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

SCIENTIFIC DISCUSSION

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II. Introduction

With the original centralised application for Ziagen film-coated tablets and oral solution, submitted in June 1998, Glaxo Group applied for the treatment of HIV infection in adults and paediatric patients. Since abacavir in combination with zidovudine and lamivudine was shown to produce, in antiretroviral naive patients, a substantial viral suppression (similar to an HAART with indinavir) at 24 weeks, the CPMP concluded on 25 March 1999 that a positive opinion could be granted provided that particular precautions were taken in relation with the hypersensitivity reactions of concern in the safety profile of this antiretroviral agent.

At that time, the risk/benefit ratio was not considered to be in favour of the recommendation of Ziagen for use in children and adolescents due to insufficient data. Particular concerns were raised about the incidence and difficulty of diagnosis of hypersensitivity reactions in paediatrics. It was decided that the paediatric indication would be re-evaluated when more clinical experience would be available in adult patients (with close monitoring and post-marketing surveillance) to better assess the impact of the hypersensitivity reactions in the therapeutic use when the final report of the PENTA (Paediatric European Network for Treatment of AIDS) 5 study would become available.

With this type II variation the Marketing Authorisation Holder of Ziagen, submits the request for the extension of the indication to paediatric patients aged 3 months up to 18 years.

The development in paediatric patients has been completed since the original submission, in particular results of one pivotal study in antiretroviral naive children, PENTA 5 is provided. Moreover, since the medicinal product has been registered in the US for more than one year, data on the US post-marketing experience are submitted.

1 Preclinical Data

Preclinical data were presented in the original centralised application dossier. It included two studies performed in the juvenile rat.

The toxicity of abacavir in young animals has been investigated in order to assess the influence of age on the toxicity profile of abacavir. Juvenile Wistar rats were treated from lactation day 3 for 31 and 61 days at dosages up to 450 mg/kg and 360 mg/kg respectively. Mortality was observed since 120 mg/kg with decreased activity, dehydratation and laboured breathing. Liver weight augmentation, hepatocellular hypertrophy, chronic kidney inflammation with tubular dilatation and medulla mineralisation were observed at 360 mg/kg. Brain weight was significantly decreased at 360 mg/kg in both males and females and in females at 120 mg/kg with no recovery at 360 mg/kg. Brain histology was normal.

The decrease in brain weight was probably related to a malnutrition of juvenile rats related to the toxicity of abacavir (reduction of lactation). The CPMP requested that this issue should be further explored.

Consequently, the Marketing Authorisation Holder committed to co-ordinate a review by an independent group of experts of the available data (brain histology) from the juvenile toxicology study to further evaluate the possibility for a direct effect of abacavir on brain growth and to submit a report on this review.

Otherwise, the toxicity profile was similar between juvenile and adults rats. No amendments to section 5.3 "Preclinical safety data" are necessary.

2 Clinical Data

2.1 Pharmacokinetics

Data in children from 3 months to 13 years of age were submitted with the original marketing authorisation application and derived from two studies with the 4 and 8 mg/kg dosage regimens; one single dose study (n=22) and one study on the steady state pharmacokinetics (n=47).

The overall pharmacokinetic parameters in children are comparable to adults with greater variability in plasma concentrations. In the single dose study, pharmacokinetics are not linear (probably due to the small number of enrolled children in any age group), between the two doses tested, 4 and 8 mg/kg bid. Exposures after administration of 4 mg/kg bid are somewhat lower than those in adult patients while they are higher after 8 mg/kg bid.

The 8 mg/kg dose was chosen based on the high variability in exposure and the risk of under-treatment of some children.

2.2 Clinical Efficacy

In order to demonstrate the utility of abacavir as part of the treatment regimen in HIV infected patients the Marketing Authorisation Holder submitted new results together with extended data of already submitted studies: 24 weeks study report of PENTA 5 in naive patients; and 48 weeks study report of CNAA3006 and 14.3 months study report of CNAAB3007 in experienced patients.

