DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Miles D. White
Chairman of the Board & Chief Executive Officer
Abbott Laboratories
100 Abbott Park Road/Dept-392, Bldg AP6D-2
Abbott Park, IL 60064-3500

RE: NDA #s 21-226; 21-251; & 21-906
Kaletra® (lopinavir & ritonavir) Tablets
Kaletra® (lopinavir & ritonavir) Oral Solution
Kaletra® (lopinavir & ritonavir) Capsules
MACMIS # 17660

WARNING LETTER

Dear Mr. White:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a consumer-directed patient testimonial DVD ("promotional DVD"),[1] submitted by Abbott Laboratories (Abbott) under cover of Form FDA-2253, titled "I know what's important" (039-96723) in which Earvin "Magic" Johnson (Magic Johnson) is being interviewed about his experience with HIV disease and Kaletra® (lopinavir/ritonavir) (Kaletra) treatment. The promotional DVD minimizes the serious risks of the drug, overstates the efficacy of Kaletra, and includes unsubstantiated claims. Thus, the promotional DVD misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(3)(i), (e)(5), (e)(6)(i), & (e)(7)(viii). In addition, it appears that the promotional DVD was accompanied by an outdated version of the FDA-approved product labeling (PI) for Kaletra, in violation of 21 CFR 201.100(d). These violations are concerning from a public health perspective because they suggest that Kaletra is safer and more effective than has been demonstrated by substantial evidence or substantial clinical experience, and encourage use in circumstances other than those for which the drug has been shown to be safe and effective.

Background

According to the Indications and Usage section of the PI[2]:

[1] The content of this promotional DVD was also available on the Kaletra product webpage (http://www.kaletra.com/consumer_healthy_magic.cfm#) (last accessed July 10, 2009).
[2] The PI submitted with the promotional piece on Form FDA-2253 was dated November 2007. However, the video was submitted on November 24, 2008, with a listed dissemination date of November 18, 2008; the most current version of the FDA-approved PI as of these dates was the October 3, 2008 version, and that is the version referred to in this letter. Although not relevant to the issues raised in this letter, we note that Kaletra's PI was again updated on April 20, 2009.

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with KALETRA:

• The use of other active agents with KALETRA is associated with a greater likelihood of treatment response….

• Genotypic or phenotypic testing and/or treatment history should guide the use of KALETRA… . The number of baseline primary protease inhibitor mutations affects the virologic response to KALETRA….

• Once-daily administration of KALETRA is not recommended for therapy-experienced adult patients or any pediatric patients.

The Clinical Studies section of the PI contains the following information regarding the efficacy of Kaletra for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults (in pertinent part):

Patients With Prior Antiretroviral Therapy

Study 888: KALETRA twice-daily + nevirapine + NRTIs compared to investigator-selected protease inhibitor(s) + nevirapine + NRTIs

Study 888 was a randomized, open-label, multicenter trial comparing treatment with KALETRA (400/100 mg twice-daily) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and nucleoside reverse transcriptase inhibitors in 288 single protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI)-naïve patients… .

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 17.

Table 17. Outcomes of Randomized Treatment Through Week 48 (Study 888)

Outcome	Kaletra + nevirapine + NRTIs (n=148)	Investigator-Selected Protease Inhibitor(s) + nevirapine + NRTIs (n=140)
Responder[1]	57%	33%
Virologic Failure[2]	24%	41%
Rebound	11%	19%
Never suppressed through Week 48	13%	23%

Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other Reasons[3]	14%	13%

[1] Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.
[2] Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48.
[3] Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the investigator-selected protease inhibitor(s) arm with HIV-1 RNA < 400 copies/mL (57% vs. 33%, respectively).

Through 48 weeks of therapy, the mean increase from baseline in $CD4^+$ cell count was 111 cells/mm^3 for the KALETRA arm and 112 cells/mm^3 for the investigator-selected protease inhibitor(s) arm.

Other Studies Supporting Approval ….

Study 765: KALETRA twice-daily + nevirapine + NRTIs

….[S]tudy 765 (patients <u>with</u> prior protease inhibitor therapy)….

