SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Ziagen. This scientific discussion has been updated until 1 September 2000. For information on changes after this date please refer to module 8B.

1.   Introduction

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI).

The approved indication is: Ziagen is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults.

The demonstration of benefit of Ziagen is mainly based on results of studies performed in treatment-naïve patients on combination therapy with lamivudine and zidovudine.

Two oral formulations are available: tablet (each contains 300 mg of abacavir) and solution (each ml of solution contains 20 mg of abacavir).

There are currently 10 approved antiretroviral drugs including 5 nucleoside reverse transcriptase inhibitors (NRTIs): zidovudine (ZDV), didanosine (ddI), zalcitabine (ddC), lamivudine (3TC) and stavudine (d4T); one nonnucleoside reverse transcriptase inhibitor (NNRTI): nevirapine (NVP); and 4 protease inhibitors (PIs): ritonavir (RTV), saquinavir (SQV), indinavir (IDV) and nelfinavir (NFV).

In principle, there is a recognised need for new therapeutic agents in this area; the long-term use of these drugs is limited by emergence of resistance and also by toxicity and inconvenient drug dosing schedules/formulations.

2.   Chemical and pharmaceutical aspects

Composition

Ziagen is presented in two pharmaceutical forms - a film-coated tablet 300 mg, and an oral solution 20 mg/ml.

Standard pharmacopoeial grade excipients have been used in the preparation of both forms, where appropriate.

Tablets

Various formulations have been used in the clinical program. Clinical trials were originally performed using abacavir succinate 'caplets' 100 mg, and abacavir sulfate tablets 300 mg. Bioequivalence between these two tablet formulations has been demonstrated at equivalent doses.

Oral Solution

The oral solution was also modified during development, in order to improve physical stability on storage. It is packed in HDPE bottles with polypropylene childproof closures. Bioequivalence between the marketed tablet formulation and the marketed oral solution has been demonstrated at equivalent doses.

Active substance

Abacavir sulfate is a new chemical entity. It is a carbocyclic nucleoside derivative synthesised via a well-controlled, reproducible, high yielding process, which has been adequately described. The active substance specification has been justified with regard to satisfactory purity (assay & impurity levels) and the test methods and qualitative limits applied are considered to provide adequate control of the quality of the active substance. The batch analytical data presented confirm reproducible and consistent synthesis, and the data are in agreement with the proposed specification. Control methods have been adequately described and are well validated.

The stability data provided for the active substance are sufficient to confirm the proposed re-test period.Other ingredients

The excipients are well established as suitable for use in pharmaceutical products and are described in Pharmacopoeias.

Finished product and product development

Tablets

Abacavir tablets are manufactured using a direct compression process: all ingredients excluding magnesium stearate are blended after sieving. The lubricated blend is compressed and the cores are then coated. The tablets are packaged into blister packs (PVC/Al). The process validation studies have demonstrated that the manufacturing process is capable of producing a product of constant quality. Tests at release are standard and include limits for assay, related impurities, disintegration, dissolution, uniformity of content etc. These tests and limits should ensure consistent clinical performance of the product. Stability studies have been carried out using validated methods and the results indicate good chemical and physical stability at all storage conditions. Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.
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Oral Solution

The manufacturing process for the oral solution consists of conventional solubilisation, mixing, filtration and filling; it is well described, as are the in-process controls (pH, fill volume). Satisfactory batch release and shelf life specifications have been proposed and justified. Stability studies have been carried out using validated methods. Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.
Abacavir solid dosage forms and abacavir solution formulations are almost completely bioavailable (C_{max} slightly lower and T_{max} slightly later for tablet).

3.   Toxico-pharmacological aspects

Pharmacodynamics

Abacavir is a nucleoside analogue with reverse transcriptase inhibition activity. Antiviral efficacy has been assessed in primary cell cultures (mononuclear cells, macrophages) and in cell lines that are susceptible to HIV-1 and HIV-2. Tested viruses included T-cell line adapted viruses and primary isolates. These *in vitro* studies in experimental models included combinations with ZDV, ddI, ddC, amprenavir and nevirapine. A significant antiviral effect of abacavir in HIV-1 and HIV-2 was supported but the combination studies were not performed with primary isolates. Published data have reported on an *in vitro* synergy of amprenavir and abacavir.

The mechanism of action of abacavir is partly known as described in the SPC. One of the enzymes that ensure its phosphorylation is unknown. The *in vivo* anti-HIV activity of abacavir is described in the clinical part of this assessment report.

A range of *in vitro* and *in vivo* safety pharmacology studies showed no adverse effects of abacavir on central and autonomic nervous system, or respiratory and cardiovascular systems, at doses exceeding the maximum proposed therapeutic dose 300 mg (base) bid, equivalent to 12 mg (base)/kg/day based on a 50 kg person. These studies involved mouse, rat and dog.

The effect of abacavir at the following receptors was assessed in isolated tissue preparations: cholinergic (guinea-pig ileum), adrenergic (rabbit aorta, guinea-pig atria and trachea), histaminergic (guinea-pig atria) and serotonergic (rat fundus). In addition, the ability of abacavir to affect tissue responsiveness to arachidonic acid (rat fundus), bradykinin (guinea-pig ileum) and angiotensin II (rabbit aorta) was determined.

There were no direct effects of abacavir on any of the isolated tissue preparations, and no significant effects on contractile responses to any of the substances studied.

Pharmacokinetics

Abacavir is rapidly absorbed in mice, rats, and monkeys following oral administration and the exposure is generally proportional to the dose; bioavailability is greater than 76% in both mice and monkeys.

The binding of abacavir to plasma proteins is low to moderate in mice, monkeys, and humans. Abacavir is extensively bound to melanin-containing tissues. Abacavir was extensively distributed with higher concentrations in gastrointestinal tract, urinary tract, nasal turbinates, uveal tissue of the eyes than in plasma.

Hepatic clearance is the principal route of excretion for abacavir. The routes of metabolism are qualitatively similar in mice, monkeys and humans. Quantitatively, the two main metabolites in monkeys and humans are a 5'-glucuronide and a 5'-carboxylic acid.

There is currently a lack of information on the accumulation of the two metabolites in man. However, pre-clinical evidence demonstrates that these metabolites are inactive. The results demonstrate that no accumulation of abacavir occurs and the two major metabolites are inactive both for anti-HIV-1 activity and cytotoxicity in PBL and MT4 cell lines based on results from *in vitro* studies.

Toxicology

The toxicology profile of abacavir was well described.

Abacavir showed a low order of toxicity following acute administration in mice and rats.