3.2.1 PENTA 5

This was a randomised partially blinded multicentre comparative phase II trial designed to evaluate new antiretroviral regimens as initial therapy for HIV infected children. Three dual NRTIs [zidovudine (ZDV) plus lamivudine (3TC) / ZDV plus abacavir (ABC)/ 3TC plus ABC] were compared each with or without a protease inhibitor [nelfinavir (NFV)].

In Part A, for mildly symptomatic or asymptomatic children, ZDV+3TC, ZDV+ABC and 3TC+ABC were compared, each with or without NFV in a factorial design. Children were randomised to either NFV or NFV placebo in a blinded fashion. The primary endpoints were serious laboratory (grade 3 or 4) or clinical events. In Part B, for advanced or symptomatic children ZDV+3TC, ZDV+ABC and 3TC+ABC were compared and all children received NFV. The primary endpoint was the effect on change in viral load by week 24 as measured by plasma HIV-1 RNA and serious laboratory (grade 3 or 4) or clinical events.

The dosing scheme was ZDV 360 mg/m²/day, ABC 16 mg/kg/day, 3TC 8 mg/kg/day and NFV 20-30 mg/kg/dose, given 3 times daily. Overall, 130 children were randomised.

The median age in the children was 5.3 years (range 0.3 – 16.7), with a baseline median viral load of 119313 copies/ml (range 29348 – 294420) and a median CD4 cell count of 545 /mm^3 (range 331 – 992).

Analysis on activity are only discussed on the pooled data (part A + part B).

Results at 24 and 48 weeks (ITT analysis)

Over 88% of children remained on their original randomised regimen at 24 weeks. Adherence in all treatment arms was good with the proportion of time spent on randomised therapy to 24 weeks of 93%, 86% and 92% for the ZDV/3TC, ZDV/ABC and ABC/3TC arms respectively.

The plasma HIV-1 RNA decreased from baseline by a mean of 2.1, 2.6 and 2.8 $\log_{10}$ copies/ml at week 24 (global p=0.01) in the ZDV/3TC, ZDV/ABC and 3TC/ABC groups respectively in the unadjusted analysis regardless of the presence of nelfinavir (see table ab 1). The differences in AUCMB (Area Under Curve Minus Baseline) of $\log_{10}$ HIV RNA between the 3 groups from baseline to 24 weeks was not statistically significant. The proportion of children with plasma HIV-1 RNA ≤

400 copies/ml was significantly greater in the abacavir containing arms than in the ZDV/3TC arm (table 2). There was no significant difference between the three arms in the proportion of children with HIV RNA ≤ 50 copies/ml.

Table 1: Change in HIV-1RNA log_{10} from baseline in the 3 different 2-drug NRTI combinations (+/- NFV)

ZDV+3TC (n) Mean (SE)	ZDV+ABC	3TC+ABC	Global p (F-test)
(36) –2.06 (0.21)	(43) –2.58 (0.16)	(45) –2.81 (016)	0.01

Table 2: Proportion with viral load ≤ 50/400 copies/ml at week 24 and 48

	ZDV+3TC (n=36) (1)	ZDV+ABC (n=45) (2)	3TC+ABC (n=47) (3)	1vs (2) p	1(vs) 3 p	2vs (3) p	Global p(x^2)
week 24							
n	36	43	45				
% ≤ 50	39 %	47 %	47 %	0.50	0.48	0.99	0.74
% ≤ 400	44 %	70 %	73 %	0.02	0.008	0.71	0.02
week 48							
n	36	43	45				
% ≤ 50	28 %	42 %	53 %	0.19	0.02	0.28	0.07
% ≤ 400	47 %	60 %	71%	0.24	0.03	0.29	0.09

This study is pivotal in the paediatric population. In antiretroviral naive children at advanced stage of HIV infection, a dual NRTI combination including abacavir (ZDV+ABC or 3TC +ABC) produces a substantial viral suppression in comparison with ZDV+3TC combination, regardless of the presence of NFV.

With this application the Marketing Authorisation Holder submitted also 48 week results that have been submitted recently for publication. The Marketing Authorisation Holder committed to submit the final publication once available.

