London, 05 October 2005
Product name: **Ziagen**
Procedure No. **EMEA/H/252/R/25**

SCIENTIFIC DISCUSSION

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1. Introduction

On July 1999, a Marketing Authorisation was granted for Ziagen Tablets and Oral solution with the currently approved dose of one 300 mg tablet orally twice daily in adolescents and adults and 8mg/ kg orally twice daily up to a maximum of 600mg/day (300mg/ dose) in paediatric patients. The active molecule, abacavir, is a nucleoside analogue reverse transcriptase inhibitor.

The current indication of Ziagen is the following:

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 in treatment-naïve patients on combination therapy with lamivudine and zidovudine.

And the current posologies are as follow:

Ziagen should be prescribed by physicians experienced in the management of HIV infection.

Adults and adolescents over 12 years: the recommended dose of Ziagen is 300 mg (one tablet) twice daily.

Children from three months to 12 years: the recommended dose is 8 mg/kg twice daily up to a maximum of 600 mg daily.

Children less than three months: the data available on the use of Ziagen in this age group are very limited.

Ziagen can be taken with or without food.

Ziagen is available as an oral solution for use in children and for those patients for whom the tablets are inappropriate.

Renal impairment: No dosage adjustment of Ziagen is necessary in patients with renal dysfunction. However, Ziagen should be avoided in patients with end-stage renal disease.

Hepatic impairment: Abacavir is primarily metabolised by the liver. No dose recommendation can be made in patients with mild hepatic impairment. No data are available in patients with moderate hepatic impairment, therefore the use of abacavir is not recommended unless judged necessary. In patients with mild and moderate hepatic impairment close monitoring is required, and if feasible, monitoring of abacavir plasma levels is recommended. Abacavir is contraindicated in patients with severe hepatic impairment.

Elderly: No pharmacokinetic data is currently available in patients over 65 years of age.

2. Marketing Authorisation History

Ziagen was first authorised in the USA on 17 December 1998 and in Europe on 8 July 1999. In Europe, Ziagen has been marketed in Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Poland, Portugal, Slovenia, Spain, Sweden, United Kingdom and Norway during the reporting period. It is approved in a total of 91 countries and has been launched in a total of 31 countries worldwide.

3. Documentation submitted

- Renewal Application Form
- Summary of Product Characteristics, Package Leaflet and Labelling in all official languages of the EU and Norway and Iceland
- Mock-ups and Specimen
- Information about the quality and clinical experts
- Quality overall Summary
- Clinical Overview
- TSE Compliance
- 13th Periodic Safety Update Report (covering the period 1 July – 31 December 2003).

4. Regulatory actions

Subsequently to the granting of the Marketing Authorisation, the following changes were approved:

- On 24 November 1999 the CPMP issued a notification to the Commission relating to changes in the Package Leaflet (PL) and Labelling not connected to the Summary of Product Characteristics (SPC). The European Commission amended the Decision on 15 February 2000.
- On 19 January 2000, recognising that respiratory symptoms are an important part of the hypersensitivity reactions (HSR) the Marketing Authorisation Holder requested an update of the Summary of Product Characteristics (SPC) and Package Leaflet (PL) through an Urgent Safety Restriction (USR) procedure in accordance with article 1(2) of Commission Regulation (EC) No. 542/95 as amended.

  The scope of the procedure was to introduce and highlight information regarding respiratory symptoms associated with HSR. It has been recognised that these patients may initially be thought of as having respiratory disease of other origin. As a consequence new warnings have been introduced in the SPC (sections 4.4 and 4.8), the labelling (alert card) and in the PL. These new warnings are aimed for physicians and patients to better recognise these HSR with respiratory symptoms.
- On 4 February 2000, the MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95. The scope of the variation was to update the SPC and as a consequence the Labelling and PL following new information provisionally introduced through the above USR and following the availability of new interaction data of abacavir with methadone, and other new safety data. The CPMP considered the changes related to the variation acceptable and issued on 25 May 2000 the Opinion on the Type II variation. The respective Commission Decision was issued on 22 February 2001.
- On 10 August 2000, the Marketing Authorisation Holder requested an update of the SPC, Labelling and PL and through an USR procedure in accordance with article 1(2) of Commission Regulation (EC) No. 542/95 as amended. This was due to reports of hypersensitivity reactions occurring when therapy with Ziagen was restarted following a break in therapy.

  The scope of the USR was to provide information to prescribers and patients regarding the recognition of hypersensitivity reactions, their occurrence after interruption of therapy and the management of restarting. As a consequence new warnings have been introduced in the SPC (sections 4.4 and 4.8), the Labelling (alert card) and in the PL.
- On 8 September 2000, the MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95. The scope of the variation was to update the SPC, and as a consequence the Labelling and PL following new information provisionally introduced through the above USR and following the CPMP assessment of the clinical follow-up measure relating to the 48 week results of study CNAA B3005. The CPMP considered the changes related to the variation acceptable and issued on 19 October 2000 the Opinion on the Type II variation. The respective Commission Decision was issued on 22 February 2001.

