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IMPORTANT PRESCRIBING INFORMATION

GLAXOSMITHKLINE SAFETY ADVISORY

November 2009

Dear Healthcare Professional:

LEXIVA® (fosamprenavir calcium) Tablets and Oral Suspension:
Myocardial Infarction and Dyslipidemia

GlaxoSmithKline would like to inform you of data presented at the 16th Conference on Retroviruses and Opportunistic Infections (CROI 2009) relating to a potential association between LEXIVA Tablets and Oral Suspension and myocardial infarction in HIV infected adults.

Action Being Taken by GSK

GSK has added myocardial infarction and hypercholesterolemia to the Adverse Reactions section of the LEXIVA Tablets and Oral Suspension prescribing information (Section 6.2 Postmarketing Experience). Elevations in triglyceride levels are already described in the Adverse Reactions section of the LEXIVA Tablets and Oral Suspension prescribing information (Section 5.8 Warnings and Precautions, Section 6.1 Clinical Trials).

GSK has modified the existing Warnings and Precautions statement (Section 5.8 Lipid Elevations) in the prescribing information for LEXIVA Tablets and Oral Suspension to highlight that increases in cholesterol have occurred with treatment. This statement highlights the importance of lipids management by including a recommendation that triglyceride and cholesterol testing should be performed prior to initiating therapy with LEXIVA Tablets and Oral Suspension and at periodic intervals during therapy.

GSK is in communication with FDA and this issue will be closely monitored.

Key Messages

- A case-control study nested in the French Hospital Database on HIV [FHDH ANRS CO4] has reported an association between exposure to fosamprenavir/ amprenavir and an increased risk of myocardial infarction (Odds Ratio (OR): 1.52 per additional year of exposure; 95% CI, 1.19-1.95). [Lang S, Mary-Krause M, Cotte L et al. CROI 2009, Abstract #43LB]
- Myocardial infarction has already been identified as a signal for the protease inhibitor (PI) class in general; the reported association is plausible and may be related to the propensity for this drug class to raise blood lipids [The D:A:D Study Group 2007].
- Prescribers are reminded that HIV infection itself has been associated with lipid disorders and ischaemic heart disease.
- Triglyceride and cholesterol levels should be checked prior to initiating therapy with LEXIVA Tablets and Oral Suspension and at periodic intervals during therapy. Appropriate clinical management of lipid disorders should be initiated as required.
- Other modifiable risk factors for cardiovascular disease (such as hypertension, diabetes and smoking) should also be monitored in HIV-infected subjects and managed as clinically appropriate.

Labelling Recommendations

Details of the new labelling for LEXIVA Tablets and Oral Suspension are described under "Action Being Taken by GSK." Please read the enclosed Prescribing Information for the full text describing these labelling changes.

Action Required by Healthcare Professionals

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV-infected patients. Clinical examination should include evaluation for physical signs of fat redistribution.

Triglyceride and cholesterol levels should be checked prior to initiating therapy with LEXIVA Tablets and Oral Suspension and at periodic intervals during therapy. Appropriate clinical management of lipid disorders should be initiated as required.

Other modifiable risk factors for cardiovascular disease (such as hypertension, diabetes and smoking) should be monitored in HIV-infected subjects and managed as clinically appropriate.

Supporting Information

At an international HIV conference (CROI, February 2009), data from a case-control study nested within the French Hospital Database on HIV were reported [Abstract #43LB].

The objective of the study, requested by the European Medicines Evaluation Agency (EMEA), was to analyse the effect of exposure to specific nucleoside reverse transcriptase inhibitors (NRTIs) and PIs on the risk of myocardial infarction. Several conditional logistic regression models were used to assess the association of (i) cumulative exposure to specific NRTIs, (ii) recent (current or within 6 months) and past exposure (>6 months ago) to specific NRTIs, and (iii) cumulative exposure to specific PIs on the risk of myocardial infarction. The study reported an association between an increased risk of myocardial infarction and cumulative exposure to fosamprenavir/amprenavir (OR 1.52 per additional year of exposure; 95% CI, 1.19-1.95).

Myocardial infarction has already been identified as a signal for the PI class in the ongoing observational Data Collection on Adverse Events of Anti-HIV Drugs (DAD) cohort. Specific analysis of ART drug classes showed the relative risk of myocardial infarction to be higher with PI therapy (16% increase per year) compared with other ART classes. The signal is plausible and may be partly explained by the propensity of the PI class to raise blood lipids.

Suppression of viral replication in HIV disease with antiretroviral therapy is of the utmost importance. Patients should NOT discontinue treatment on their own. All treatment decisions should be explored in consultation with healthcare professionals.

Physicians should continue to monitor a patient's cardiovascular risk as part of regular reviews and seek to adjust modifiable risk factors. The profile of each antiretroviral agent is different and treatment decisions should always be personalized for an individual patient with careful consideration of the overall absolute risks and the benefits of effective long term treatment.