When comparing proportions ≤ 50 copies/m, although only a trend in favour of the abacavir containing treatments arms is seen at 24 weeks, by 48 weeks the proportion of children receiving 3TC/ABC with ≤50 copies/ml is significantly greater than that in the ZDV/3TC arm. This change over time can be explained by it taking longer for patients, in particular children with high baseline viral loads, to achieve a reduction to less than 50 copies than to less than 400 copies. The smaller numbers of patients achieving a viral response ≤50 copies/ml at 24 weeks therefore made it difficult to demonstrate an early treatment difference. At 48 weeks the percentage of subjects in the 3TC/ABC group with less than 50 copies/ml had increased from that observed at 24 weeks, whilst the proportion of subjects with less than 400 copies/ml remained very similar to that at 24 weeks.

The Marketing Authorisation Holder proposed to include this information in the SPC section 5.1 “Pharmacodynamic properties” as follows:

Clinical experience: Clinical studies in antiretroviral-naïve patients:

“In a study comparing the unblinded NRTI combinations (with or without blinded nelfinavir) in children, a greater proportion treated with abacavir and lamivudine (71%) or abacavir and zidovudine (60%) had HIV-1 RNA ≤ 400 copies/ml at 48 weeks compared with those treated with lamivudine and zidovudine (47%)[p=0.09, intention to treat analysis]. Similarly, greater proportions treated with the abacavir containing combinations had HIV-1 RNA ≤50 copies/ml at 48 weeks (53%, 42% and 28% respectively, p=0.07)”

The CPMP agreed to this amendment.

3.2.2 CNAA3006

Randomised, double-blind 48-weeks study in anti-retroviral experienced [>12 weeks previous therapy either ZDV (79%), 3TC (55%) or other therapy] children aged >90 days and <12 years old. The primary endpoint of the study was the proportion of patients with HIV-1 RNA <10000 copies/ml. Medicinal products were administered as follows: placebo or abacavir solution (20 mg/ml, 8 mg/kg) added on to ZDV (180 mg/m^3 bid) + 3TC (4 mg/kg bid). The switch criterion was viral load ≥10000 copies/ml where patients either received open label triple therapy or other combinations or continued blinded treatment or withdrawal from the trial. 24 weeks data were available in the original submission, the Marketing Authorisation Holder now provides 48 week data.

Median age in the children were 5.7 (range 0.6 - 13) years with no patients under 5 months and a few under 30 months of age. Other baseline characteristics are summarised below:

	Treatment groups		
	ABC/3TC/ZDV N=102	3TC/ZDV n=103	Total n=205
CDC Classification (%)			
. A (mildly symptomatic)	38 (37%)	41 (40%)	79 (39%)
. B (moderately symptomatic)	33 (32%)	32 (31%)	65 (32%)
. C (severely symptomatic)	24 (24%)	23 (22%)	47 (23%)
. N (asymptomatic)	7 (7%)	7 (7%)	14 (7%)
Baseline viral load			
≤10000 copies/ml	18 (18%)	25 (24%)	43 (21%)
>10000 copies/ml	84 (82%)	78 (76%)	162 (79%)
≤400 copies/ml	2 (2%)	1 (<1%)	3 (1%)
>400 copies/ml	100 (98%)	102 (>99%)	202 (99%)
Median baseline CD4 count (range)	647 (28 to 6846)	724 (10 to 5707)	690 (10 to 6846)

Results at 48 weeks

A total of 155 of 205 patients completed 48 weeks, 73 in the triple therapy and 82 in the double therapy group. Overall, 24% of subjects withdrew by week 48, predominantly due to adverse events in the abacavir group. Therefore, these long term data should be interpreted with precaution.