- On 14 December 2000, the MAH submitted an application for extension of shelf-life as foreseen at time of authorisation. On 19 January 2001 the EMEA approved the variation. The respective Commission Decision was issued on 26 March 2001.
- On 12 January 2001, the MAH submitted an application for an extension of indication to include HIV-infected paediatric patients aged 3 months up to 18 years. The CPMP considered the changes related to the variation acceptable and issued on 27 June 2001 the Opinion on the Type II variation. The respective Commission Decision was issued 24 October 2001.
- On 12 January 2001, the MAH submitted an application for a Type II variation to update of SPC and PL, following changes requested by the CPMP following the adoption of a class labelling for nucleoside analogues in September 2000, changes requested by the CPMP in May 2001 following the assessment of safety follow-up measures and changes proposed by the Marketing Authorisation Holder following the availability of new safety data. The changes include a new recommendation for an adjusted dose of abacavir in patients with mild hepatic impairment, contra-indications in patients with moderate and severe hepatic impairment, changes related to the hypersensitivity reaction and a statement about the findings in preclinical carcinogenicity studies with abacavir in mice and rats. The CPMP considered the changes related to the variation acceptable and issued on 27 June 2001 the Opinion on the type II variation. The respective Commission Decision was issued 24 October 2001.
- On 11 September 2001, an application for a Type I variation was submitted for minor change of manufacturing process of the active substance and a change in specification of starting material/ intermediate used in manufacturing of the active substance. On 9 January 2001 the EMEA approved the variation. The respective Commission Decision was issued 23 October 2001.
- On 11 September 2001, an application for a Type I variation was submitted to make a change in test procedure for starting material/intermediate used in manufacturing of active substance. On 9 January 2001 the EMEA approved the variation. The respective Commission Decision was issued 23 October 2001.
- On 15 May 2002, the MAH submitted an application for a Type II variation to update the SPC further to the revised class labelling relating to lactic acidosis, to update symptoms and signs of hypersensitivity reaction in section 4.4 (“Special warnings and special precautions for use”) and 4.8 (“Undesirable effects”), inclusion of skin and subcutaneous tissue disorders as undesirable effects not associated with hypersensitivity reactions in section 4.8, and related relevant sections of PL, following the assessment of the Periodic Safety Update Reports (PSUR) 7 & 8 covering July 2000 to December 2000 and January 2001 to June 2001, respectively as well as new safety reports on skin disorders. Furthermore, the MAH proposed some minor changes in the SPC in order to bring the text in line with the latest QRD/ EMEA templates. In addition, the list of local representatives has been revised. The CPMP considered the changes related to the variation acceptable and issued on 25 July 2002 the Opinion on the type II variation. The respective Commission Decision was issued 28 October 2002.
- On 13 June 2002 an application for a Type I variation was submitted for a change in or addition of manufacturer(s) of active substance. On 2 July 2002 the EMEA approved the variation. The respective Commission Decision was issued 11 July 2002.
- On 13 June 2002 an application for a Type I variation was submitted for a minor change of manufacturing process of the active substance. On 2 July 2002 the EMEA approved the variation. The respective Commission Decision was issued 11 July 2002.
- On 13 June 2002 an application for a Type I variation was submitted to make a change in the batch size of active substance. On 2 July 2002 the EMEA approved the variation. The respective Commission Decision was issued 11 July 2002.
- On 13 June 2002 an application for a Type I variation was submitted to make a change in a test procedure for starting material/intermediate used in manufacturing of active substance. On 2 July 2002 the EMEA approved the variation. The respective Commission Decision was issued 11 July 2002.