….Through 144 weeks of treatment in study 765, the proportion of patients with HIV-1 RNA < 400 (< 50) copies/mL was 54% (50%) [n = 70], and the corresponding mean increase in $CD4^+$ cell count was 212 cells/mm^3. Twenty-seven patients (39%) discontinued the study, including 5 (7%) discontinuations secondary to adverse reactions and 2 (3%) deaths.

Kaletra is associated with serious and potentially life-threatening risks, including significant drug interactions. For example, the PI lists a number of drugs that are contraindicated, require dosage adjustments or should be used cautiously with Kaletra because of potentially life-threatening adverse events or loss of virologic activity. Serious risks associated with Kaletra noted in the Warnings and Precautions section of the PI include pancreatitis; hepatotoxicity; new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia; immune reconstitution syndrome; redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance;" large increases in the concentration of total cholesterol and triglycerides; and increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B. This section also notes that "[b]ecause the potential for HIV cross-resistance among protease inhibitors has not been fully explored in KALETRA-treated patients, it is unknown what effect therapy with KALETRA will have on the activity of subsequently administered protease inhibitors…."

Prior Communications with DDMAC

DDMAC has expressed concerns regarding Abbott's promotion of Kaletra in an earlier letter. On October 29, 2004, DDMAC sent Abbott an untitled letter for a print advertisement and poster that overstated the effectiveness of Kaletra and omitted the indication and material information about the risks of the drug. The pieces cited implied that patients taking Kaletra can expect to survive and be healthy for at least five years, in the absence of substantial evidence or substantial clinical experience to support such an implication. We are concerned that you are continuing to promote your product in a similarly violative manner.

Minimization of Risk

Promotional materials are misleading if they fail to present information about risks associated with a drug with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug. The promotional DVD minimizes the risks of Kaletra by failing to convey any of the serious risks of Kaletra during the interview portion of the DVD. Specifically, the first 11½ minutes of the promotional DVD are devoted to an engaging and lively discussion with Magic Johnson presented in an interview format. This interview portion includes a discussion of the benefits Magic Johnson has experienced from Kaletra. In contrast, the presentation of serious risks associated with Kaletra is relegated to the end of DVD after the interview is over, where it is unlikely to draw the viewer's attention, and is displayed as a running telescript. The only risk information included during the interview are a brief acknowledgement by Magic Johnson that he experiences "fatigue[] sometimes" and disclosures in SUPERs that Kaletra "is not a cure for HIV infection," that "[t]he most commonly reported side effects of moderate severity that are thought to be drug-related are: abdominal pain, abnormal bowel movements, diarrhea, feeling weak/tired, headache, and nausea," and that "[C]hildren taking KALETRA may sometimes get a skin rash." The discussion/interview portion of the promotional DVD omits any discussion of serious risks, such as contraindications, warnings, and precautions associated with Kaletra. This overall presentation misleadingly minimizes the serious risks associated with Kaletra because it fails to convey this important risk information with a prominence and readability reasonably comparable to the claims of effectiveness. The overall effect of this presentation undermines the communication of important risk information, misleadingly suggesting that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Overstatement of Efficacy & Unsubstantiated Claims

Promotional materials are misleading if they represent or suggest that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The promotional DVD primarily consists of an interview with Magic Johnson, during which he discusses how he was diagnosed with HIV, his experience living with HIV, and his treatment with Kaletra.[3]

(b) (6)

Magic Johnson's statements include the following:

- "[T]he most important thing is that I do manage my disease, and it enables me to then do all the other things. You know, I make sure I take my meds, I make sure that I try to get some form of exercise. It enables me to also be a businessman once I manage my HIV."

- "I started taking Kaletra over five years ago and it's really been a great part of my regimen…."

- In response to the question "What has your experience been on Kaletra?", Magic Johnson states: "I can still exercise, … I still work and have a long day in the office, and I think that the medicine has really been good for me…."

- "Well the good thing is, Kaletra is a part of my regimen, and for five years I have been undetectable, so I just hope that that continues."

- In response to the question "How has having HIV changed your life?", Magic Johnson states: "You're going to have the same good times. You're going to, you know, go to the movies ... we just live a normal life …. You just take medicine. We still go out and dance. We still have a good time, you know, we … take our kids to school …. It's a normal life … nothing really changes other than you're taking medicine and you're managing your disease…."