Repeated dose-toxicity studies were conducted using the oral route in CD1 mice (one month and 3 months at dosages up to 708 mg/kg, 6 months at dosages up to 234 mg/kg) CD and Wistar rats (one month at dosages up to 400 mg/kg, 3 months at dosages up to 375 mg/kg) and cynomolgus monkeys (one month and 3 months at dosages up to 297 mg/kg, one year at dosages up to 297/212 mg/kg). The main target organ found following repeated administration of abacavir is the liver with augmentation of the weight and hepatocellular hypertrophy. Other signs of liver toxicity such as necrosis or cholestasis were not observed in the species tested. Hepatic effects were reversible.

Animal exposure resulted in safety margin between 1 and 10 according to the species evaluated. But in general toxicity observed at higher dosages was not very high and did not induce overt toxicity.

Abacavir has a weak mutagenic potential as previously observed with other nucleoside analogues.

The carcinogenic potential has not been evaluated so far.

The toxicity profile of abacavir is generally similar in juvenile and adult rats. However there was a reduction in brain weight in juvenile rats associated with reductions in body weight.

Abacavir is toxic in rats for reproductive functions with: augmentation of early intra-uterine death, reduced foetus and offspring (during the duration of the post-natal life) weights and augmentation in the percentage of malformations/variations. These observations could not be associated with maternal toxicity since reduced body weight of F0 animals was minimal. The foetotoxic and malformative effects of abacavir observed in rats are reflected in the SPC. In rabbits, no foetotoxicity or increase in malformations was observed.

Fertility was not affected.

High dose combination of abacavir and amprenavir (up to 530 and 750 mg/kg/day, respectively) in rats significantly increased the heart weight. This effect was not accompanied with significant changes in histopathology but was still present in females after the recovery period showing that this effect seems to be irreversible. This effect was not achieved with either of the products administered alone. The applicant will further address the finding.

4.   Clinical aspects

Clinical pharmacology

Data from 327 adults (299 receiving abacavir) were used to define pharmacokinetics, pharmacodynamics, and safety and dose range. In addition pharmacokinetic data in children from

3 months to 13 years of age were 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).

Pharmacodynamics

Abacavir is a nucleoside analogue with reverse transcriptase inhibition activity. Antiviral efficacy has been confirmed in primary cell cultures (mononuclear cells, macrophages) and in cell lines that are susceptibility to HIV-1 and HIV-2 as further described in part III of this report.

As mentioned in part III, anti-HIV activity of abacavir was evaluated in the presence of some other drugs that are currently used in HIV-disease therapy implying synergistic and no antagonistic effects. The applicant's data implied synergism *in vitro* with ZDV, ddI and ddC and no observed antagonism with the other drugs tested (3TC, amprenavir, nevirapine).

Mutations associated with abacavir resistance selected during in vitro passage (K65R, L74V, Y115F, and M184V) have also been detected among isolates from subjects participating in clinical studies, with M184V and L74V being the most common. Treatment emergent mutations were less frequent when abacavir was given in combination with other antiretrovirals.

In general, subjects harbouring virus with wild-type RT genotype or 1-2 NRTI-associated mutations at baseline responded to abacavir with substantial decreases in plasma HIV-1 RNA while subjects with ≥3 NRTI-associated mutations had attenuated or no plasma HIV-1 RNA response to abacavir. The most common single RT mutation seen at baseline in these trials was the M184V, which has been associated with resistance to 3TC. As described in the clinical part (study CNAB 3002, CNAAB 3003, CNAA 3006), abacavir as add on to ART-experienced patients offers added antiretroviral activity irrespective of prior 3TC therapy. For example plasma HIV-RNA response at week 16 by viral genotype in study CNAB 3002 (therapy experienced patients) were:

RT mutations	Proportion of patients with VL decrease >0.5 $\log_{10}$ or <400 copies/ml	
	ABC + SBG	PBO + SBG
M184V alone	20/26 (77%)	1/30 (3.3%)
1 ZDV codons without M184V*	13/18 (72%)	3/16 (18.8%)
1 ZDV codons** + M184V	12/24 (50%)	3/21 (14.3%)

SBG = Stable background therapy
* +/- any other codon changes
** ZDV codon changes: 41L, 67N, 70R, 210W, 215F/Y and/or 219Q

One possible explanation for the slightly better response in the 3TC experienced group (see clinical efficacy) is that the M184V mutation delays the emergence of resistance conferring mutations and can re-sensitise resistant variants to ZDV. However, in this study an increase in phenotypic resistance has been observed in the abacavir group patients previously exposed to 3TC (25% of baseline patients and 41% after 16 weeks. More information on phenotypic/genotype resistance is available in the report on CNAB 3002, below).

Phenotypic susceptibility of primary isolates were tested throughout the clinical studies and involved the RVA as run by Virco nv, Belgium, but the information on phenotypic resistance in the dossier will need to be supplemented. Most of these genetic studies were done after 12 and 16 weeks of treatment. The applicant is committed to report on resistance data after longer periods of follow-up. Viral genotype and phenotypic resistance to all approved antiretrovirals will be assessed to week 48 for approximately 200-400 patients. In addition, results of currently ongoing phenotypic resistance analysis will be submitted as soon as they are available. Isolates known to be resistant to protease inhibitors did not disclose resistance to abacavir.

Dose finding studies will be further described under "clinical efficacy".

Pharmacokinetics

Pharmacokinetic properties of abacavir are adequately established (validated HPLC methods) in adults with the tablet formulation and in children with the solution formulation.

ADME

The absolute bioavailability of abacavir is high (average of 83%). Regarding the proposed formulations, tablet (300 mg) and solution (20 mg), these formulations lead to comparable systemic exposure.

Food does not affect the overall exposure (single dose study of 300 mg, n=18).

Plasma protein binding to human plasma is low to moderate (approximately 49% at therapeutic range).

It has been shown that abacavir penetrates the cerebrospinal fluid. The clinical relevance of this finding is however not established (see study CNAB 3001 in AIDS dementia).

Abacavir is extensively metabolised (alcohol dehydrogenase, UDP-glucuronyl transferase). Two major metabolites were identified (5'-carboxylate and glucuronide). The metabolites and unchanged abacavir account for 83% of the administered abacavir dose in the urine and the remainder is eliminated in the faeces.

Abacavir is neither a major substrate nor an inhibitor of CYP3A4. Therefore, potent interactions are unlikely to occur with drugs that are substrates, inducers or inhibitors of this enzyme, which are numerous among concomitant medications commonly used by AIDS patients. There were 2 interaction studies: one with zidovudine and lamivudine and the second with alcohol. The results of those studies did not justify any specific dose recommendations. Products such as rifampicin, rifabutin and ritonavir that may induce UDP-glucoronyl transferase are not expected to clinically impact on the exposure levels of abacavir. In an interaction study with ethanol exposure levels of abacavir were increased by about 41%, (clinically insignificant). Abacavir has no effect on the metabolism of ethanol. Retinoid compounds are eliminated via alcohol dehydrogenase and interaction with abacavir is possible but has not been studied.