- On 9 January 2003 an application for a Type I variation was submitted to make a change in or addition of manufacturing site(s) for part or all of the manufacturing process. On 14 February 2003 the EMEA approved the variation. The respective Commission Decision was issued 26 February 2003.
- On 9 January 2003 an application for a Type I variation was submitted for a change in or addition of manufacturing site(s) for part or all of the manufacturing process. On 25 February 2003 the EMEA approved the variation. The respective Commission Decision was issued 8 April 2003.
- On 9 January 2003 an application for a Type I variation was submitted to make a change in the qualitative composition of immediate packaging material. On 19 March 2003 the EMEA approved the variation. The respective Commission Decision was issued 26 March 2003.
- On 9 January 2003 an application for a Type I variation was submitted to make a change in test procedures of the medicinal product. On 14 February 2003 the EMEA approved the variation. The respective Commission Decision was issued 26 February 2003.
- On 12 February 2003, the MAH submitted an application for a Type II variation to update the SPC to include the class labelling on Lipodystrophy in sections 4.4 ("Special warnings and special precautions for use") and 4.8 ("Undesirable effects"). Relevant changes are equally proposed for the PL. Additionally, the contact details of the local representatives for Finland, Greece, Ireland and Spain have been updated in Section 6 of the PL. The CPMP considered the changes related to the variation acceptable and issued on 19 March 2003 the Opinion on the type II variation. The respective Commission Decision was issued 14 July 2003.
- On 17 July 2003, the MAH submitted an application for a Type II variation to update sections 4.2 "Posology and method of administration", 4.4 "Special warnings and special precautions of use" and 5.2 "Pharmacokinetic properties" of the SPC to implement the class labelling on liver impairment adopted by the CPMP for all anti-retroviral medicinal products in April 2003. The section 2 of the PL is amended accordingly. Furthermore, the MAH has taken this opportunity to update the section 4.8 "Undesirable effects" of the SPC by repositioning words on skin reactions. Furthermore, the MAH updated the PL, section 4, to revise the wording on lipodystrophy as adopted by the CPMP in March 2003 and amended the address of the Luxembourg local representative. The CPMP considered the changes related to the variation acceptable and issued on 20 November 2003 the Opinion on the type II variation. The respective Commission Decision was issued 30 January 2004.
- On 23 October 2003, an application for a Type IA variation was submitted for a change in BR/QC testing - repl./add. of batch control/testing site. On 29 October 2003 the EMEA approved the variation.
- On 15 January 2004, an application for a Type IB variation was submitted to make a minor change in the manufacturing process of the active substance. On 13 February 2004 the EMEA approved the variation.
- On 4 February 2003, an application for a Type IA variation was made for a submission of TSE Ph. Eur. certificate for exc. - approved/new manufacturer. On 10 February 2004 the EMEA approved the variation.
- On 1 March 2004, the MAH submitted an application for a Type II variation to update section 4.4 (Special warnings and Special precaution for use) of the SPC and section 2 of the PL under subheading "Pregnancy of Ziagen 300 mg film coated tablets and 20 mg/ml oral solution, to implement the class labelling for nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) regarding mitochondrial toxicity in children with in utero and post natal exposure, as adopted by the CPMP in November 2003. In addition the MAH completed the list of local representatives in the PL to include the 10 accession countries and changed the format according to the latest EMEA/QRD template. The CPMP considered the changes related to the variation acceptable and issued on 22 April 2004 the Opinion on the type II variation

5. Quality

The Marketing Authorisation Holder has confirmed that the quality, with respect to the method of preparation and control, has been regularly updated by variations to take account of technical and scientific progress in accordance with article 9a of directive 65/65/EEC and that the product conforms to current CPMP quality guidelines.

All the relevant sites of manufacture and testing have undergone GMP inspection from an EU Member State competent authority and documentation has been supplied to confirm this. The sites are satisfactory.

The Company has provided a summary on follow-up as indicated in the table below. All follow-up measures have been completed.

Ziagen Follow up measures:

Date requested	Activity	Date Submitted	Status
• **Chemical, Pharmaceutical and Biological Aspects:**			
25/03/1999	• Addition of a non routine test for TLC to the finished product specification.	27/05/1999, D991210	Complete 27/09/1999
25/03/1999	• Real-time stability data to be provided, by 28/02/2000	28/02/2000, D2000-0497	Complete 29/05/2000
13/11/2001	• The synthetic flowcharts for Avecia and Lonza should be completed to include solvents and reagents. • In the two diagrams, an enzymatic resolution step is mentioned. The Company should specify in each case if the enzymatic material used is from animal origin or if animal materials are used to prepare it. In the case of an affirmative answer, the Company should validate the viral and TSE safety by relevant data.	23/01/2002, D2002-0249 23/01/2002, D2002-0249	Complete, 10/06/2002 Complete, 10/06/2002

The currently authorised specifications for the active substance and the finished product and qualitative and quantitative composition are identical to those in the original Marketing Authorisation Application approved on 8 July 1999 for Ziagen tablets and oral solution.

The CPMP concluded that no specific concern has been raised in terms of quality for Ziagen tablets and oral solution.

6. Clinical Efficacy

A type II variation EMEA/H/C/252/II/20 supporting the introduction of a 600 mg (two tablets) once daily dosing regimen for Ziagen tablets in adults and adolescents over 12 years is currently being assessed by the CPMP (opinion expected in July 2004). Outstanding issues have been raised by the CPMP in April 2004 in particular with regard to the non-inferiority demonstration between Ziagen once and twice daily regimens.

The abstract for Study CNA30024 performed with abacavir and lamivudine administered as a twice daily regimen has been provided with the renewal dossier. The MAH will submit the full study report of this study for assessment in the frame of the above variation procedure.

The Design of Study CNA30024 is described below:

Title of the study	Randomised, Double-blind, Controlled, Multicenter Trial Comparing the Efficacy and Safety of Abacavir **BID** versus Zidovudine when Combined with Lamivudine **BID** and Efavirenz for Treatment of HIV-1 Infection in Antiretroviral Therapy Naïve Adults
Phase	III
Duration of treatment	48 weeks
Treatment	• **Abacavir (300 mg twice daily)** + zidovudine placebo (BID) + lamivudine (150mg twice daily) + efavirenz (600 mg OAD) • Abacavir placebo (BID) **+ Zidovudine (300mg twice daily) +** lamivudine (150mg twice daily) + efavirenz (600 mg OAD) SWITCH : Subjects **who permanently discontinued randomised (assigned) study drugs (ABC or ZDV) due to an adverse event** were permitted to substitute other licensed antiretroviral drugs and continue in the study; for analysis purposes, these subjects were considered **treatment failures at the time of switch**. Subjects could substitute other licensed antiretrovirals for background (non-assigned) study drugs (3TC or EFV) due to an adverse event and continue on the study. A switch of background study drugs was not considered a treatment failure, however, an intensification of study treatment by the addition of a fourth active antiretroviral agent would be defined as a treatment failure
Population	HIV1 infected patients ≥18 years of age who were ART-NAÏVE (less than 7 days of any prior approved or experimental antiretroviral therapy) with HIV-1 RNA level >400 copies/ml and a CD4+ cell count >50 cells/mm3 on at least one occasion within 21 days of study entry.
Objectives	**Primary objective** to compare the efficacy of abacavir (ABC) based therapy to zidovudine (ZDV) based therapy by determining the proportion of subjects (ITT exposed population) with plasma HIV-1 RNA ≤**50 copies/ml** through 48 weeks and adjusted by the randomisation strata **(screening plasma HIV-1 RNA ≤100,000 copies/ml vs >100,000 copies/ml**) **Secondary objectives** comparison of safety, as-treated antiviral efficacy, time to loss of virologic response (TLOVR), cumulative antiviral efficacy, immunologic effects, disease progression rates, rash/hypersensitivity reaction (HSR) rates, and viral resistance development between the two treatment groups.
Statistical methods	628 subjects with a 1:1 randomisation stratified by screening HIV- 1 RNA would provide 85% power to assess the non-inferiority of ABC compared to ZDV at the two-sided 0.05 level of significance. This calculation assumed identical 50% success rates in the treatment arms. Non-inferiority was defined as a 95% confidence interval adjusted for randomisation strata that excluded differences as large as 12% in the direction of inferiority of the ABC + 3TC + EFV treatment arm. If non-inferiority was established, then superiority of the ABC + 3TC +EFV arm was tested.
Number of patients	654 randomised – 649 ITT exposed (ABC+3TC+EFV N=324; ZDV+3TC+EFV N=325)

The results for the primary efficacy endpoint are given below:

Statistical Evaluation of Non-inferiority of Virological Response at Week 48 Based on Plasma HIV-1 RNA <50 copies/ml using the TLOVR algorithm (ITT-Exposed Population - CNA30024)

Strata	**ABC + 3TC + EFV N=324 n (%)**	**ZDV + 3TC + EFV N=325 n (%)**	**Point Estimate**	**95% Confidence Interval**
Stratified			0.8	-6.3, 7.9
<100,000 copies/ ml	142/198 (72%)	140/199 (70%)		
>100,000 copies/ ml	84/126 (67%)	84/126 (67%)		
Unstratified			0.8	-6.3, 7.9
Total	226/324 (70%)	224/325 (69%)		

As set in the protocol, the stepwise hypothesis test of superiority was performed and the null hypothesis was not rejected (p=0.8176). Results of the ITT analysis are compatible with a non-inferiority demonstration based on a 12% margin. Therefore, the abacavir BID containing regimen can be considered as non-inferior to the zidovudine regimen. The non-inferiority is still demonstrated

when considering the difficult-to-treat population with a high viral load > 100 000 copies/ml at baseline.

The CPMP concluded that these results would deserve to be included in the SPC of Ziagen. Indeed, whereas the clinical development of Ziagen was mainly performed in combination with zidovudine and lamivudine, this study provides further efficacy/ safety data within a different triple combination. Therefore, the MAH was requested to take the opportunity of the ongoing type II variation to update section 5.1 ("Pharmacodynamic properties") of the SPC of Ziagen with results of study CNA30024.

Conclusion on Clinical Efficacy

Ziagen is still considered as a valuable tool in the therapeutic management of HIV infected patients.

7. Clinical safety

The safety profile of abacavir has been regularly reviewed through periodic safety update reports (PSURs). Since the approval of abacavir in the European Union on 8 July 1999, 13 PSURs have been completed covering safety data up to 31 December 2003. The worldwide estimated cumulative patient exposure to abacavir (Ziagen & Trizivir) since first marketing approval is estimated to be approximately 508,958 patient-years of treatment.

Changes to safety information in the Abacavir SPC between 8 July 1999 and 31 December 2003

The main changes in the SPC related to safety are listed below:

SPC Sections	Description of Main Safety-Related Changes
HSR SPC Sections	
4.4	Addition of "abnormal chest X-ray findings (predominantly infiltrates, which can be localized") to the description of respiratory symptoms associated with HSR
4.8	Addition of "*respiratory failure*" and "*adult respiratory distress syndrome*" to the description of HSR
	Addition of "*myolysis*" as a rare symptom of HSR
	Addition of "*hepatic failure*" to highlight the potentially severity of hepatic reactions in HSR
	Signs and symptoms of HSR were reformatted according to body system and those occurring in at least 10% of patients were highlighted in bold
	Addition of a statement to indicate that rash and gastrointestinal manifestations of HSR are more frequently reported in children compared to adults
4.4 and 4.8	HSR incidence estimate based on clinical trial data updated from 3 to 4%.
	Addition of respiratory events to the description of HSR
	Addition of information on HSR following a therapy interruption
4.3	The statement on abacavir HSR was strengthened by including cross-references to sections 4.4 and 4.8
Non-HSR SPC sections	
4.2, 4.4, 5.2	On the basis of pharmacokinetic data in hepatically impaired patients, no recommendations on dosage reduction in these patients are possible. Due to the potential high levels of exposure in some patients, close monitoring in this