The proportion of patients with HIV-1 RNA < 10 000 copies/ml at week 48 is described in the following table which controls for randomisation stratum (by age and previous treatment) and baseline plasma HIV-RNA category (using the Cochran Mantel-Haenszel test):

Analysis Population	ABC	PBO
Intent To Treat (switch=failure)		
< 30 months, prior ZDV/3TC	1/6 (17%)	0/7 (0)
> 30 months, no prior ZDV/3TC	3/9 (33%)	1/12 (8%)
≥ 30 months, prior ZDV/3TC	19/44 (43%)	16/44 (36%)
≥ 30 months, no prior ZDV/3TC	14/43 (33%)	10/40 (25%)
Total population	37/102 (36%)	27/103 (26%)

	p = 0.135	
As Treated		
< 30 months, prior ZDV/3TC > 30 months, no prior ZDV/3TC ≥ 30 months, prior ZDV/3TC ≥ 30 months, no prior ZDV/3TC	1/3 (33%) 3/3 (100%) 16/23 (70%) 14/23 (61%)	0/0 1/3 (33%) 16/22 (73%) 9/16 (56%)
Total population	34/52 (65%)	26/41 (63%)
	p = 0.633	

In the primary efficacy analysis, the proportion of patients in the Intent To Treat Population who achieved plasma HIV-1 RNA < 10 000 copies/ml at week 48 is not significantly different in the ABC/ZDV/3TC group and in the ZDV/3TC group, but a trend is observed for a greater viral suppression in the ABC group.
However, an inherent bias of the As Treated analysis is that it excludes patients who discontinued randomised treatment prior to Week 48, and this percentage was higher in the ABC group than in the control group (28% versus 20%).

Greater antiviral activity with the addition of ABC was evidenced by greater median reduction from baseline plasma HIV-1 RNA with ABC/ZDV/3TC versus ZDV/3TC through 48 weeks of treatment.
The median AUCMB for plasma HIV-1 RNA was significantly lower in ABC group than in the control group (ITT : - 0.47 versus - 0.21 $\log_{10}$ copies/ml, $p<0.0001$). It should be underlined that ABC has only demonstrated a slight impact in terms of HIV-1 RNA change from baseline (approximately - 0.5 $\log_{10}$ copies/ml).

The normalised area under the curve (NAUC) for CD4+cell count (which allows to stabilise the variability naturally observed in the CD4+ cell counts in children) through week 16 was slighty greater in the ABC group than in the control group (ITT : 1.11 versus 1.01, p=0.279). Besides the median increase from baseline in CD4+ cell count was 52 cells/mm^3 in the ABC/ZDV/3TC group compared with 5 cells/mm^3 in the ZDV/3TC group. The clinical relevance of this slight effect on the CD4+ cell count is not known.

3.2.3 CNAA 3007

This was an open label, compassionate use study aiming at providing access to abacavir for infants and children [mean age 7.9 years (range 0.7-18.6)] with advanced HIV-1 infection, failing or intolerant to standard therapy. The regimen initiated in the study included abacavir and at least one other antiretroviral that the child had not received previously. The dosage of abacavir was 8 mg/ kg BID.
Data on 74 enrolled patients were presented with the original submission. Now data on 154 patients are presented with this application.

The paediatric population in this 'compassionate use' of abacavir was at advanced stage of the disease. Two thirds of the subjects had at least one prior AIDS-defining illness. Over 98% of children had prior NRTI therapy, 25% NNRTIs and 73% PIs. Concomitant antiretrovirals at month 1 included d4T (59% of children), nelfinavir (41%), ritonavir (30%) and nevirapine (27%).
Baseline median CD4 cell count was 245 cells/mm^3, median CD4 % at 13.5% and a median viral load at 240 000 copies/ml. After 2 months a modest - 0.44 log copies/ml viral load change from baseline has been demonstrated.

3.3 Clinical Safety

3.3.1 Patients exposure

Up to 30 September 2000, approximately 657 children and adolescents between 3 months and 18 years of age have received abacavir through clinical trials, including expanded access and named patient programmes. Three hundred and seven children (47%) are between 6 and 12 years old.

3.3.2 Deaths

A total of 8 deaths in paediatric subjects have been reported to the Marketing Authorisation Holder, all of which were reported in patients enrolled in clinical trials. Of these, none were related to possible hypersensitivity reactions to abacavir and 7 were considered to be unrelated to abacavir therapy.

