Promotion Analyst
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/

Jennifer Murphy

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