4.2, 4.4	population is recommended. Due to the potential high levels of exposure in some patients, close monitoring in this population is recommended.
4.4	Warning statement on moderate/severe hepatic impairment was updated to reflect that abacavir is contraindicated in severe hepatic impairment whilst in moderate hepatic impairment, abacavir is not recommended unless judged necessary and requires close monitoring
	The NRTI class statement on lactic acidosis for abacavir was strengthened by inclusion of a boxed warning and provides more detailed information on (i) identification of possible symptoms of lactic acidosis to facilitate early diagnosis, (ii) its prognosis (ii) how it may occur with pancreatitis, liver failure or renal failure (iii) time to onset and (iv) at risk populations e.g. those with hepatic steatosis or those co-infected with hepatitis C receiving alpha interferon and ribavarin
	Class warning concerning antiretroviral use in patients with underlying liver disease including hepatitis B/C co-infection.
4.4 and 4.8	Antiretroviral class statement concerning lipodystrophy
4.8	Addition of "pancreatitis" as a rare adverse event
	Addition of "rash (without systemic symptoms)" as a common adverse event
	Addition of "erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis" as very rare adverse events
	The Undesirable Effects section was reformatted according to MedDRA system organ class. CIOMS frequency categories were assigned for abacavir associated adverse events
4.6 and 5.3	Statements on findings from embryo-foetal toxicity in rats were moved from the Pregnancy section to the Preclinical safety section
5.3	Wording regarding lack of information on the tumourigenic risk of abacavir in animals was replaced by a new statement detailing the results from preclinical carcinogenicity studies with abacavir in mice and rats

Regulatory Actions related to the clinical safety

January 2000: Urgent Safety Restriction and 'Dear Healthcare Professional' letter concerning respiratory events. Some patients were initially thought to have an infectious respiratory disease with regard to respiratory symptoms they developed, and this may have resulted in the re-introduction of abacavir or continued abacavir therapy, leading to more severe HSR or death.

August 2000: Urgent Safety Restriction and 'Dear Healthcare Professional' letter concerning updated information on the management of HSR and including new recommendations:

- Patients who re-start abacavir having experience of one or none of the common HSR symptoms should do so in a setting where medical assistance is readily available.
- Abacavir should be discontinued if HSR cannot be ruled out, even if other diagnoses are possible e.g. respiratory disease, flu-like illness, gastroenteritis or reactions to other medicines.

July 2003: 'Dear Healthcare Professional' letter concerning early virologic non-response in patients receiving the triple nucleoside therapy regimen lamivudine/tenofovir/abacavir.

Hypersensitivity reaction to Abacavir

Hypersensitivity reaction (HSR) is the most important safety issue for abacavir, leading to specific monitoring and analysis:

- Abacavir Monthly Listing of possible HSR and cases with a fatal outcome were submitted until 31 August 2000.
- Six-monthly updates on activities and investigations on the hypersensitivity reaction to abacavir have been regularly reviewed. The last update (data up to 27 February 2004) is currently being reviewed.
- Analysis of HSR cases through PSURs.

Cumulative data to 31 December 2003				
	Ziagen	**Trizivir**	**Abacavir-Lamivudine FDC**	**All ABC-containing products**
Total HSR cases	2,912	569	31	3,512
HSR cases-spontaneous	889	276	0	1,165
HSR cases-Clinical trials	2,023	293	31	2,347
HSR cases where death is possible associated with HSR	24	6	0	30 (22 spontaneous 8 clinical trials)
HSR cases involving a positive rechallenge	176	24	0	200
HSR cases involving a positive rechallenge after interruption of therapy for non HSR reasons	4	4	0	8

The MAH has proactively undertaken a number of risk management activities and investigations to improve the management of HSR including an extensive education programme for prescribers and patients, and a pharmacogenetic programme to identify patients at risk for this reaction.

Evolution of the definition of HSR

A broad understanding of abacavir HSR has been acquired from clinical trials, spontaneous adverse event reports and non-clinical research activities. Consequently the definition of HSR has evolved with understanding and characterisation of this syndrome. Several changes have been instituted over the years to facilitate diagnosis, data collection, and management of HSR. Since early 1999 GSK clinical trials have included a specific case report form (CRF) module which encourages clinical investigators to capture pertinent data on HSR. The HSR case definition was expanded to include respiratory signs and symptoms.

Clinical description of HSR

The signs and symptoms of HSR are closely monitored in clinical trials and PSURs to ensure that the current description of HSR in the abacavir SPC and the patient Alert Card that is provided with abacavir-containing products, are accurate and up to date.

Time to onset of HSR

The symptoms of HSR usually manifest within the first 6 weeks after commencing therapy. HSR cases with a time to onset greater than 6 weeks are regularly assessed in PSURs, but to date these represent a low proportion of the total dataset, and these cases often do not have the characteristic features of HSR or are confounded by other factors.