Children

The overall pharmacokinetic parameters in children are comparable to adults with greater variability in plasma concentrations (studies CNAA 1001 and ACTG 330). 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 applicant has based the choice of the recommended 8-mg/kg doses on this consideration. The choice of the dose in children is further discussed under "efficacy".

Other Special populations

Limited data (6 patients) are available on pharmacokinetics from patients with end-stage renal dysfunction indicating unaltered abacavir pharmacokinetics. Based on limited experience, abacavir should be avoided in patients with end stage renal disease. A warning has been included in section 4.4 of the SPC to reflect this concern.

In addition, no data on patients with hepatic failure are available but a clinical trial in these patients is ongoing. Results will be made available as follow-up measure. In the absence of data, the use of abacavir should be avoided in patients with moderate hepatic impairment. In addition, there is no information on the disposition of abacavir in patients with severe hepatic disease. This information has been reflected in the SPC (Contraindications and Warning sections).

The pharmacokinetics of abacavir has not been studied in elderly patients (>65 years). Since there is no effect of ageing on alcohol dehydrogenase activity, it appears unlikely that ageing will affect abacavir pharmacokinetics. The clinical data, although limited (31 patients over 50 years of age) provided further reassurance that elderly patients are unlikely to have clinically significant pharmacokinetic alterations. The genetic polymorphism exhibited by alcohol dehydrogenase, which may result in interindividual variability, is expected to have little impact on the clinical usage of abacavir based on the current dose recommendation (300 mg bid) and the relatively safe use

experienced in study CNAB 3001 (600 mg bid for up to a year). In poor metabolisers (2-4% in a Caucasian population), exposure would likely be increased by about 40% (based on the interaction study with ethanol).

Thus, the expected variability due to genetic difference in alcohol dehydrogenase activity in different ethnic groups and in women is not considered clinically relevant given the current knowledge of the safety profile for abacavir.

Clinical efficacy

The pivotal database comprised 1059 adult patients (4 patients >65 years). Data from 253 children (<13 years of age) made the major contributions to substantiate dose/dose regimen and efficacy. This is displayed in the tabular overview of clinical studies in adults and children (supportive studies not included):

Study number	Objective	Design	No of patients	Population	Duration
CNAA 2001	Dose-finding	Parallel dosing cohorts: 200 mg tid/400 mg tid/300 mg bid/600 mg tid	79	Anti-retroviral naive adults	12 w
CNAB 2002	Main dose finding study	Randomised, blinded. 100/300/600 mg bid abacavir	60	Anti-retroviral naive adults	72 w (randomised 24w)
CNAAB 3003	Superiority trial. Antiviral activity	Randomised blinded comparison of 3TC/ ZDV/+/- ABC	173	Anti-retroviral naive adults	48 w
CNAAB 3005	Equivalence trial	Randomised blinded comparison of Abacavir/ZDV/3TC vs. Indinavir/ZDV/3TC	562	Anti-retroviral naive adults	24 w (planned for 48 weeks)
CNAB 3002	Superiority trial.	Randomised, double blind, placebo controlled. Abacavir as add on to stable background therapy (different combinations)	185	Treatment experienced patients	16 weeks (planned for 48 weeks)

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Tabular overview of clinical studies in children

Study	Objective	Design	No of Patients	Population	Duration
ACTG 330	Dose finding	Dose escalating 4 mg/kg and 8 mg/kg stratified by age	46	Children between 3mo and 12 years	36 w
CNAA 3006	Superiority trial	Double blind, randomised, controlled 3TC/ZDV/+/- ABC	205	Antiretroviral experienced (>12 w) children, 3 mo – 12 years	24 w (Planned for 48 w)

ADULTS

Dose response studies:

Two dose-response studies have been performed in antiretroviral naive patients.

In the first study (CNAA 2001, n=79) a strong antiviral effect is observed with abacavir (-1 to -2 $\log_{10}$ copies/ml at 12 weeks). It was not possible to conclude on any dose related antiviral effects, but for tolerance a possible trend of increased incidence of nausea, headache and dizziness with increased dose was noted.

Study CNAB 2002 (randomised, double-blind, n=60) which is the main dose justification study, clearly demonstrates the superiority, in terms of reduction of viral load, of the 300 mg and 600 mg bid doses of abacavir monotherapy compared to the 100 mg bid dose at week 4, with no difference between these two higher dosages. Moreover, taking into account a possible trend of increasing adverse events with dose (mainly nausea), the choice of the recommended dose of abacavir (300 mg bid) was established.

The median HIV-1 RNA changes from baseline are summarised below:

	Median HIV-1 RNA $\log_{10}$ copies/ml by treatment group		
	100 mg bid	**300 mg bid**	**600 mg bid**

Week 4
  LOCF*
  As treated analysis
	-0.63 (n=20)
	-0.63 (n=20)
		-1.55 (n=20)
		-1.60 (n=19)
			-1.61 (n=19)
			-1.61 (n=19)

Week 12
  LOCF*
  As treated analysis
	-0.41 (n=20)
	-1.00 (n=11)
		-1.02 (n=20)
		-1.25 (n=14)
			-1.49 (n=20)
			-2.01 (n=13)

Week 24 LOCF* As treated analysis	-0.57 (n=20) -0.76 (n=2)	-0.70 (n=20) -1.01 (n=8)	-1.30 (n=19) -2.11 (n=7)

*The last measurement on randomised monotherapy carried forward through 24 weeks, if treatment switches prior to week 24.

After 24 weeks all patients received abacavir/3TC/ZDV. At week 72, 31/42 (74%) of patients had plasma HIV-1 RNA <400 copies/ml, and 21/42 (50%) had plasma HIV-1 RNA <50 copies/ml.

CD4+ cell counts increased during both the monotherapy phase with abacavir and also during the combination phase, with a median increase at week 72 of 163 cells/mm^3.

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Antiretroviral naive adult patients

Main studies

CNAAB 3003

The primary objective of this study changed (amendment of the protocol) from comparing the durability of the plasma HIV-1 RNA response following 48 weeks of treatment with ABC/ZDV/3TC versus 3TC/ZDV to comparing antiviral activity following 16 weeks treatment.

173 patients (>13 years of age) were randomised into the initial double blind 16-week phase (Group A) and a second cohort was added (Group B) that allowed patients to enrol into an open-label arm with ABC/ZDV/3TC. In Group A, at week 16 and thereafter, if the switch criterion of plasma HIV-1 RNA >400 copies/ml was met, patients could remain on randomised therapy, discontinue study drug or receive open-label abacavir in combination with other ART. Patients with <400 copies/ml could switch to open-label abacavir only. The primary endpoints were the proportions of subjects with plasma HIV-1 RNA <400 copies/ml, plasma HIV-1 RNA profiles and CD4 lymphocytes profiles.

