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

London, 24 January 2000
EMEA/1952/00

EMEA PUBLIC STATEMENT ON
ABACAVIR (Ziagen) – IMPORTANT SAFETY INFORMATION ON HYPERSENSITIVITY REACTIONS AND RESPIRATORY SYMPTOMS

The European Commission granted marketing authorisations for the European Union to Glaxo Group Ltd on 8 July 1999 for the medicinal product Ziagen®, which contains the active substance abacavir sulfate. Ziagen® is marketed in Austria, Denmark, Finland, France, Germany, Ireland, Italy, Portugal, Spain, Sweden and United Kingdom.

Ziagen® is an inhibitor of the reverse trancriptase of the HIV virus and indicated for antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults. The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP), has been evaluating new safety information as it emerges.

Hypersensitivity reactions (HSR) are the major points of concern with this product. These potentially serious reactions are characterised by the appearance of symptoms indicating multi-organ system involvement. Nearly all patients with HSR experience fever or rash. These reactions usually occur within the first 6 weeks of treatment.

Respiratory symptoms have been recognised as part of the hypersensitivity reaction in approximately 20% of HSR-patients, and may include dyspnoea, pharyngitis or cough in the initial presentation. **Deaths have occurred among patients initially thought to have acute respiratory diseases (pneumonia, bronchitis, or flu-like illness) who were only later recognised to have had a hypersensitivity reaction to abacavir that included respiratory symptoms.** In cases where there was a fatal outcome respiratory symptoms were present in approximately 80% of the patients. A delay in diagnosis of hypersensitivity can result in Ziagen being continued or re-introduced, leading to more severe hypersensitivity reactions or to death.

Following a review of the above information, the EMEA wishes to draw attention to the following:

- **Prescribers must ensure that patients are fully informed regarding hypersensitivity reactions. Each patient should be reminded to read the package leaflet and the alert card included in the pack.**
- **Some patients with hypersensitivity reactions were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases.**
- **Ziagen MUST NEVER be restarted in patients who have stopped therapy due to hypersensitivity reaction.**
- **Restarting Ziagen must be avoided in patients in whom a hypersensitivity reaction cannot be excluded.**
- **Patients experiencing TWO OR MORE symptoms of the following:**
  1) fever
  2) shortness of breath, sore throat or cough
  3) skin rash (redness and/or itching)
  4) nausea or vomiting or diarrhoea or abdominal pain
  5) severe tiredness or achiness or generally ill feeling

  <u>SHOULD CALL THEIR DOCTOR IMMEDIATELY for advice on whether they should stop taking Ziagen.</u>

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As an urgent measure, the prescribing and patient information has 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.

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PROVISIONAL CHANGES INTRODUCED
TO PRESCRIBING AND PATIENT INFORMATION

INFORMATION TO PATIENTS:

- **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 you have symptoms from **TWO OR MORE** of the following groups:

1) fever
2) shortness of breath, sore throat or cough
3) skin rash (redness and/or itching)
4) nausea or vomiting or diarrhoea or abdominal pain
5) severe tiredness or achiness or generally ill feeling

If you have discontinued Ziagen due to this reaction, **YOU MUST NEVER TAKE** Ziagen again as **within hours** you may experience a life-threatening lowering of your blood pressure or death.

(see reverse of card)

- **PACKAGE LEAFLET**

Ziagen 300 mg film-coated tablets

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 you have symptoms from **TWO OR MORE** of the following groups:

1) fever
2) shortness of breath, sore throat or cough
3) skin rash (redness and/or itching)
4) nausea or vomiting or diarrhoea or abdominal pain
5) severe tiredness or achiness or generally ill feeling

If you have discontinued Ziagen due to this reaction, **YOU MUST NEVER TAKE** Ziagen again as **within hours** you may experience a life-threatening lowering of your blood pressure or death.

Special warnings and precautions for use

Hypersensitivity reaction (serious allergic reaction): About 3 in every 100 patients, who are treated with Ziagen, develop a hypersensitivity reaction to the active ingredient abacavir. Frequently observed signs or symptoms include high temperature, skin rash, nausea, vomiting, diarrhoea, abdominal pain and severe tiredness. Other symptoms may include shortness of breath, sore throat, cough, joint or muscle pain, swelling of the neck, headache. Occasionally inflammation of the eye (conjunctivitis), ulcers in the mouth or low blood pressure may occur. The symptoms of this allergic reaction usually occur in the first six weeks of treatment with Ziagen, and get worse with continued treatment.

CALL YOUR DOCTOR IMMEDIATELY for advice on whether you should stop taking Ziagen if you have symptoms from **TWO OR MORE** of the following groups:

1) fever
2) shortness of breath, sore throat or cough
3) skin rash (redness and/or itching)
4) nausea or vomiting or diarrhoea or abdominal pain
5) severe tiredness or achiness or generally ill feeling

If you have discontinued Ziagen due to this reaction, **YOU MUST NEVER TAKE** Ziagen again as **within hours** you may experience a life-threatening lowering of your blood pressure or death.

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

INFORMATION FOR PRESCRIBERS:

4.4 Special warnings and special precautions for use

Hypersensitivity Reaction:

- In clinical studies approximately 3% of subjects receiving abacavir develop a hypersensitivity reaction; some of these cases were life threatening and resulted in fatal outcome despite taking precautions. 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, and may lead to misdiagnosis of hypersensitivity as respiratory disease (pneumonia, bronchitis, pharyngitis).** Other frequently observed signs or symptoms of the hypersensitivity reaction include gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, lethargy and malaise (see 4.8 Undesirable effects).
- **Ziagen MUST NEVER be restarted in patients who have stopped therapy due to a hypersensitivity reaction.** Restarting Ziagen 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. **Restarting Ziagen must be avoided in patients in whom a hypersensitivity reaction cannot be excluded.**
- **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.**

4.8 Undesirable effects

Other signs and symptoms may include respiratory symptoms (dyspnoea, shortness of breath, sore throat, cough), musculoskeletal symptoms (myalgia, arthralgia), headache, paraesthesia and oedema. Physical findings may include lymphadenopathy and, occasionally mucous membrane lesions (conjunctivitis and mouth ulceration) and hypotension.

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.

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. Ziagen MUST NEVER be restarted in patients who have stopped therapy due to a hypersensitivity reaction. Restarting Ziagen must be avoided in patients in whom a hypersensitivity reaction cannot be excluded.