GlaxoSmithKline

IMPORTANT SAFETY INFORMATION

GlaxoSmithKline
Pharmaceuticals
Stonemasons Way
Rathfarnham
Dublin 16
Ireland

Tel. +353-1-495 5000
Fax. +353-1-495 5105
www.gsk.com

07 March 2008

GM2008/00002/00

Re: Direct Healthcare Professional Communication on screening for carriage of the HLA-B*5701 allele prior to the initiation of treatment with any abacavir sulfate- containing product; these include ZIAGEN Tablets and Oral Solution, KIVEXA Tablets and TRIZIVIR Tablets

Summary

In agreement with the Committee for Medicinal Products for Human Use (CHMP) and the Irish Medicines Board (IMB), GlaxoSmithKline (GSK) would like to inform you of new important information to reduce the incidence of abacavir hypersensitivity through the use of genetic screening for HLA-B*5701.

The clinical utility of HLA-B*5701 screening to avoid abacavir hypersensitivity has been demonstrated by a prospective, randomised, controlled trial (CNA106030 [PREDICT-1]). Results from this study have led to additions to the Summary of Product Characteristics (SmPC) for abacavir sulfate-containing medicinal products, as follows:

- Before initiating treatment with abacavir, screening for carriage of HLA-B*5701 should be performed in any HIV-infected patient, irrespective of racial origin.
- Abacavir should not be used in patients known to carry HLA-B*5701, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing.

Updates to the Prescribing Information are presented in Annex 1 for ZIAGEN (Tablets and Oral Solution), but are identical for TRIZIVIR (Tablets) and KIVEXA (Tablets). These updates have been assessed by the CHMP as Type II variations to the Product Licences granted under the Centralised procedure.

Further information on the safety concern

Carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir.

CNA106030 (PREDICT-1) was a GSK sponsored, double-blinded study in which 1956 abacavir naïve, HIV-1 infected patients were randomised to either: 1) prospective HLA-B*5701 screening; or 2) a standard of care control arm with retrospective HLA-B*5701 ascertainment. Pre-therapy screening for HLA-B*5701 and avoidance of abacavir in HLA-B*5701 positive patients significantly reduced the incidence of abacavir hypersensitivity reactions in this study.

In populations similar to that enrolled in the PREDICT-1 study, it is estimated that 48% to 61% of patients with the HLA-B*5701 allele who receive abacavir will develop an abacavir hypersensitivity reaction within 6 weeks of therapy initiation, compared with 0% to 4% of patients who do not have the HLA-B*5701 allele. While the PREDICT-1 study population was predominantly white, the association between HLA-B*5701 and abacavir hypersensitivity appears to be generalisable across racial groups [Saag, 2007; Saag, in press; Sun, 2007]. These results are consistent with those of prior retrospective studies.

Further information on recommendations to healthcare professionals

In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making. Among the patients in PREDICT-1 who were diagnosed with a clinically suspected hypersensitivity reaction, some did not carry HLA-B*5701. Therefore, even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

Call for reporting

GlaxoSmithKline encourages healthcare professionals to report suspected adverse reactions, pregnancy, overdose and unexpected benefits to the company in the usual way.

In the case of suspected adverse reactions you can report to:

GlaxoSmithKline (Ireland) Ltd., Stonemasons Way, Rathfarnham, Dublin 18 (Freephone 1800 244 255, Fax 01 4938839 or e-mail ireland.drugsurveillance@gsk.com)

or

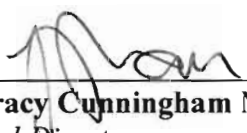
Pharmacovigilance Section, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2 (Telephone 01 6764971 or 01-6764976, Fax 01 6767836 or on-line via www.imb.ie)

Communication information

The PREDICT-1 data have been presented at the 4th International AIDS Society Conference in Sydney, Australia, in July 2007, and have been published in the New England Journal of Medicine [Mallal, 2008].

The abacavir hypersensitivity education materials have been updated to reflect this new information.

For further information please contact GlaxoSmithKline (Ireland) Ltd., Stonemasons Way, Rathfarnham, Dublin 18 (Freephone 1800 244 255).