Baseline characteristics:

	By treatment group		
	ABC/ZDV/3TC **n=87**	**ZDV/3TC** **N=86**	**Total** **n=173**
CDC Classification (%) . Class A (asymptomatic) . Class B (symptomatic, not AIDS) . Class C (AIDS) . Missing	 65 (75%) 15 (17%) 2 (2%) 5 (6%)	 58 (67%) 20 (23%) 3 (3%) 5 (6%)	 123 (71%) 35 (20%) 5 (3%) 10 (6%)
Baseline median $\log_{10}$ Plasma HIV-1 RNA [a]	4.51 (2.60 - 5.56)	4.64 (2.69 - 6.01)	4.54 (2.60 - 6.01)
Baseline median CD4 cell count (cells/mm^3)[a]	473 (154 - 1223)	427 97 - 1478)	450 (97 - 1478)
HIV-1 Risk Factors . Homosexual contact . Injectable drug use . Occupational exposure . Heterosexual contact . Transfusion . Other	 48 (55%) 10 (11%) 1 (1%) 21 (24%) 1 (1%) 1 (1%)	 36 (42%) 8 (9%) 0 (0%) 34 (40%) 0 (0%) 1 (1%)	 84 (49%) 18 (10%) 1 (<1%) 55 (32%) 1 (<1%) 2 (1%)

a *Baseline was defined as the mean of the Day -3 and Day 1 values.*

Results

Accountability

152 patients completed the 16 week study (withdrawals evenly distributed between groups). Sixty two (71%) of patients from the triple therapy group with abacavir remained on randomised therapy at week 48 compare with only 8 (9%) from the 3TC/ZDV group. There were only 4 patients in the triple therapy group who switched therapy after week 16:

	ABC/3TC/ZDV N (%)	3TC/ZDV N (%)
Randomised	87	86
Did not initiate study drug treatment	4 (5%)	5 (6%)
Remained on randomised study drug through week 48	62 (71%)	8 (9%)
Added ABC only at 16 weeks or later	N/A	50 (58%)
Added ABC &/or other nucleosides at week 16 or later	1 (1%)	8 (9%)
Added ABC + protease inhibitors +/- other nucleosides	3 (3%)	7 (8%)
Discontinued before week 48	17 (20%)*	8 (9%)¤

* One additional patient withdrew after switching therapy

¤ Ten additional patients withdrew after switching therapy, and two additional patients withdrew after week 48

Plasma HIV-1 RNA

Plasma HIV response up to 48 weeks were analysed by ITT (i.e. missing patients were regarded as failures or data were carried forward) or ITT (Switch = Failure). The proportions of patients with HIV-1 RNA assay threshold values <400 copies/ml were:

By week	Number of patients with HIV-1 RNA<400copies/ml per treatment group			
	ABC/3TC/ZDV		3TC/ZDV	
	n (%)		n (%)	
Baseline	3/87 (3%)		0/86 (0%)	
	ITT	ITT (Switch = Failure)	ITT	ITT, (Switch = Failure)
Week 16	67/87 (77%)	63/87 (72%)	33/86 (38%)	29/86 (34%)
Week 24	64/87 (74%)	60/87 (69%)	51/86 (59%)	11/86 (13%)
Week 36	65/87 (75%)	57/87 (66%)	57/86 (66%)	8/86 (9%)
Week 48	62/87 (71%)	53/87 (61%)	52/86 (60%)	5/86 (6%)

A post hoc analysis with the more sensitive Roche Amplicor Ultra Sensitive HIV-1 RNA assay allowed a limit of detection of 50 copies/ml confirmed the superiority of the triple therapy regimen showing that 54% and 15% of had undetectable levels in the triple and double therapy group, respectively in the ITT switch equals failure population at week 16.

CD4 cell count

Notably, there were no relative benefits in terms of CD4 cell counts for the triple therapy group. The median changes from baseline were 47 (16 weeks) and 150 cells/mm^3 (48 weeks) in the triple therapy group with abacavir and 113 (16 weeks) and 158 cells/mm^3 with the double combination group.

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CNAAB 3005

This randomised, double blind study evaluated the safety and efficacy of abacavir/3TC/ZDV and indinavir/3TC/ZDV in ART naive adult patients. A total of 562 patients with plasma HIV-1 RNA >10000 copies/ml and CD4+ cell counts ≥100 cells/mm^3 were enrolled in the study. Preliminary data are now available for all patients at week 16 and for almost all patients at week 24.

Plasma HIV-1 RNA

The ITT analysis up to week 16 accounts for all patients (week 12 values are carried forward to week 16 as appropriate.). If a patient is switched into open label treatment per-protocol or prematurely discontinued study medication prior to week 16 the outcome was classified as a failure. The proportions given on patients having plasma HIV-1 RNA <400 copies/ml at week 24 are based on the patients that reached at least 24 weeks on study; these sample sizes are noted in the table below. The proportion of patients with undetectable viral load is given in the table and preliminary results indicate equivalence between the abacavir and indinavir containing regimens:

Study Week	ABC/3TC/ZDV	IDV/3TC/ZDV
Baseline ITT as treated	0% (n=280) 0% (n=262)	0% (n=282) 0% (n=266)
Week 8 ITT as treated	58% 68% (n=209)	54% 63% (n=214)
Week 16 ITT as treated	67% 83% (n=192)	66% 83% (n=190)
Week 24 ITT as treated	66% (n=270) 85% (n=151)	65% (n=268) 86% (n=157)

CD4 cell count

The median change of CD4 cell count from baseline was of 86 and 105/mm^3 for the ABC/3TC/ZDV group and 103 and 102/mm^3 for the IDV/3TC/ZDV group at week 16 and week 24, respectively.

Antiretroviral experienced adult patients

CNAB 3002

The aim of this randomised double-blind, parallel-group multicentre study was to evaluate the safety and efficacy of ABC versus placebo as add on therapy in combination with stable background therapy (SBG) in ART experienced patients.

Patients could enter the study if they had received unchanged SBG for at least 12 weeks (which could include any combination of NRTI, NNRTI and PIs provided the patient had less than 36 months NRTI experience) and were expected to continue to derive benefit from their current SBG for at least 16 weeks. In addition patients had a CD4+ cell count ≥100 cell/mm^3 and plasma HIV-1 RNA between 400 - 50000 copies/ml. Randomisation was stratified according to whether patients were 3TC naive or experienced and the duration of prior NRTI therapy. A total of 185 patients were randomised to receive either abacavir 300 mg bid in combination with SBG (92 patients) or placebo in combination with SBG (93 patients).

Eligible patients were to continue on randomised treatment until the last patient completed 48 weeks of treatment unless they met a protocol-defined switch criterion, based upon viral load (at week 8 ≥0.5 log increase in plasma HIV-1 RNA from baseline value and/or plasma HIV-1 RNA

≥50000 copies/ml, at week 16 and every 8 weeks thereafter if plasma HIV-1 RNA was ≥400 copies/ml) or new AIDS (CDC C) defining events. If a patient met a switch criterion, they could receive open-label abacavir at the next scheduled visit or continue on randomised therapy (in both cases with or without changes to their background antiretroviral therapy).