While these statements may be an accurate reflection of Magic Johnson's own experience, as a treatment-experienced individual, with HIV and Kaletra, this promotional testimonial suggests that Kaletra has been shown to allow all or most antiretroviral treatment-experienced individuals to successfully manage their disease and continue to do well, i.e., live a "normal life" while maintaining undetectable HIV-1 RNA levels, for five or more years. FDA is not aware of substantial evidence or substantial clinical experience to support effectiveness for five or more years of treatment with Kaletra in treatment-experienced adults. The personal experience of a Kaletra patient such as Magic Johnson does not constitute such evidence.

We acknowledge that the PI includes data through 360 weeks of treatment with Kaletra for patients without prior antiretroviral therapy (Study 720). However, these data are not applicable to the patient population represented by the claims in the promotional DVD (antiretroviral treatment-experienced individuals). According to the Clinical Studies section of the PI, in antiretroviral treatment-experienced subjects, analyses of plasma HIV-1 RNA levels were conducted only through 48 weeks in Study 888, and 144 weeks in Study 765. In addition, the FDA-approved patient labeling (PPI) explicitly states that "The long-term effects of KALETRA are not known at this time. People taking KALETRA may still get opportunistic infections or other conditions that happen with HIV-1 infection." Furthermore, as indicated in the Background section above, a portion of patients treated with Kaletra experienced virologic failure or were never suppressed through week 48. According to the PI, in Study 888, 24% of patients in the Kaletra arm experienced virologic failure, and 13% were never suppressed through Week 48. Additionally, in both Study 888 and Study 765, some patients died. The statement by Magic Johnson that "everybody is different" and the inclusion of the SUPER

stating "Individual results may vary" in conjunction with some of the claims about Magic Johnson's experience with Kaletra does not mitigate the misleading impression created by the promotional DVD that all or most treatment-experienced patients taking Kaletra can expect to survive and be healthy for at least five years.

In addition, these claims misleadingly overstate the efficacy of Kaletra by suggesting that the usual outcome of treatment with Kaletra is the preservation and continuance of a "normal life," including activities of daily living, work productivity, and social, emotional, and physical functioning, for at least five years. FDA is not aware of substantial evidence or substantial clinical experience to support such effects of Kaletra treatment for patients. In fact, as discussed above, Kaletra's PI indicates in Study 888, for subjects in the Kaletra arm, 24% experienced virologic failure and 13% were never suppressed through Week 48. Furthermore, patients treated with Kaletra may also experience adverse drug events, either of which would adversely affect a patient's ability to preserve a "normal life" and engage in their professional occupation. These claims of treatment benefit require substantial evidence or substantial clinical experience as demonstrated through adequate and well-controlled trial(s) using well-developed instruments that reliably and validly measure the specific concepts at issue. If you have such data to support these claims, please submit them to FDA for review.

Use of Outdated Product Labeling

It appears that the promotional DVD was disseminated with an outdated version of the approved product labeling (PI), in violation of 21 CFR 201.100(d). The PI submitted with the promotional piece on Form FDA-2253 was dated November 2007. However, the listed dissemination date of the DVD was November 18, 2008; the most current version of the FDA-approved PI as of this date was the October 3, 2008 version, not the November 2007 version. This outdated version of the PI did not include, among other things, important safety information added to the October 3, 2008 PI regarding the use of Kaletra in pediatric patients 14 days to six months of age, and from 12 to 18 years of age.

Conclusion and Requested Actions

For the reasons discussed above, the promotional DVD misbrands Kaletra in violation of the Act, 21 U.S.C. 352(a) & 321(n), and FDA implementing regulations. 21 CFR 201.100(d); *cf.* 21 CFR 202.1(e)(3)(i), (e)(5), (e)(6)(i), & (e)(7)(viii).

DDMAC requests that Abbott immediately cease the dissemination of violative promotional materials for Kaletra such as those described above. Please submit a written response to this letter on or before July 28, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Kaletra as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to

me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS# 17660 in addition to the NDA number(s). We remind you that only written communications are considered official. 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.

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 each applicable requirement of the Act and FDA implementing regulations.

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

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
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
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