The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 14 August 2000
EMEA/CPMP/23842/00

EMEA PUBLIC STATEMENT ON ZIAGEN (abacavir)
Abacavir hypersensitivity cases following an interruption of therapy

The following public statement contains essential information for anyone prescribing or taking Ziagen (abacavir)[1].

The European Agency's for the Evaluation of Medicinal Products (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP), has recently been made aware of new information related to serious hypersensitivity reactions associated with Ziagen (abacavir).

Hypersensitivity reactions (HSR) are a known concern with this product. These potentially serious reactions are usually characterised by the appearance of symptoms indicating multi-organ system involvement. Nearly all the patients with HSR experience fever or rash but symptoms may mimic other common gastrointestinal or respiratory diseases. These reactions usually occur within the first 6 weeks of treatment, but can occur at any time, and were the subject of an urgent safety restriction in January of this year (please see EMEA public statement EMEA/1952/00 dated 24th January 2000 for further information.)

Hypersensitivity reactions with rapid onset may occur when treatment with Ziagen is restarted in patients who were not previously diagnosed as having a hypersensitivity reaction. These patients typically had only <u>one</u> of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping Ziagen. 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.

The EMEA wishes to draw attention to the following updated information on the management of hypersensitivity reactions to Ziagen:

- **MANAGING HYPERSENSITIVITY REACTIONS**
  - **To avoid a delay in diagnosis and minimise the risk of a life threatening hypersensitivity reaction, Ziagen must be discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medicines.) If re-introduction is judged necessary it must be done in a hospital setting.**
  - **If a decision is made to re-start Ziagen in patients who had stopped for any other reasons (such as occurrence of only one of the key symptoms of hypersensitivity or no preceding symptoms of hypersensitivity prior to stopping Ziagen), this must be done in a setting where medical assistance is readily available.**
- **INFORMING PATIENTS**
  - **Patients must be made aware of the possibility of a hypersensitivity reaction to Ziagen and the need to contact their doctor immediately for advice should they develop signs or symptoms possibly linked to a hypersensitivity reaction.**

[1] Ziagen 300 mg film-coated tablets and 20 mg/ml oral solution contain abacavir, a nucleoside reverse transcriptase inhibitor, and were authorised in the EU on the 8th July 1999 for the antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus infected adults. Ziagen is marketed in Austria, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden and United Kingdom.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eudra.org http://www.eudra.org/emea.html

- **Patients who have stopped Ziagen due to symptoms which indicated or which were possibly due to a hypersensitivity reaction, should not restart Ziagen (or any other abacavir containing medicinal product) since restarting results in a return of symptoms within hours. The reoccurrence is usually more severe and may be life-threatening or fatal.**
- **Patients who have stopped Ziagen for any reason, and particularly if due to possible adverse reactions or illness must be advised to contact their doctor before re-starting.**
- **Patients should be reminded to read the package leaflet and to keep the alert card included in the pack with them at all times.**

As an urgent measure, the prescribing and patient information and the labelling have been modified through a rapid procedure at the request of the marketing authorisation holder. The EMEA thought it necessary to provide this new information to the public. Relevant changes to the product information are indicated below. For the complete scientific evaluation of Ziagen and the complete revised product information see the European Public Assessment Report, also available on the EMEA website.

For further information contact:

Mr Noel Wathion
Head of Sector Pharmacovigilance and Regulatory Affairs
Unit of Evaluation of Medicines for Human Use
Tel: +44 207 418 85 92
Fax: +44 207 418 8420

PROVISIONAL CHANGES INTRODUCED
TO INFORMATION TO PRESCRIBERS AND PATIENTS AND LABELLING

Ziagen 300 mg film-coated tablets as relevant example

INFORMATION TO PRESCRIBERS

4.4 Special warnings and special precautions for use

Hypersensitivity Reaction (see also 4.8 Undesirable effects):

In clinical studies approximately ***4***% of subjects receiving abacavir develop a hypersensitivity reaction; some of these cases were life threatening and resulted in ***a*** fatal outcome despite taking precautions.

- ***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 symptoms such as dyspnoea, sore throat, or cough***, 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 abacavir containing medicinal product,* 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 discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications). If reintroduction is judged necessary, it must be done in a hospital setting.