Full week 16 data are available for study CNAB 3002. Baseline characteristics for the patients are summarised in the table:

Treatment Group	ABC + SBG	PBO + SBG
Baseline plasma $\log_{10}$ HIV-1 RNA (copies/ml)	3.68	3.52
Baseline CD4+ cell count (cells/mm^3)	408	410
Duration of prior NRTI 3-9 months 9-18 months 18-36 months	22% 73% 5%	24% 69% 8%
Commonest Treatment in SBG* NRTI PI NNRTI	3TC (72%) SQV (12%) Nevirapine (1%)	3TC (70%) SQV (10%) Nevirapine (2%)

*The most common baseline SBG therapies were 3TC/ZDV (36%), 2NRTIs + PI +/- NNRTI (21%) and d4T/3TC (19%).

SBG = stable background therapy

Viral load response

At week 16, a decrease in median plasma HIV-1 RNA from baseline of 0.44 $\log_{10}$ copies/ml for the abacavir/SBG group was observed compared to an increase of 0.12 $\log_{10}$ copies/ml for the placebo/SBG group, ITT population.

Proportion of patients with plasma HIV-1 <400 copies/ml at week 16:

Population	ABC+SBG	PBO+SBG	Treatment comparison
ITT population, all patients	36/92 (39%)	7/93 (8%)	P<0.001
Subgroup: 3TC experienced	28/67 (42%)	5/67 (7%)	P<0.001
Subgroup: 3TC naive	8/25 (32%)	2/26 (8%)	P=0.038
Subgroup: 3-9 months prior ART	9/20 (45%)	4/44 (18%)	P=0.096
Subgroup: 9-18 months prior ART	27/67 (40%)	1/64 (2%)	p<0.001

Results for the As Treated analyses were similar to those for the ITT population.

CD4+ cell count response

The abacavir/background group had a median increase in CD4+ cell count at week 16 of 30 cells/mm^3 compared to a median increase of 1 cells/mm^3 in the placebo/background group.

Genotypic and phenotypic data

The baseline genotypic and phenotypic characteristics of the patients' isolates were very similar in both treatment arms. Over 95% of the baseline isolates from the 3TC experienced population had the M184V mutation and 49% had ZDV associated mutations. The baseline isolates from the 3TC naive patients did not, with one exception, have the M184V mutation but had a higher incidence of ZDV associated mutations than the 3TC experienced patients (81%), suggesting, as other studies have, that a 3TC containing regimen may delay the emergence of ZDV mutations.

Of the 26 abacavir treated patients with the M184V mutation alone at baseline, nineteen (73%) experienced $\geq 1 \log_{10}$ copies/ml reduction in plasma HIV-1 RNA or had a value <400 copies/ml by week 16.

The presence of ≥ 3 ZDV resistance mutations with or without the M184 was associated with a lesser response to the abacavir-containing regimen. No mutation known to be associated with reduced susceptibility to abacavir had developed following 16 weeks of therapy with abacavir in combination with stable background therapy in either 3TC naive or experienced patients. Although no new abacavir associated mutations were detected a slight increase in the incidence of isolates with reduced phenotypic susceptibility to abacavir was observed at week 16 in this group as previously described.

Baseline phenotypes from the 3TC-experienced patients in the abacavir treated group were phenotypically resistant to 3TC (97%), but the majority remained fully sensitive to abacavir (75%).

Supportive data

Therapy naïve patients

Supportive data were provided in study CNAB 2002 described above which provided data up until week 72.

An open, randomised study, CNAA 2004 investigated abacavir in dual therapy with different protease inhibitors:

Plasma HIV-1 RNA response at week 48

	ABC+IDV	ABC+SAQ	ABC+RIT	ABC+NFV	ABC+APV
HIV-1 RNA <400 copies/ml ITT As treated	9/17 (53%) 9/10 (90%)	8/16 (50%) 8/10 (80%)	8/16 (50%) 8/8 (100%)	7/17 (41%) 7/9 (78%)	9/16 (56%) 9/10 (90%)

CD-4 cell count:

In the as treated analysis the overall change from baseline at week 4 was 88 cells/mm^3, at week 16 was 157 cells/mm^3 and at week 48 was 159 cells/mm^3 showing durability of effect across all treatment groups.

Therapy experienced patients

Week 16 data is available for study CNAB 3009, together with preliminary week 48 efficacy data. The aim of this open-label single-arm multicentre study was to evaluate the safety and antiretroviral activity of abacavir as an add-on therapy in previously antiretroviral naive patients treated with the 3TC/ZDV combination for at least 12 weeks (in study NUCB 3027).

The results of the ITT analysis are given in the table

	% <400copies/ml	% <20 copies/ml	Median CD4 change from baseline (cells/mm^3)
Day 0	15/52 (29%)	3/50 (6%)	
Week 16	39/52 (75%)	17/50 (34%)	+70 (n=49)
Week 40	33/49 (67%)	15/50 (30%)	+97 (n=47)
Week 48	36/50 (72%)	Not available	+118 (n=49)

CNAA 2007

The aim of this open label, single arm multicentre study was to evaluate the safety and antiviral activity of abacavir in combination with amprenavir (APV, 1200 mg bid) and efavirenz (EFV, 600 mg QD) in patients with a screening plasma HIV-1 RNA >500 copies/ml despite at least 20 weeks prior therapy with indinavir, ritonavir, saquinavir and/or nelfinavir. A total of 99 patients were enrolled and treated in the study; 87% of the exposed patients had >2 years of prior antiretroviral therapy and approximately one third were NNRTI experienced.

Overall 19/74 (26%) patients had plasma HIV-1 RNA <400 copies/ml at week 16.

As previously described, the M184V mutation alone or in combination with ≤2 ZDV mutations was not associated with reduced susceptibility to ABC. Isolates containing ≥3 ZDV + M184V mutations were more likely to show decreased susceptibility to ABC. Overall, the presence of multi-drug resistant viral isolates, NNRTI-associated mutations, ≥3 ZDV mutations or the T69D insertion were more frequently associated with an antiviral response <1 $\log_{10}$ HIV-1 RNA by week 16.

In addition the applicant provided information from rollover studies following on from ACTG 320 (IDV/3TC/ZDV); conclusive results from studies ACTG 368 (combination with indinavir and efavirenz) and ACTG 372 (efavirenz and adefovir ± nelfinavir) are pending.

One, open, expanded access study (**CNAA 3008**) addressed the addition of abacavir to heavily pre-treated patients. No conclusions on efficacy can be drawn from this study.