Rechallenge

The MAH has proactively taken steps to ensure that prescribers and patients are fully aware of the issues concerning rechallenge, via updates to the SPC, Package Leaflet and Alert Card and through an

educational programme. Within GSK, a rigorous assessment of all suspected HSR rechallenge cases is conducted on an ongoing basis and follow-up information is sought to identify the possible reasons for restarting abacavir after an interruption of therapy.

With the launch of new abacavir containing products such as Trizivir, the potential for the risk of inadvertent rechallenge with Trizivir due to lack of awareness that Trizivir contains abacavir, was recognised. The SPC, Package Leaflet and Alert Card and the educational programme for abacavir were therefore updated to ensure that patients and prescribers were aware of this risk so that re-challenge with any abacavir-containing product could be avoided. GSK has set up an epidemiological programme to examine differences in the risk of HSR (including rechallenge) with Trizivir relative to abacavir.

The overall HSR rechallenge reporting rate for abacavir within the time period covering 1 July 1999 to 31 December 2003 is approximately 1.6 per 10,000 patient years.

Therapy interruption

Analysis of post marketing safety data revealed infrequent reports of rapid onset, life-threatening HSR, after re-starting abacavir or Trizivir in patients who had only one of the key HSR symptoms prior to therapy interruption. On very rare occasions, HSR was reported in patients who restarted therapy and had no apparent preceding HSR symptoms. The potential risk of HSR following interruption in abacavir dosing is now highlighted in the SPC, Package Leaflet and Alert Card and in the abacavir educational programme.

HSR cases with a fatal outcome

Cases in which a fatal outcome was possibly related to HSR are closely monitored and actively followed-up, and a cumulative assessment of deaths possibly due to HSR is also presented in each PSUR. Approximately one third of spontaneous reports of HSR-related deaths have involved a rechallenge. The overall reporting rate of deaths possibly due to HSR within the time period covering 1 July 1999 to 31 December 2003 for abacavir is approximately 0.4 per 100,000 patient years.
The number and the reporting rate of possible HSR have fluctuated from 1 July 1999 to 31 December 2003. The number of HSR-associated deaths has remained low, despite a substantial increase in the number of patients exposed to abacavir containing products during this period.

Incidence of HSR

First estimated incidence of HSR reported in the SPC, based on clinical studies, was 4%. In a recent analysis conducted on the largest and most robust dataset of over 8,000 subjects recruited from 34 clinical trials, the overall incidence of HSR was estimated to be approximately 5%. The MAH has been requested to update the SPC and Package Leaflet accordingly within the frame of this renewal procedure. Changes in the estimated incidence of HSR over time are closely monitored. Since the launch of abacavir a number of steps have taken place to manage the potential risk of HSR and improve data collection, but these actions may also have influenced the rates of reporting of HSR. The case definition was expanded to include respiratory symptoms. Since early 1999, investigators in GSK clinical trials have been asked to report all HSR cases in an expedited fashion and as serious adverse events. In addition they have completed a specific case report form (CRF) module which captures detailed information on each HSR case. These changes, together with an extensive and ongoing educational programme, have contributed to an increased awareness of HSR amongst study investigators, prescribers and patients. In addition investigators and prescribers are also encouraged to take a conservative approach to the diagnosis and management of potential HSR cases and to consider HSR in any patient with fever, rash, respiratory or gastrointestinal symptoms.

Risk factors for HSR

The current abacavir SPC states that "*Risk factors which could predict the occurrence or severity of abacavir HSR have not been identified"*.

GSK has undertaken an extensive and comprehensive programme to investigate possible risk factors for HSR. Reduced risk to patients may be achieved by identifying patient groups at higher or lower risk of HSR to abacavir. Such understanding may be gained through identifying possible genetic

determinants of HSR reactions, by analysis of data pooled from a number of clinical studies, or by epidemiology studies. Progress made in the various ongoing studies concerning identification of possible risk factors (clinical and genetic) has been regularly reviewed.

Retrospective analysis of clinical trial data to identify potential risk factors for HSR (submitted as an EU Follow-up measure in August 2003). A total of 8038 subjects receiving abacavir were included of which 403 cases developed suspected HSR. Identified prognostic factors for Abacavir HSR were ethnic origin, gender, baseline CDC classification or treatment status at ABC initiation.

Prospective, observational study of subjects taking abacavir and the occurrence of HSR based on the CHORUS database (full report submitted in the 6 month HSR update). Based on this analysis, potential risk factors included previous hepatitis B or C infection and female gender. Age, race, CD4 lymphocyte count, HIV-1 RNA viral load, prior AIDS diagnosis, prior antiretroviral therapy, prior abacavir use, prior or current non-nucleoside reverse transcriptase inhibitor use, elevated alanine and aspartate aminotransferases, and alkaline phosphatase, concurrent use of trimethoprim-sulfamethoxazole, tobacco use, alcohol use, abnormal white blood cell or haemoglobin levels, prior allergy history, or use of abacavir during influenza season were not associated with abacavir HSR. Additional studies are required to confirm these findings.