Dr. Tracy Cunningham MB FRCPI AFPM
Medical Director
GlaxoSmithKline Ireland

ANNEX 1: REVISED PRESCRIBING INFORMATION

The Prescribing Information for abacavir sulfate (ZIAGEN) has been revised based on the findings from prospective GSK sponsored study CNA106030 (PREDICT-1). These changes have affected the sections of the SPC relating to 'Therapeutic Indication' (Section 4.1), 'Warnings and Precautions' (Section 4.4) and the 'Patient Information Leaflet', and are presented below. All new wording is indicated by shaded text. The new wording is identical for the abacavir sulfate- containing combination products TRIZIVIR and KIVEXA.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ziagen is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.

The demonstration of the benefit of Ziagen is mainly based on results of studies performed with a twice daily regimen, in treatment-naïve adult patients on combination therapy (see section 5.1).

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing (see section 4.4 and 4.8).

4.4 Special warnings and precautions for use

Hypersensitivity Reaction (see also section 4.8)*:*

In clinical studies approximately 5% of subjects receiving abacavir develop a hypersensitivity reaction; some of these cases were life-threatening and resulted in a fatal outcome despite taking precautions.

Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. Based on the prospective study CNA106030 (PREDICT-1), use of pre-therapy screening for the HLA-B*5701 allele and subsequently avoiding abacavir in patients with this allele significantly reduced the incidence of abacavir hypersensitivity reactions. In populations similar to that enrolled in the PREDICT-1 study, it is estimated that 48% to 61% of patients with the HLA-B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0% to 4% of patients who do not have the HLA-B*5701 allele.

These results are consistent with those of prior retrospective studies.

As a consequence, before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele,

unless no other therapeutic option is available based on the treatment history and resistance testing (see section 4.1).

In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making. It is noteworthy that among patients with a clinically suspected hypersensitivity reaction, a proportion did not carry HLA-B*5701. Therefore, even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

Skin patch testing was used as a research tool for the PREDICT-1 study but has no utility in the clinical management of patients and therefore should not be used in the clinical setting.

- **Description**

Hypersensitivity reactions are characterised by the appearance of symptoms indicating multi-organ system involvement. Almost all hypersensitivity reactions will have fever and/or rash as part of the syndrome.

Other signs and symptoms may include respiratory signs and symptoms such as dyspnoea, sore throat, cough and abnormal chest x-ray findings (predominantly infiltrates, which can be localised), gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, **and may lead to misdiagnosis of hypersensitivity as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis.** Other frequently observed signs or symptoms of the hypersensitivity reaction may include lethargy or malaise and musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia).

The symptoms related to this hypersensitivity reaction worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of Ziagen.

- **Management**

Hypersensitivity reaction symptoms usually appear within the first six weeks of initiation of treatment with abacavir, although these reactions **may occur at any time during therapy.** Patients should be monitored closely, especially during the first two months of treatment with Ziagen, with consultation every two weeks.

Patients who are diagnosed with a hypersensitivity reaction whilst on therapy **MUST discontinue Ziagen immediately.**

Ziagen, or any other medicinal product containing abacavir (i.e. Kivexa, Trizivir), MUST NEVER be restarted in patients who have stopped therapy due to a hypersensitivity reaction. Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, Ziagen must be permanently discontinued if hypersensitivity cannot be ruled out,

even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications).

Special care is needed for those patients simultaneously starting treatment with Ziagen and other medicinal products known to induce skin toxicity (such as non-nucleoside reverse transcriptase inhibitors - NNRTIs). This is because it is currently difficult to differentiate between rashes induced by these products and abacavir related hypersensitivity reactions.

- **Management after an interruption of Ziagen therapy**

If therapy with Ziagen has been discontinued for any reason and restarting therapy is under consideration, the reason for discontinuation must be established to assess whether the patient had any symptoms of a hypersensitivity reaction. **If a hypersensitivity reaction cannot be ruled out, Ziagen or any other medicinal product containing abacavir (i.e. Kivexa, Trizivir) must not be restarted.**

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting Ziagen in patients who had only one of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping Ziagen. The most common isolated symptom of a hypersensitivity reaction was a skin rash. Moreover, on very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction. In both cases, if a decision is made to restart Ziagen this must be done in a setting where medical assistance is readily available.