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). This is because it could be 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 prior to stopping.

***Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after re-starting 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. On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no preceding symptoms* of a hypersensitivity reaction. *If a decision is made to re-start 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**.

- 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.

Occurrences of lactic acidosis (in the absence of hypoxaemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis have been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued in the setting of rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology. Benign digestive symptoms, such as nausea, vomiting and abdominal pain, might be indicative of lactic acidosis development. Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease. These patients should be followed closely.

Pancreatitis has been reported, but a causal relationship to Ziagen treatment is uncertain.

Insufficient data are available to recommend the use of Ziagen in children. In this population, hypersensitivity reactions are particularly difficult to identify.

Data to support the use of Ziagen in patients with moderate hepatic impairment are not currently available, therefore, administration of Ziagen should be avoided in these patients.

Ziagen should not be administered to patients with end-stage renal disease (see 5.2 Pharmacokinetic properties).

Patients receiving Ziagen or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Patients should be advised that current antiretroviral therapy, including Ziagen, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

4.8 Undesirable effects

Hypersensitivity ***(see also 4.4 Special warnings and special precautions for use)***:

In clinical studies, approximately ***4***% of subjects receiving abacavir developed a hypersensitivity reaction; some of these were life threatening and resulted in fatal outcome despite taking precautions. This reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, ***however reactions have occurred without rash or fever.***

The signs and symptoms of this hypersensitivity reaction are listed below. Those reported in at least 10% of patients with a hypersensitivity reaction are in bold text.

Skin:-	***Rash*** *(usually maculopapular or urticarial)*
Gastrointestinal tract:-	***Nausea, vomiting, diarrhoea, abdominal pain,*** *mouth ulceration*
Respiratory tract:-	*Dyspnoea, sore throat, cough*
Miscellaneous:-	***Fever, lethargy, malaise,*** *oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis*
Neurological/Psychiatry:-	***Headache,*** *paraesthesia*
Haematological:-	*Lymphopenia*
Liver/pancreas:-	***Elevated liver function tests***
Musculoskeletal:-	***Myalgia,*** *rarely myolysis, arthralgia, elevated creatine phosphokinase*
Urology:-	*Elevated creatinine, renal failure*

Some patients with hypersensitivity reactions were initially thought to have gastroenteritis, respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. This delay in diagnosis of hypersensitivity has resulted in Ziagen being continued or re-introduced, leading to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases.

Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, although these reactions may occur at any time during therapy. Close medical supervision is necessary during the first two months, with consultations every two weeks.

Risk factors that may predict the occurrence or severity of hypersensitivity to abacavir have not been identified. However, it is likely that intermittent therapy may increase the risk of developing sensitisation and therefore occurrence of clinically significant hypersensitivity reactions.

Consequently, patients should be advised of the importance of taking Ziagen regularly.

Restarting Ziagen following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction was 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 discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications). If reintroduction is judged necessary it must be done in a hospital setting.

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after re-starting 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. On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to restart Ziagen this must be done in a setting where medical assistance is readily available.

Each patient ***must*** be warned about this hypersensitivity reaction to abacavir.

For many of the other adverse events reported, it is unclear whether they are related to Ziagen, to the wide range of medicinal products used in the management of HIV disease or as a result of the disease process.

The following adverse ***reactions*** may be related to Ziagen. The majority of these have not been treatment limiting. ***Care however must be taken to eliminate the possibility of a hypersensitivity reaction if any of these symptoms occur.***

Gastrointestinal: nausea, vomiting, diarrhoea
Other: headache, fever, lethargy, fatigue, anorexia

Pancreatitis has been reported, but a causal relationship to Ziagen treatment is uncertain.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4 Special warnings and special precautions for use).

In controlled clinical studies laboratory abnormalities related to Ziagen treatment were uncommon, with no differences in incidence observed between Ziagen treated patients and the control arms.