Pharmacogenetic/Pharmacogenomic studies: GSK has an ongoing research programme to identify possible genetic markers associated with abacavir HSR. An overview of the progress made in the various ongoing studies is provided in the 6 monthly HSR updates.

Two retrospective, case control studies (CNA30027 and CNA30032) were conducted to compare genetic polymorphisms in HIV infected subjects who developed abacavir HSR with those who did not (submitted as an EU Follow-up measure in August 2003). In summary, the first phase of the GSK genetic research has been completed and preliminary data has shown that HLA-B5701 may be a useful marker in Caucasian males and females. However, HLA-B5701 is not predictive of the risk of HSR in all ethnic groups. Furthermore, no other genetic markers have been found which identify patients at risk of HSR in all ethnic groups and both genders. Work is ongoing to identify a combination of markers with the appropriate sensitivity and specificity that will accurately identify patients at risk of HSR across diverse patient populations.

HSR Pharmacovigilance and Risk Management Activities

Information on clinical, genetic and epidemiological HSR studies has been submitted to the EMEA through the 6-monthly HSR updates.

Non-clinical research activities relating to HSR

A series of non-clinical studies directed towards understanding the basic mechanism of HSR have been conducted or are ongoing. Full details of these studies are presented in the 6 monthly HSR updates.

Results from *in vitro*, *in vivo* and *ex vivo* studies have been reported in the 6 monthly HSR updates and PSURs. The immunogen and its immunological presentation remain unknown, although preliminary *ex vivo* experiments suggest that HSR may be consistent with Class I immune restricted immune responses. The pharmacogenetic studies mentioned previously may also provide information to assist in the identification of a pathophysiological mechanism for HSR.

Safety Reviews

Lactic acidosis

A review of lactic acidosis in pregnant patients was conducted for all GSK NRTIs at the request of the CPMP (January 2001). No changes to the SPC were made as a result of this safety assessment.

In September 2001, CPMP requested all manufacturers of NRTIs to provide an analysis of reports of lactic acidosis and neuromuscular weakness, and symptoms mimicking the Guillain-Barre syndrome (GBS) without signs of lactic acidosis. A response was submitted in November 2001, and the CPMP concluded that there was insufficient evidence to show that abacavir was causally associated with

GBS-like symptoms with or without lactic acidosis, but requested that a warning be introduced and that "motor weakness" be included as a possible symptom of lactic acidosis.

Bone Disorders

A review of bone disorders including osteonecrosis and osteoporosis was submitted in September 2000. No changes to the SPC were recommended on the basis of this analysis. An updated cumulative review (to 31 December 2003) has been recently conducted at the request of CPMP and is presented in the latest safety update**.** Currently, there is still insufficient evidence to demonstrate a causal relationship between abacavir and bone disorders, and hence no update to the SPC is warranted.

Disorders of Glucose Metabolism

A cumulative review of blood glucose disorders in association with abacavir was conducted up to 31 May 2003. No changes to the SPC were recommended on the basis of this analysis.

Suicide/Depression

A cumulative review of suicide or depression in association with abacavir was conducted up to 30 April 2003. Based on this review, it was concluded that there was insufficient evidence to support the inclusion of depression or suicidal behaviour to the abacavir SPC.

Psychotic Symptoms

A cumulative review of psychotic symptoms (up to 31 May 2003) was completed further to the receipt of a published case report of psychosis involving abacavir. No change to the abacavir SPC was recommended on the basis of this analysis.

Mitochondrial toxicity

The Pharmacovigilance Working Party sent a list of questions to Marketing Authorisation Holders in October 2001 with a request to review the risk of potential mitochondrial toxicity in children following *in utero*/post-natal exposure for all NRTIs. An overall joint assessment report for NRTIs was discussed at the June 2003 PhVWP and CPMP meetings where it was proposed to implement a class label in section 4.4 ("Special warnings and special precautions for use") of the SPCs for NRTIs. In November 2003 a class statement was finalised and implemented for all NRTIs, including abacavir. GSK is currently supporting a number of studies, and is discussing potential further collaborative research efforts to explore potential consequences (short and long-term) of *in utero* exposure to NRTIs.

Safety in patients with hepatic impairment and/or co-infection with hepatitis B/C

Following discussions of the *Ad-hoc Group of Experts on Anti-HIV Medicinal Products* in November 2001, the CPMP adopted a list of questions on 17 January 2002 that were required to be addressed by the Marketing Authorisation Holders for all antiretroviral products. These questions related to the safety and pharmacokinetic profile of antiretrovirals in patients with impaired liver function and/or co-infection with hepatitis B or C. Following review of data, the CPMP proposed the inclusion of a class labelling regarding treatment of patients with liver impairment or hepatitis B or C virus co-infection for all antiretrovirals. A class statement has been included in section 4.4 ("Special warnings and special precautions for use) of the abacavir SPC. In addition section 4.2 ("Posology and method of administration"), was updated to clarify abacavir dosing in patients with hepatic impairment and additional data were added to section 5.2 ("Pharmacokinetic properties").