CNAB 3001

In 105 previously treated patients suffering from **AIDS Dementia Complex** a 12 week, randomised, double-blind placebo controlled study was conducted to assess changes in neuropsychological performance using abacavir 600 mg bid. This study has not demonstrated any further benefit with the addition of abacavir compared to placebo to current antiretroviral therapy in terms of neurological performance. This is despite consistent drug penetration into CSF, attaining antiviral levels. This study demonstrates a benefit of adding abacavir to current anti-retroviral therapy as measured by proportion of patients with undetectable plasma viral load (46% versus 13%, p=0.002). However, no formal conclusion can be drawn, as the median baseline viral load was lower in the ABC treatment group (3.7 versus 4.5 $\log_{10}$ copies/ml).

<u>CHILDREN</u>

Three studies have been performed with abacavir as oral solution, which represents an adequate formulation for paediatric use.

Based on the two pharmacokinetic studies (CNAA 1001 and ACTG 330), where two doses were tested, 4 and 8 mg/kg bid, exposures after administration of 4 mg/kg bid are in the same range as those in adult patients whereas they are higher after 8 mg/kg bid.

Study ACTG 330

Age Group	AUCτ µg.h/ml Mean (CV, %)		C$_{max}$ µg/ml Mean (CV, %)	
	4 mg/kg	8 mg/kg	4 mg/kg	8 mg/kg
3 months to 2 years	3.06 (39) (n=9)	8.67 (48) (n=10)	1.51 (39) (n=9)	3.84 (38) (n=10)
>2 to 6 years	5.72 (107) (n=15)	9.38 (52) (n=15)	2.02 (66) (n=15)	3.48 (36) (n=15)
>6 to 13 years	5.75 (61) (n=14)	10.71 (43) (n=19)	2.25 (53) (n=14)	3.81 (38) (n=20)
Pooled paediatric pharmacokinetic parameters	5.10 (88) (n=38)	9.8 (47) (n=44)	1.98 (58) (n=38)	3.71 (37) (n=45)
Adult (dose 300 mg bid)	6.02 (28) (n=20)		3.00 (29) (n=20)	

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

CNAA 3006

Ongoing randomised, double-blind 48-week study in anti-retroviral experienced (>12 weeks previous therapy; ZDV (79%), 3TC (55%) or other therapy in the last 6 months) children aged >90 days and <12 years old. The primary endpoint was the proportion of patients with HIV-1 RNA <10000 copies/ml. Drugs 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 and thereafter patients either received open label triple therapy or abacavir in other combinations or continued blinded treatment or withdrew from the trial. Full 16 week and preliminary 24-week data are reported here. Median age in these children was 5.7 (0.6 - 13 y) years with no patients under 5 months and 34 under 30 months of age. Other baseline characteristics were:

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

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Results at 16 weeks

A total of 191 of 205 patients completed 16 weeks, 91 in the triple therapy and 100 in the double therapy group. Between weeks 16 and 24, 7 patients in the triple therapy group added additional anti-retroviral therapy and in the double therapy group 20 patients switched to open label treatment (11 with added antiretroviral therapy). Overall, 7% of subjects withdrew by week 16, predominantly due to adverse events in the abacavir group.

The proportion of patients with HIV-1 RNA <10000 copies/ml at Week 16 (primary endpoint) 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 (CMH):

Analysis Population	ABC	PBO
ALL PATIENTS		
Intent To Treat		
Prior ZDV/3TC No prior ZDV/3TC	21/50 (42%) 29/52 (56%)	21/51 (41%) 15/52 (29%)
Total population	50/102 (49%)	36/103 (35%)
	p = 0.006	
As treated		
Prior ZDV/3TC No prior ZDV/3TC	21/45 (47%) 29/47 (62%)	20/49 (41%) 14/47 (30%)
Total population	50/92 (54%)	34/96 (35%)
	p <0.001	

The percentage of patients with HIV-1 RNA level below 10000 copies/ml is significantly greater in the triple therapy group with abacavir as compared with the double therapy ZDV/3TC (ITT: 49% versus 35%, p=0.006). Data seem to suggest that benefits are more prominent in patients with high baseline HIV-1 RNA levels (but the number of patients with low virus levels is relatively small) and in patients without prior ZDV/3TC experience. Moreover, the proportion of patients achieving plasma HIV-1 RNA below the level of detection (400 copies/ml) at week 16 was significantly greater with ABC/ZDV/3TC therapy than with ZDV/3TC (ITT: 13% (13/102) versus 2% (2/103), p=0.003). Overall the change from baseline was approximately - 0.5 $\log_{10}$ copies/ml for HIV-1 RNA in the abacavir group and approximately - 0.20 $\log_{10}$ copies/ml in the placebo group.

The median increase from baseline in CD4 cell count was 60 and 11 cells/mm in the abacavir and placebo group, respectively.

Results at 24 weeks

Analysis at this timepoint was performed by ITT (all patients irrespective of switch) and modified ITT (assigning switched patients as failures) and as treated patients (patients on randomised treatment). At 24 weeks, the proportion of patients with plasma HIV-1 RNA <10000 copies/ml was greater in the ABC/3TC/ZDV treatment group than for the 3TC/ZDV group for all populations analysed. Since approximately one-fifth of study patients entered the trial with plasma HIV-1 RNA <10000 copies/ml, additional analyses were completed using the CMH test controlling for baseline plasma HIV-1 RNA as well as randomisation stratum at week 24. These analyses demonstrated, as shown at 16 weeks, a significant treatment difference in both the ITT (switch included) and the As Treated populations.

There was very little change from week 16 in the proportion of patients with HIV-1 <400 copies/ml and the median changes from baseline (ITT) also remained similar to week 16. The CD4 response described at 16 weeks was sustained at 24 weeks.

CNAAB 3007

This is an ongoing, open label, compassionate study. Data are available on 74 enrolled patients between 6 months and 13 years of age failing or intolerant to standard therapy. Baseline CD4 cell count was 150 cells/mm^3 and viral load was about 450000 copies/ml. Data indicated that 18% of patients had a reduction to <10000 copies/ml (9% <400 copies/ml) after 2 months.

Clinical safety

Patient exposure

Safety of abacavir sulfate has been evaluated in a series of controlled and uncontrolled clinical studies. Approximately 4400 HIV-1 infected patients had received abacavir therapy within clinical trials up to 18 March 1998 and were included in the original submission. Of these, about 4100 were adults and over 200 were children. This number of exposed patients is subject to inaccuracies due to incomplete databases for ongoing and blinded clinical studies.

Provided up to the time of the CPMP opinion were safety data from over 191 children older than 30 months who had received multiple doses of abacavir. In children younger than 30 months data are derived from approximately 45 patients who had received multiple doses of abacavir.