- **Essential patient information**

Prescribers must ensure that patients are fully informed regarding the following information on the hypersensitivity reaction:

- patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death.
- patients developing signs or symptoms possibly linked with a hypersensitivity reaction **MUST CONTACT their doctor IMMEDIATELY.**
- patients who are hypersensitive to abacavir should be reminded that they must never take Ziagen or any other medicinal product containing abacavir (i.e. Kivexa, Trizivir)
- in order to avoid restarting Ziagen, patients who have experienced a hypersensitivity reaction should be asked to return the remaining Ziagen tablets or oral solution to the pharmacy.
- patients who have stopped Ziagen for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.
- patients should be advised of the importance of taking Ziagen regularly.
- each patient should be reminded to read the Package Leaflet included in the Ziagen pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

2. BEFORE YOU TAKE ZIAGEN

Do not take Ziagen:

- if you are allergic (hypersensitive) to the active substance abacavir, which is also included in medicines called Kivexa and Trizivir.
- if you are allergic to any of the other ingredients in Ziagen
- if you have severe liver disease.

If you are not sure about any of these please consult your doctor.

Take special care with Ziagen

Hypersensitivity reaction (serious allergic reaction): About 5 in every 100 patients, who are treated with Ziagen, develop a hypersensitivity reaction to the active ingredient abacavir.

Research has found that people with a gene called HLA-B (type 5701) are more likely to have a hypersensitivity reaction to abacavir. However, even if you do not have this gene type it is still possible for you to get this reaction. If you know you have this gene type, be sure to tell your doctor before you take abacavir.

The most common symptoms of this reaction are high temperature (fever) and a skin rash. Other frequently observed signs are nausea, vomiting, diarrhoea, abdominal pain and severe tiredness. Other symptoms may include joint or muscle pain, swelling of the neck, shortness of breath, sore throat, cough, headache. Occasionally inflammation of the eye (conjunctivitis), mouth ulcers or low blood pressure may occur.

The symptoms of this allergic reaction can occur at any time during treatment with Ziagen. However they usually occur in the first six weeks of treatment. The symptoms worsen with continued treatment and may be life-threatening if treatment is continued.

If you are caring for a child who is being treated with Ziagen, it is important that you understand the information about this hypersensitivity reaction. If your child gets the symptoms described below it is essential that you follow the instructions given.

CONTACT YOUR DOCTOR IMMEDIATELY for advice on whether you should stop taking Ziagen if:

1) you get a skin rash OR

2) you get one or more symptoms from at least TWO of the following

groups

-fever

-shortness of breath, sore throat or cough

-nausea or vomiting or diarrhoea or abdominal pain

-severe tiredness or achiness or generally ill feeling

If you have discontinued Ziagen due to a hypersensitivity reaction, **YOU MUST NEVER TAKE** Ziagen or any other medicine containing abacavir (i.e. Kivexa, Trizivir) again, as **within hours** you may experience a life-threatening lowering of your blood pressure or death.

If you have stopped taking Ziagen for any reason, particularly because you think you are having side effects or for other illness, it is important that you contact your doctor before restarting. Your doctor will check whether any symptoms you had may be related to this hypersensitivity reaction. If your doctor thinks there is a possibility that they were related, you will be instructed **never to take Ziagen or any other medicine containing abacavir (i.e. Kivexa, Trizivir) again.** It is important that you follow this advice.

Occasionally life-threatening hypersensitivity reactions have occurred when Ziagen was restarted in patients who reported **only one** of the symptoms on the Alert Card before stopping.

On very rare occasions hypersensitivity has been reported when Ziagen was restarted in patients who had no symptoms of hypersensitivity before stopping.

If you are hypersensitive to Ziagen you should return all of your unused Ziagen for disposal. Ask your doctor or pharmacist for advice.

ANNEX 2: APPLICABLE REFERENCES

Mallal S, Phillips E, Carosi G, et. al. HLA-B*5701 screening for abacavir hypersensitivity. *New England Journal of Medicine.* 2008;358:568-79.

Saag M, Balu R, Brachman P, et al. High sensitivity of HLA-B*5701 in Whites and Blacks in Immunologically-confirmed cases of abacavir hypersensitivty (ABC HSR). *4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, July.* 2007:Abstract WEAB305.

Saag M, Balu R, Phillips E, et. al. High sensitivity of HLA-B*5701 in immunologically-confirmed cases of abacavir hypersensitivity in White and Black patients. *Clinical Infectious Diseases.* In Press.

Sun H-Y, Hung C-C, Lin P-H, et. al. Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan. *Journal of Antimicrobial Chemotherapy.* 2007;60:599–604.