3.3.3 Serious Adverse events

The main point of concern is the occurrence of hypersensitivity reactions, which may be fatal with hypotension and with risk of multi-organ involvement.

Hypersensitivity reactions

Up to 30 September 2000, a total of 43 serious cases have been reported in children and adolescents aged 3 months up to 18 years (28 cases in clinical trials and expanded access programmes and 15 cases through spontaneous reporting).

The children were aged between 4 months to 16 years: 5 (12%) were aged between 4 months – 2 years, 7 (16%) were aged between 2 – 5 years and 31 (72%) were aged 6 – 12 years. Thirty children (70%) were male.

The time to onset of symptoms ranged from 1 day to 61 weeks. The majority of the hypersensitivity reactions were in clinical trials (65%, 28/43). In 22 cases (51%), a hospitalisation was required. No cases were fatal but three cases (7%) were considered to be life-threatening.
Five cases of the 43 (11.6%) possible hypersensitivity reactions involved rechallenge with abacavir. Hypersensitivity reactions in children were seen with the same frequency as has been described in adults (4.3% and 4.1%, respectively in children and adults). The clinical symptoms are not different, however rash (81% and 67%) and gastrointestinal manifestations (70% and 54%) were more frequent in children than in adults. Even though there were no fatal cases of hypersensitivity reactions and only 3 life-threatening cases, particular attention in the diagnosis of hypersensitivity reactions in children has to be ensured. Indeed some symptoms are difficult to report in this population (nausea, arthralgia, malaise). Other symptoms such as fever, diarrhoea, pharyngitis are common in small children, which might render the diagnosis more hazardous. Therefore, information for the adult in charge of the child must be particularly clear.

Serious adverse events other than hypersensitivity reactions reported in clinical trials and in post-marketing surveillance

Eighty-nine cases with at least one serious adverse event have been reported to the Marketing Authorisation Holder in subjects participating in clinical trials, excluding possible hypersensitivity reactions. Of these, 23 were considered possibly related to study medication or the causality was unknown and 66 were considered to be unrelated by investigator to study medication.

Events possibly related to mitochondrial toxicity

Mitochondrial toxicity has been causally attributed to the use of some nucleoside reverse transcriptase inhibitors. The pattern of events ascribed to mitochondrial toxicity varies with different agents but includes lactic acidosis, pancreatitis, peripheral neuropathy, lipid disorders, myopathy and haematological toxicity.

Peripheral neuropathy

Only one case of peripheral neuropathy has been reported as a serious adverse event possibly attributable to abacavir. This case occurred in a child with late stage HIV disease and does not provide evidence that this event was related to mitochondrial toxicity. This case was clearly confounded by

other factors and showed an improvement following stopping abacavir, although was this effect confirmed by subsequently restarting therapy. However, there is little evidence to suggest that this case is indicative of new safety signals. Peripheral neuropathy is known to be associated with HIV disease and the child also had a history of recurrent zoster and MAI infection and wasting. Dizziness has been reported in some cases of hypersensitivity reactions where it is considered to be secondary to other systemic effects of the reaction. Overall, it has been reported with a similar incidence in the abacavir and control groups in most clinical trials in adults but is rarely reported in children.

Lipid disorders

Clinical adverse events suggestive of lipid disorders have not been identified to date in children receiving therapy with abacavir. Fasting lipid data were available for 73 children enrolled in PENTA 5. Using the closest measurement to week 48, differences between the 3 nucleoside backbone groups and between the nelfinavir and nelfinavir placebo groups were not clinically relevant but numbers were very small.

Myopathy

No cases of myopathy, including cardiomyopathy, have been reported to date in children either as serious adverse events in clinical trials or through post marketing surveillance. There is no evidence from CNAA3006 or PENTA5 that myopathy is associated with abacavir therapy; creatine phosphokinase levels were not measured in these studies.