Please refer to the accompanying Indication and Important Safety Information for LEXIVA given below and the enclosed Full Prescribing Information for LEXIVA Tablets and Oral Suspension.

Call for Reporting

GlaxoSmithKline reminds healthcare professionals to continue to report adverse reactions to FDA MedWatch at 1-800-FDA-1088 or www.fda.gov/medwatch in accordance with the national spontaneous reporting system rules.

GlaxoSmithKline encourages healthcare professionals to continue to report suspected adverse reactions, pregnancy, overdose and unexpected benefits of LEXIVA Tablets and Oral Suspension to GSK at 1-888-825-5249.

References

Lang S, Mary-Krause M, Cotte L et al. Impact of Specific NRTI and PI Exposure on the Risk of Myocardial Infarction: A Case-Control Study Nested within FHDH ANRS CO4. 16th Conference on Retroviruses and Opportunistic Infections (CROI 2009) February 8 - 11, 2009, Montreal, Canada. Abstract #43LB. (Slides and audio from the oral presentation by D Costagliola in session "Oral Abstract: Pharmacogenetics, Pharmacoenhancement, and Complications of ART" on Monday, Feb 9, 2009 10:00 AM available from the CROI webpage at:
http://app2.capitalreach.com/esp1204/servlet/tc?c=10164&cn=retro&e=10649&m=1&s=20415&&espmt=2&mp3file=10649&m4bfile=10649&br=80&audio=false)

DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med. 2007;356(17):1723-35.

Important Information about LEXIVA® (fosamprenavir calcium) Tablets and Oral Suspension

INDICATION

LEXIVA is indicated in combination with other antiretroviral agents for the treatment of HIV infection.

For PI-experienced patients, the following should be considered:

- The PI–experienced patient study was not large enough to reach a definitive conclusion that LEXIVA/ritonavir and lopinavir/ritonavir are clinically equivalent.
- Once-daily administration of LEXIVA plus ritonavir is not recommended for PI–experienced patients.

LEXIVA (fosamprenavir calcium) is available in 700-mg tablets and 50 mg/mL oral suspension.

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- LEXIVA is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product or to amprenavir.
- Hyperglycemia, new onset or exacerbations of diabetes mellitus, and spontaneous bleeding in hemophiliacs have been reported with protease inhibitors.
- Treatment with LEXIVA/r has resulted in increases in the concentration of triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating therapy with LEXIVA and at periodic intervals during therapy.
- Caution should be exercised when administering LEXIVA to patients with hepatic impairment, including those with hepatitis B or C or marked elevation in transaminases prior to treatment. Increased AST/ALT monitoring should be considered in these patients.
- LEXIVA taken with oral contraceptives may alter hormonal levels. LEXIVA plus ritonavir taken with oral contraceptives may result in clinically significant hepatic transaminase elevations. Therefore, alternate methods of non-hormonal contraception are recommended.
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including LEXIVA. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond 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.
- Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The causal relationship, mechanism, and long-term consequences of these events are currently unknown.
- LEXIVA should be used with caution in patients with a known sulfonamide allergy.
- Cases of nephrolithiasis were reported during post-marketing surveillance in HIV-infected patients receiving fosamprenavir calcium. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of therapy may be considered.
- Severe or life-threatening skin reactions were reported in <1% of 700 patients treated with LEXIVA in clinical studies, including 1 case of Stevens-Johnson syndrome.
- Skin rash (all grades, without regard to causality) occurred in approximately 19% of patients treated with LEXIVA in the pivotal efficacy studies. This led to the discontinuation of LEXIVA in <1% of patients.

Drug Interactions

- LEXIVA is contraindicated with ergot derivatives, PROPULSID® (cisapride), ORAP® (pimozide), VERSED® (midazolam), HALCION® (triazolam), rifampin, MEVACOR® (lovastatin), ZOCOR® (simvastatin), RESCRIPTOR® (delavirdine), or St. John's wort (*Hypericum perforatum*). If LEXIVA is coadministered with ritonavir, TAMBOCOR® (flecainide) and RHYTHMOL® (propafenone) are also contraindicated.
- Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4.
- Serious and/or life-threatening drug interactions could occur between LEXIVA and CORDARONE® (amiodarone), lidocaine (systemic), tricyclic antidepressants, and quinidine. Concentration monitoring of these agents is recommended if these agents are used concomitantly with LEXIVA.
- Particular caution should be used when prescribing phosphodiesterase (PDE-5) inhibitors for erectile dysfunction (e.g., sildenafil or vardenafil) in patients receiving LEXIVA.
- This list of potential drug interactions is not complete.

Resistance

- Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect therapy with LEXIVA will have on the activity of subsequently administered protease inhibitors.
- Clinical relevance of resistance data is unknown.

Please refer to the enclosed Full Prescribing Information for LEXIVA Tablets and Oral Suspension.