INFORMATION TO PATIENTS

HYPERSENSITIVITY REACTION

Patients taking Ziagen may develop a hypersensitivity reaction (serious allergic reaction) which **can be life threatening** if treatment with Ziagen is continued. It is essential you read the information on this reaction in the Special Warnings section of this leaflet. There is also **an alert card** included in the Ziagen pack, to remind you and medical staff about Ziagen hypersensitivity. This card should be removed and kept with you at all times.

CALL 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 abacavir containing medicine*** again, as **within hours** you may experience a life-threatening lowering of your blood pressure or death.

2. BEFORE YOU TAKE ZIAGEN

➢ **Do not take Ziagen:**

- ***if you have previously suffered an allergic reaction to Ziagen or any other abacavir containing medicine***
- ***if you are allergic to any ingredient in Ziagen***
- if you have severe liver disease

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

➢ **Special warnings and precautions for use:**

Hypersensitivity reaction (serious allergic reaction): About ***4*** in every 100 patients, who are treated with Ziagen, develop a hypersensitivity reaction to the active ingredient abacavir.

The most common symptoms of this reaction are high temperature (fever) and a skin rash. Other frequently observed signs or symptoms include 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.***

CALL 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 abacavir containing medicine*** 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. In some cases your doctor will ask you to restart Ziagen in a place where you will be able to get ready access to medical care if needed.

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 re-started in patients who had no symptoms of hypersensitivity before stopping

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

The class of medicines to which Ziagen belongs (NRTIs) can cause a condition called lactic acidosis, together with an enlarged liver. This rare, but serious side effect occurs more often in women, particularly if very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with Ziagen, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

You should not take Ziagen if you have moderate liver disease. Discuss this with your doctor if you are unsure.

Inflammation of the pancreas (pancreatitis) has been reported in some patients taking Ziagen. However it is not certain whether this is caused by Ziagen.

Ziagen helps to control your condition but is not a cure for HIV infection. You will need to take it every day. Do not interrupt your medication without first talking to your doctor. If however, ***you suspect that you are developing*** a hypersensitivity reaction (see above) call your doctor immediately who will advise you whether you should stop taking Ziagen.

Treatment with Ziagen has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should continue to use appropriate precautions to prevent this.

You may continue to develop other infections and other illnesses associated with HIV disease. You should therefore keep in regular contact with your doctor while taking Ziagen.

3. HOW TO TAKE ZIAGEN

Take Ziagen as your doctor has advised you, ***and take great care not to miss any doses if at all possible***. If you are unsure about how to take it, ask your doctor or pharmacist.

The usual dose in adults is 300 mg (one tablet) twice a day. Each tablet of Ziagen should be taken approximately 12 hours apart. Swallow the tablet whole with water.

An oral solution (20 mg abacavir/ml) is available for the treatment of patients unable to take tablets.

- **If you take more Ziagen than you should:**

Accidentally taking too much of your medicine is unlikely to cause any serious problems. However, you should tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

- **If you forget to take Ziagen:**

If you forget to take ***a dose*** of your medicine, take it as soon as you remember, and then continue as before. Do not take a double dose to make up for forgotten individual doses. It is important to take Ziagen regularly because irregular intake may increase the risk of hypersensitivity reactions.

- ***If you have stopped Ziagen***

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. In some cases your doctor will ask you to restart Ziagen in a place where you will be able to get ready access to medical care if needed.

LABELLING

ALERT CARD TEXT

SIDE 1

IMPORTANT - ALERT CARD
ZIAGEN (abacavir sulfate) Tablets
Carry this card with you at all times

Patients taking Ziagen may develop a hypersensitivity reaction (serious allergic reaction) which **can be life threatening** if treatment with Ziagen is continued. **CALL 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 this reaction, **YOU MUST NEVER TAKE** Ziagen ***or any other abacavir containing medicine*** again, as **within hours** you may experience a life-threatening lowering of your blood pressure or death.

(see reverse of card)

SIDE 2

You should immediately contact your doctor if you think you are having a hypersensitivity reaction to Ziagen. Write your doctor's details below:

Doctor: .....…… Tel: .....……..

If your doctor is not available, you must urgently seek alternative medical advice (e.g. the emergency unit of the nearest hospital).

For general Ziagen information enquiries, contact Glaxo Wellcome ….Tel …… (local company name and telephone number will be inserted here)