Adverse events and serious adverse events/deaths

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

Based on information received by Glaxo Wellcome up until 30 September 1998, an incidence of 3% has been reported, i.e. 406 cases in 13000 exposed patients. The most common symptoms are fever and rash. Notably those events were less frequent in patients with a positive rechallenge (67% and 52%, respectively/n=33) than in those with no re-challenge (87% and 73% respectively). Thus, the absence of rash or fever may potentially delay the diagnosis of a hypersensitivity reaction and increase the risk of reintroducing abacavir inappropriately. Almost all hypersensitivity reactions will have fever and/or rash as part of the syndrome. Other frequently observed signs or symptoms of the hypersensitivity reaction include gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, lethargy and malaise. Some patients with hypersensitivity reaction were initially thought to have a viral infection such as flu-like syndrome, gastroenteritis or respiratory syndrome.

- The median time to onset of symptoms was 11 days (mean time: 15.7 days). In 376 patients (94%), the reaction occured within the first 6 weeks. For 25 other cases, the time to onset was over 6 weeks.

- 98% of patients with hypersensitivity reaction had fever or rash or both.

- Life threatening reactions were more frequently reported in patients who were rechallenged with abacavir following an initial hypersensitivity reaction. Of the 406 cases, 8% (34/406) were rated as life threatening by the investigator: of the 49 rechallenges, 35% (17/49) were rated as life threatening, including one fatal outcome, compared to 5% (18/357) in patients who did not undergo rechallenge.

In an update of hypersensitivity reactions performed on cases reported between 1 October 1998 and 31 December 1998 230 of 8000 patients receiving abacavir experienced hypersensitivity reactions confirming the 3% overall risk of hypersensitivity reactions. It was noted that the incidence of rechallenge decreased from 13% (before 1 October 1998, 49/406) to 6% in the 4Q 1998 (14/230). Two deaths were related to hypersensitivity reaction during this period of time. Dear doctor letters, patient alert cards and modified consent forms began to be instituted early in 1998.

Currently the mechanism of the hypersensitivity reaction is unknown. A programme to investigate this is underway but results are not yet available. In addition no risk factors have been identified which may predict the occurrence or severity of hypersensitivity reaction to abacavir but intermittent therapy with abacavir may increase the risk of developing a state of hypersensitivity. The SPC reflects this concern.

In <u>adults</u>, nausea was the most frequently reported adverse event (AE) in both phase II and III studies. It was significantly more common in patients receiving abacavir-containing regimens. The available

data (table below) did not suggest a dose-related impact on the risk of AE although this was mentioned as a concern during dose-finding studies. Seven % of adults withdrew due to AE (3% due to hypersensitivity reactions).

Summary of most common drug-related adverse events reported in ≥5% of subjects (CNAB 3001, CNAAB 3003 and CNAA 3006)						
	CNAAB 3003 ABC 300 mg bid dose		CNAB 3001 randomised phase ABC 600 mg bid dose		CNAA 3006 ABC 8 mg/kg dose	
Adverse event	ABC/3TC/ ZDV N=83	3TC/ZD V N=81	ABC+ Background therapy N=49	PBO+ background therapy N=50	ABC/3TC/ ZDV N=102	3TC/ZDV N=103
Number of subjects reporting any drug-related adverse event	54 (65%)	49 (60%)	34 (69%)	36 (72%)	39 (38%)	24 (23%)
Nausea	39 (47%)	32 (40%)	20 (41%)	9 (18%)	4 (4%)	2 (2%)
Malaise and fatigue	21 (25%)	20 (25%)	8 (16%)	6 (12%)	3 (3%)	1 (1%)
Headache	20 (24%)	12 (15%)	5 (10%)	9 (18%)	6 (6%)	2 (2%)
Nausea and vomiting	10 (12%)	6 (7%)	5 (10%)	2 (4%)	20 (20%)	4 (4%)
Diarrhoea	4 (5%)	3 (4%)	8 (16%)	4 (8%)	3 (3%)	6 (6%)
Feeding problems	7 (8%)	8 (10%)	2 (4%)	2 (4%)	5 (5%)	0

During the post marketing phase respiratory symptoms have been recognised as an important part of the hypersensitivity reaction in approximately 20% of HSR-patients. These symptoms 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.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, Abacavir must be discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g. 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 abacavir in patients who had only one of the key symptoms of hypersensitivity reaction (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping abacavir. 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.

Consequently, if a decision is made to re-start abacavir in patients who had only one of the key symptoms of hypersensitivity or no symptoms prior to stopping abacavir, this must be done in a setting where medical assistance is readily available. This information has been included in the relevant parts of the Summary of Product Characteristics, Package Leaflet and labelling (alert card).

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<u>Children</u>

In children the adverse event profile was similar to adults. Vomiting was more frequent (38%) than in adults and led to discontinuation in 4% of children.

Also in children, the major point of concern is the hypersensitivity reaction which appears with a higher frequency than in adults (5.2%, p=0.04).

This serious adverse event is difficult to monitor and especially so in young children. In this age group, the difficulty to capture subjective adverse events such as nausea, malaise raises great concerns. Moreover, gastrointestinal symptoms are more frequent in children and could be misunderstood.

Laboratory findings

Neutropenia and anaemia were the most frequent grade 3 or 4 haematological abnormalities (4% and 2%, respectively), but there appears to be no association between abacavir and haematological toxicity. Changes in ALT, AST, CPK, triglycerides, amylase and lipase appeared at similar frequencies in treatment groups.

5. Overall Conclusions and Benefit Risk Assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physiochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated, and are controlled in a satisfactory way.

Pre-clinical pharmacology and toxicology

- Overall, the primary pharmacodynamic studies provided adequate evidence that abacavir exerts a significant antiviral effect on HIV-1 and HIV-2. The general pharmacology studies in mouse, rat and dog showed no adverse effects on nervous, respiratory or cardiovascular systems.

- From the pharmacokinetic point of view it was noted that hepatic clearance is the principal route of excretion for abacavir. The routes of metabolism are qualitatively similar in mice, monkeys and humans. Quantitatively, the two main metabolites in monkeys and humans are a 5'-glucuronide and a 5'-carboxylic acid.

- Overall, the toxicology programme revealed the liver to be the main target organ following repeated administration with weight increases and hepatocellular hypertrophy. These effects were reversible. As for other nucleoside analogues abacavir has a weak mutagenic potential. Abacavir is toxic for reproductive functions with reductions in foetus and offspring weights and increased intra-uterine death and malformation. This information has been included in the SPC.

    There was a finding related to the high dose combination of abacavir and amprenavir indicating increased heart weights in rats. The applicant will further investigate this finding.

    The carcinogenicity studies in rats and mice are in progress and results will be available by the end of June 2001.

Efficacy

- Due to the twice daily dosing and the absence of significant interaction with food, <u>compliance</u> with abacavir treatment in the clinical setting might be favourable.

- The <u>resistance</u> pattern of abacavir appeared favourable since, in general, subjects harbouring virus with wild-type RT genotype or 1-2 NRTI-associated mutations at baseline responded to abacavir with substantial decreases in plasma HIV-1 RNA. However, subjects with ≥3 NRTI-associated mutations had attenuated or no plasma HIV-1 RNA response to abacavir. The most common single RT mutation at baseline in these trials in experienced patients was the M184V, which has been associated with resistance to 3TC but not abacavir. Subjects harbouring virus with the M184V alone have comparable HIV-1 RNA response to those with wild-type virus. The applicant will submit further data on resistance.