Haematological disorders

There is no evidence to suggest that haematological disorders are causally related to abacavir therapy, either in adults or children. The incidence of these events is similar in clinical trials between the treatment and control groups and post marketing surveillance has not indicated any previously unrecognised effects. Clinically significant anaemia was reported in one child (1%) receiving abacavir/lamivudine/zidovudine in PENTA5, and grade 3 or 4 decreased haemoglobin in one child receiving abacavir in CNAA3006
compared to 3 (3%) in the control group. Clinically significant neutropenia was reported in 6/92 children (7%) in the abacavir group in PENTA5 compared to 3/36 (8%) in the group not receiving abacavir, and grade 3 or 4 neutropenia was recorded in 2% in the abacavir/lamivudine/zidovudine group and 3% in the control group in CNAA3006.

Pregnancies

One pregnancy has been reported in a 17 year old adolescent female who received abacavir therapy in the first trimester of pregnancy; therapy was continued and the outcome of pregnancy is not yet known.

Children below 3 months of age

No safety concerns have been raised from the limited data available from children aged <3 months. Marketing authorisation is not sought for this age group at this time.

Available safety data are limited to that obtained from neonates born to mothers who
received abacavir during pregnancy and 9 neonates enrolled in an ongoing single dose study of abacavir in pharmacokinetics in newborn infants (PACTG321).

There have been four cases of foetal or neonatal abnormalities reported in pregnant women receiving abacavir but not discernible pattern in birth defects. Three cases involved live births and the reported abnormalities were hypospadias, an extra digit on the right hand, and bilateral club foot (the twin of this infant was normal). In a further set of twins, twin to twin transfusion resulted in intrauterine death of both babies at 24 weeks gestation; one twin was reported to have an enlarged bladder. In the pharmacokinetic study, PACTG321, 9 neonates less than 30 days of age were given a single oral dose

of 2mg/kg (Johnson et al, 2000). Abacavir disposition appeared to be substantially different from that observed in children or adults and dose of 2 mg/kg of abacavir yielded AUC values in the infants that was similar or greater than the recommended dose of 8 mg/kg in older children. This dose was well tolerated; one infant developed neutropenia, which resolved without intervention, which was felt to be related to the background zidovudine therapy.

Long term treatment effects

Approximately 227 children have been treated for more than a year and the maximum duration of abacavir treatment in children and adolescents in clinical studies to date is about 142 weeks. No long term effects have been identified to date.

Withdrawal effects

No withdrawal effects have been reported in patients receiving abacavir, regardless of age.

3 Changes to the Product Information

The proposal of the Marketing Authorisation Holder to amend the Product Information was overall endorsed.

Furthermore the CPMP decided the following additional amendments :

Sections 4.8 "Undesirable effects"

The profile of HSR is highlighted by the frequency (4.3 %) and by the characteristics of clinical symptoms. Since in particular, gastrointestinal symptoms commonly accompany various viral/ bacterial infections in children, they could easily be overlooked and misinterpreted. Therefore, the profile of HSR in children should be highlighted by the factual characteristics of clinical symptoms in section 4.8 of the SPC.

Therefore the following sentence has been added:

"*Rash (81% vs 67%, respectively) and gastrointestinal manifestations (70% vs 54%, respectively) were more frequently reported in children compared to adults*."

Section 5.1 "Pharmacodynamic Properties"

The CPMP decided to delete the following sentence:

« Similarly, in children with extensive antiretroviral exposure, a modest but sustained effect of the combination of abacavir, lamivudine and zidovudine was observed (median reduction 0.61 log_{10} copies/ml at 48 weeks). »

The question of the durability of the virological response is particularly difficult to solve through clinical studies in HIV infection, since the proportions of lost to follow-up, of switch are usually important at long term.
As a matter of fact, this question has not been adequately addressed in the well designed pivotal study CNAAB 3005 (ABC/ZDV/3TC vs IDV/ZDV/3TC, in antiretroviral naive adult patients). This question is even more difficult to solve in paediatric patients, and considering the high proportion of patients who switch therapy at long term in study CNAAB 3006, no relevant information is considered to be provided in term of durability from this study. The CPMP considered that the 48 weeks results of study CNAAB 3006 are not substantial and should not be mentioned in section 5.1. It is falsely reassuring in term of durability. Overall, the use of antiretroviral drug in paediatric patients is mainly based on the substantial efficacy data derived from clinical studies in adults patients with specific pharmacokinetic data in paediatric population. Clinical studies in paediatric patients are helpful to

confirm the adequacy of the extrapolation of adults data to paediatric population. The issue of durability is crucial and is not adequately addressed by the 48 weeks data of the CNAAB 3006 study, with a premature discontinuation rate of 47%.