Lipodystrophy and Lipid abnormalities

A review of lipodystrophy in association with antiretroviral therapy was submitted in May 2002 in response to a request from the EMEA. On 21 November 2002, the CPMP endorsed a recommendation from the Pharmacovigilance Working Party to include a class labelling relating to lipodystrophy in the SPCs for all antiretroviral medicinal products. The Ziagen SPC was updated accordingly.

Conclusion on PSUR covering the period from 1 July 2003 to 31 December 2003

No new safety issues concerning abacavir HSR have arisen during the period of this PSUR. The latest incidence estimate of HSR from clinical trial data is 5%. No new major safety findings regarding non-HSR events have been identified during this period.

A total of 265 reports (143 serious) for Ziagen (123 reports), Trizivir (135 reports) and the not yet marketed fixed dose combination tablet containing abacavir and lamivudine (7 clinical trial reports) were received from 1 July 2003 to 31 December 2003.

The immune system remains the system order class that accounted for the majority of adverse event reports.

A total of 118 HSR cases were identified (47 Ziagen, 66 Trizivir, 5 Abacavir-Lamivudine FDC), representing 45% of all adverse events reports included in this safety update. The decrease in percentage of HSR cases compared to all reported adverse events is maintained during the period of this PSUR. The HSR symptoms distribution has not changed during this period with fever, rash and gastrointestinal symptoms as most common. However review of cumulative data highlights some HSR symptoms unlisted in the SPC (and for some of these unlisted in the CRF module) including rigors, fatigue, asthenia, and pharyngolaryngeal pain. The relevance of these events for HSR diagnosis should be discussed in the next PSUR. The number of HSR with a time to onset greater than six weeks has decreased during this period (6% compared to 12% in the last PSUR). These cases remain uncommon but close monitoring should be maintained. In the next PSURs, the MAH should give the number of cases for both reporting period and cumulative periods. The trend of an increased number of HSR cases without rash and fever was maintained during this period, even though these cases remain uncommon. However, several cases were not enough documented to definitely exclude occurrence of rash/and fever. Described symptoms reported in these cases are known as key symptoms of HSR, and do not raise any new safety issues. Cases of positive HSR rechallenge remained rare during this period (6/118).

Cardiovascular events, particularly ECG abnormalities (ST segment changes and T wave changes), myositis, events possibly related to an immune reconstitution syndrome, cases of eye disorders (with cumulative review), particularly visual acuity reduced and skin pigmentation disorders should be discussed in the next PSUR.

A number of switch studies have demonstrated that replacing stavudine with abacavir may improve body fat disorders and related metabolic effects. However, at this time no conclusions can be drawn from data reporting in PSURs on the risk of lipodystrophy and lipid disorders with Ziagen and Trizivir compared with the other antiretroviral drugs.

Adverse events in co-infected patients with hepatitis B or C represent 10% of all the reported adverse events during the 6-month period (decrease compared to the previous PSUR). Hepatic events associated with HSR and reported in this population should continue to be particularly monitored even if the reported cases do not raise any new safety issue or increased hepatotoxicity in patients with underlying liver disease or co-infection with HBV/HCV who experience HSR to abacavir.

The MAH should continue to monitor: blood and lymphatic events, glucose metabolism disorders, lipids abnormalities, lipodystrophy, psychiatric symptoms, lactic acidosis, hyperlactaemia, hepatic events, pancreatitis, respiratory events, renal disorders, serious skin reactions, musculoskeletal disorders, pregnancy.

In the next PSURs, the MAH should provide all publications mentioned, including those where the ADRs are reported.

Conclusion on clinical safety

The most important safety issue with abacavir is the risk of hypersensitivity reaction (occurring in approximately 5% of patients in clinical trials). At this time, the HSR to abacavir is well characterised

with a defined period of greatest risk. Overall, HSR is currently well managed in clinical practice. The number of life-threatening or fatal reactions remains small despite a large increase in the number of patients treated with abacavir-containing products since marketing approval. Risks related to this event have been managed by regularly updating of the SPC, Package Leaflet and Patient's Alert Card, by recommendations on its appropriate management, and by an educational programme addressed to patients and prescribers.

No new major safety issues have emerged during this five-year period.

As a consequence of the ADRs which require monitoring, the CPMP decided that the MAH should continue to submit 6-monthly PSURs for Ziagen.

8. Benefit/risk assessment and conclusion

No new safety concern has been raised. Ziagen is still considered as a valuable tool in the therapeutic management of HIV infected patients. Therefore, the benefit/risk is still considered favorable.
As requested by the CPMP, the MAH took the opportunity of the renewal to strengthen the advice regarding use of Ziagen during lactation in the SPC and to increase the mentioned incidence of hypersensitivity reactions in the SPC and Package Leaflet from 4 to 5%.

V. OVERALL CONCLUSIONS

Based on the CHMP review of the available information, the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore, considers by consensus that the benefit/risk profile of Ziagen continues to be favourable.

The Committee for Medicinal Products for Human Use recommends therefore the renewal of the Marketing Authorisation for Ziagen, subject to the follow-up measures undertaken by the MAH (see Annex 5 of this Assessment report).

Changes to the Community Marketing Authorisation

The renewal requires amendments to the terms of the Community Marketing Authorisation (Annex I, II and IIIAB).