- The <u>dose rational</u> for adults has been sufficiently substantiated.

- <u>In therapy naive patients</u>, the durability of the antiviral effect of abacavir is mainly corroborated by long term results in study CNAAB 3003. The virological response observed at week 16 in the ABC arm is sustained at week 48 (proportion of patients with undetectable viral load (400 copies/ml) is 77% and 71% respectively at week 16 and 48). The limited proportion of switches in the ABC arm confirms the virological impact of ABC. At week 48, 71% of patients remained on treatment with abacavir. It should be emphasised that other studies such as CNAB 2002, CNAA 2004 and CNAB 3009 (therapy experienced) underscored this durable impact on the viral load, but their interpretation is much more limited since there are open label studies and/or performed in few patients. No additional benefit has been demonstrated in terms of CD4 cell counts.

- <u>In therapy-experienced patients,</u> short-term data (16w) from (CNAB 3002) 185 patients moderately exposed to previous antiretroviral therapy and moderately advanced (CD4 409 cells) provided most information. Abacavir demonstrated a slight impact on the viral load (median change of viral load -0,44 $\log_{10}$ copies/ml). These results are in accordance with genotypic and phenotypic analyses, which demonstrate that ≥3NRTI mutations at baseline are not favourable for a response to ABC. Information provided by other studies such as CNAB 3009, CNAA 2007, ACTG 368 and ACTG 372 are limited since there are mainly open label studies and/or performed in few patients and/or need to be completed since only preliminary data are currently available. Final reports from studies currently ongoing (CNAB 3002, CNAB 3009, ACTG 368 and ACTG 372) are requested as follow-up measures. No additional benefit has been demonstrated in terms of CD4 cell counts.

- Study CNAAB 3005 is particularly interesting in terms of antiviral strategy, because it demonstrates <u>equivalence of a NRTI triple therapy with a PI containing triple therapy</u>. However, the applicant only provided short-term data with results at week 16 supplemented with preliminary results at week 24 and 48 indicating similar immuno-virological effects between the abacavir triple combination and the indinavir-containing regimen. In the context of protease inhibitors sparing strategy these data are particularly important and final results from this ongoing study has been requested.

  In response to a CPMP request to provide complementary data <u>in combination with protease inhibitors and non-nucleoside analogues</u>, information was made available from ACTG368 (indinavir/efavirenz) and ACTG372 (efavirenz/adefovir ± nelfinavir); 48 week data from CNAA 2004 (above); 16 week data from CNAB 3002 (above); CNAA 2007 (above). Taken together these studies provide preliminary information from over 500 patients but are as yet insufficient to allow any definitive conclusions. Final reports from studies CNAB 3002, ACTG 368 and ACTG 372 are awaited as follow-up measures.

  There is no information available on therapy after treatment with abacavir has failed. Ongoing studies (e.g. CNAA 3005) will address this issue although cross-resistance to non-nucleoside analogues and protease inhibitors may not be expected.

- <u>The dose rational for children</u> has been sufficiently substantiated. The pivotal placebo controlled trial performed in 205 children, CNAA 3006, demonstrated a superior effect (antiviral and on CD4 cells) of abacavir/3TC/ZDV over 3TC/ZDV that seemed sustained over 24 weeks. A final report from this study is awaited. In addition a final report from the MRC-run study, Penta 5 (a study with factorial design and including nelfinavir), will be submitted.

Safety

- The main concern relates to the 3% incidence of hypersensitivity reactions which have been evaluated up until 31 December 1998 and described in 636 patients. This is a potentially life threatening condition with hypotension and multi organ involvement. The mortality rate from hypersensitivity reactions is 0.014% (3/21000). A majority of cases of hypersensitivity reaction (94%) appear within the first 6 weeks of abacavir treatment but 6% of cases appear after 6 weeks of treatment.

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- Rechallenge confers a 35% risk of life threatening consequences. Of the 636 patients with hypersensitivity reactions, 63 (10%) were rechallenged with abacavir in the overall database. Although various precautionary measures have reduced the risk of rechallenge with abacavir, the risk of rechallenge remains at about 6% for the period 1 October to 31 December 1998.

- In children, the major concern is the hypersensitivity reaction. In this population, hypersensitivity reactions are particularly difficult to identify particularly in young children. Insufficient data are available to recommend the use of abacavir in children.

Benefit/risk assessment

The data demonstrates the efficacy of abacavir treatment, particularly in combination with lamivudine and zidovudine in treatment naïve patients where the antiviral effect appears sustained to at least 48 weeks and non-inferior to a combination with indinavir.

A major point for discussion in the CPMP pertained to the risk of hypersensitivity reactions, which might have a fatal outcome. There were concerns that hypersensitivity reactions appeared in well-monitored patients and that rechallenges had occurred despite recommendations not to reintroduce abacavir after primary symptoms compatible with a hypersensitivity reaction.

Despite the urgent need for paediatric formulations of antiretroviral medicinal products, major concerns are raised regarding the safety profile in children rendering the benefit risk assessment negative in children at the present time. This position could be re-evaluated with additional clinical experience.

The applicant discussed issues on efficacy (duration of antiviral effect, PIs sparing treatment effects, advanced patient populations) and safety (hypersensitivity reaction) raised by the CPMP during a hearing before the Committee:

During their presentation the applicant provided results from study CNAAB 3005 indicating a sustained antiviral response up to 48 weeks with abacavir in combination with zidovudine and lamivudine, similar to the control arm with the triple combination with indinavir.

The CPMP made the following points in relation to the concerns over hypersensitivity reaction:

- Conditions of prescription should be restricted as indicated in section 4.2 of the SPC.

- Patients should be clinically evaluated every 2 weeks during the first 2 months of treatment.

- The alert card for patients could help to emphasise the major concerns of hypersensitivity reaction and to prevent re-challenge.

- Intensive surveillance safety reviews to be carried out post opinion. Monthly safety updates taking into consideration the US experience in particular. If necessary to introduce revisions in the SPC.

- To present monthly line-listings of all hypersensitivity reactions and deaths during the first year after marketing.

- Quarterly PSURs to be requested during the first year of marketing.

- A development program of tests aimed at confirming the diagnosis of hypersensitivity reaction.

In addition, complimentary information and analyses of safety issues were requested as commitments and were detailed in the letter of undertaking signed by the applicant on 25 March 1999, appended to the CPMP opinion.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit risk profile of Ziagen in the combination treatment of HIV infection was favourable and issued a positive opinion on the following indication:

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

The demonstration of benefit of Ziagen is mainly based on results of studies performed in treatment-naïve patients on combination therapy with lamivudine and zidovudine."