4 Additional Commitments

Educational Programme

The Marketing Authorisation Holder commits to extend the core information from the current HSR educational programme to include paediatric-specific elements as described below, to highlight to prescribers, healthcare providers and parents/guardians the serious nature of hypersensitivity reactions. The key objectives and messages of the HSR educational programme will be consistent with those previously implemented for adults.

The Marketing Authorisation Holder will supplement the current core information by expansion of the current education program, all paediatric marketing literature will always mention the hypersensitivity reaction, the information booklet which currently accompanies the HSR video will be supplemented with an additional insert to cover paediatric issues, the development of a parent/guardian-oriented Questions and Answers », brochure to cover hypersensitivity to abacavir and paediatric-specific issues.

Furthermore, the Marketing Authorisation Holder commits to submit all paediatric HSR educational materials, the video and the corresponding information booklet to the national agencies before promotion of the indication in the EU member states. The national agencies will be requested to provide any comments on the proposed HSR educational materials within three weeks.

The Marketing Authorisation Holder commits to submit the educational programme and material proposed for the paediatric population (parents and /or legal guardians) by 20 July 2001 for a thorough critical review by the CPMP.

Specific Post-Marketing Surveillance

The Marketing Authorisation Holder committed to

- provide monthly line listings of all cases of hypersensitivity reactions and cases with a fatal outcome in children aged under 18 years, for the first six-months following the Commission Decision on this variation

- present in the further PSURs of Ziagen, the adverse events in paediatric patients separately from those occurred in adults. When possible the Marketing Authorisation Holder will make a distinction between antiretroviral naive and experienced children in the presentation of the adverse events in paediatric patients.

5 Benefit/risk assessment

Abacavir is available as oral solution, which is an adequate formulation for paediatric use. Based on the previously submitted pharmacokinetic studies, the dose has been adequately determined in children over 3 months compared to pharmacokinetic parameters in adults: the recommended dose should be 8 mg/kg BID.

Three studies have been performed with abacavir as oral solution in paediatric patients. Like for adults, abacavir has demonstrated a substantial virological response in antiretroviral naive patients whereas the benefit was limited in experienced children.

The main problem with abacavir are the hypersensitivity reactions. The frequency of hypersensitivity reactions in children does not differ from that seen in adults. Clinical manifestation of hypersensitivity reaction in children are similar to those observed in adults, even though rash and gastrointestinal

symptoms are more common in children. Particular attention has to be given to the information dealing with HSR reactions provided to prescribers and the adult in charge of the child.

To ensure the safe use in paediatric patients, the Marketing Authorisation Holder has made commitments to enlarge the educational programme already implemented since the Marketing Authorisation of Ziagen, to encompass prescribers in charge of paediatric population and to perform a specific post marketing surveillance in paediatric patients. In addition, the profile of HSR in children is highlighted by the factual characteristics of clinical symptoms in section 4.8 of the SPC .

Altogether these particular precautions are expected to control the risk of HSR in the paediatric population.

Based on the CPMP review of data on safety and efficacy and the commitments undertaken by the Marketing Authorisation Holder, the CPMP considered by consensus that the benefit/ risk profile of Ziagen in the combination treatment of HIV infection of paediatric patients was favourable and issued a positive opinion on the extension of the therapeutic indications to include the paediatric population.

III. CONCLUSION

The CPMP considered this Type II variation to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics and reflected in the Package Leaflet, based on the observations and the appropriate conclusions.

The CPMP adopted on 27 June 2001 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation.