SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Trizivir. For information on changes after approval please refer to module 8.

1. Introduction

Trizivir is a fixed dose combination tablet containing 300 mg abacavir (as abacavir sulphate), 150 mg lamivudine and 300 mg zidovudine in each tablet for the treatment of Human Immunodeficiency Virus (HIV) infection in adults. Trizivir is a new combination of previously known active substances. Zidovudine 300 mg tablets were first registered as Retrovir in 1995 via the Mutual Recognition procedure. Lamivudine 150 mg tablets (Epivir) were registered via the Centralised procedure in 1996, and a combination tablet (Combivir) consisting of lamivudine 150 mg and zidovudine 300 mg was approved via the Centralised procedure in March 1998. Finally, abacavir 300 mg tablets were approved via the Centralised procedure in July 1999 as Ziagen tablets. Retrovir, Epivir, Combivir and Ziagen are all indicated in antiretroviral therapy for the treatment of HIV infection.

Because of the high pill burden associated with one of the current standard triple therapy regimens including a protease inhibitor (PI), which may eventually lead to non-adherence to treatment, other potent antiretroviral regimens without a PI could be an alternative option for treatment of HIV infected patients. Adherence of patients is indeed a crucial point, as non-adherence to treatment has been identified as a predictive factor of failure to achieve viral suppression. A triple nucleoside therapy could provide a simpler treatment for the patient to take long term in terms of adherence and dosing regimen (pill burden, rhythm of administration, impact of food, pharmacokinetic interactions). In addition, triple nucleoside therapy may provide an effective therapeutic option preserving protease inhibitors and non-nucleoside reverse transcriptase inhibitors in future treatment strategies.

The recommended dose of Trizivir in adults is one tablet twice daily.

Currently, insufficient data are available to recommend the use of Trizivir in children or adolescents.

2. Chemical, pharmaceutical aspects

Composition

The film-coated tablet is a conventional immediate release formulation containing the three active substances together with microcrystalline cellulose, sodium starch glycollate Type A and magnesium stearate as excipients. The film-coating aqueous suspension contains Opadry Green.

The film-coated tablets are packaged in high-density polyethylene bottles with a child-resistant closure or in a PVC/Aclar blister pack with push-through foil lidding.

Tablets identical to the commercial product were used in the clinical trials.

Active substance

The three active substances have been already authorised as active ingredients of other dosage-forms, and are already on the EU market with the same specifications and methods of synthesis. The compatibility between these three active substances has been correctly studied.

The active substance abacavir sulphate is a carbocyclic nucleoside derivative synthesised via a well controlled, reproducible, high yielding, three stage process which has been adequately described. The active substance specification was justified with regard to satisfactory purity (assay & impurity levels) and in general 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 confirmed reproducible and consistent synthesis, and the data were in agreement with the proposed specification. Control methods were adequately described and are generally well validated.

Lamivudine is (2R, cis)-4-amino-1-(2hydroxymethyl 1,3-oxathiolan-5S-yl)-(1H)-pyrimidin2-one and has not yet been described in any pharmacopoeia. The (-) enantiomer of lamivudine, which was shown to be less cytotoxic than the (+) enantiomer or the racemate is selected for the manufacture of the finished medicinal product. Two polymorphic forms I (partial hydrate) and II were identified. Manufacture of lamivudine involves a four-step synthesis, which includes isolation of the desired stable crystalline form (II). Evidence of structure was appropriate and complete, and an identification test ensures that only form II is used for the manufacture of the finished product. Test results for production batches show that values for each of the single related impurities and total related impurities are nearly constant. The validation of the test methods used (determination of contents for lamivudine, enantiomer and impurities, and lamivudine identification) was considered sufficiently documented.

Zidovudine (3'azido-3'deoxythymidine) is controlled according to the European Pharmacopoeia (Ph. Eur.) requirements.

For abacavir sulfate a retest period of 2 years when stored below 30°C is approved.

For lamivudine a retest period of 3 years when stored between 2°C – 30°C is approved.

For zidovudine a retest period of 3 years when stored up to 50°C is approved.

Other ingredients

The excipients selected for Trizivir are microcrystalline cellulose, sodium starch glycollate Type A, magnesium stearate and Opadry film-coating concentrate. All the ingredients are European Pharmacopoeial grade with the exception of Opadry Green for which the qualitative and quantitative composition has been adequately provided.

Product development and finished product

Pharmaceutical development and evaluation of Trizivir has been relatively straightforward, considering the fact that similar formulations with the active substances mentioned above are already authorised in the EU.

The main development objective was to design a conventional immediate release formulation, able to deliver the three active ingredients in a form that is physically and chemically stable and is convenient for administration to facilitate patient compliance.

Direct compression was selected as the preferential method of manufacturing.

The active substances have the same quality characteristics as those common to the single entity products, commercially available.

The excipients used are the same as in the individual single entity tablet formulae, excluding PVP, a component used as binder in the wet granulation manufacturing process for Retrovir. The use of colloidal silicone as inert glidant (used in the direct compression for Ziagen) was not required in the combination tablet formula.

The particle size of the product blend, as derived from the particle sizes of the 4 main constituents (3 active ingredients and microcrystalline cellulose), indicated that acceptable blend uniformity of cores, dissolution and assay were obtained.

The combination tablet has been designed to exhibit rapid dissolution while also being bioequivalent to the single entity tablets. In general the dissolution profiles are very similar and the active substances are almost completely released from the combination tablet after 30 minutes. The dissolution data provided for release and stability batches are consistent, showing systematically individual values of more than 85% after 30 minutes.

In addition the results of the bioequivalence study prove that each active substance in the combination tablet is bioequivalent to its relevant single entity tablet (see clinical assessment report).

Stability of the Product

Three batches (two of 40.5 kg and one of 405 kg) each in two different packaging configurations (PVC/Aclar and HDPE bottles) have been monitored for long term stability (12 months at 30°C/60% RH) and during accelerated conditions (6 months at 40°C/75% RH).

The stability results gained show that the Trizivir tablets remained in conformity with the proposed end of shelf life specifications and remained practically unchanged when compared to the initial quality at release for the major quality parameters investigated (content, dissolution, appearance, moisture).

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

3. Toxico-pharmacological aspects

The CPMP Note for Guidance on Fixed Combination Medicinal Products (CPMP/EWP/240/95) allows for the absence of new data from non-clinical investigations on the combination when extensive clinical experience with the combination exists. The CPMP concluded that no toxicological investigations with the triple combination, Trizivir were necessary. This decision was taken, firstly, as the triple combination merely represents the physical combination of two centrally authorized medicinal products prescribed together and with substantial reassurance from the clinical use of the individual products used in combination. Secondly, toxicity testing would require usage of animals unjustified by the low value of information that would be generated, in the light of extensive clinical experience.

In summary, Abacavir, lamivudine and zidovudine are nucleoside analogue reverse transcriptase inhibitors with potent anti-HIV activity. No antagonistic antiviral activity is expected for the combination of all three compounds. An extensive programme of absorption, distribution, metabolism and excretion studies has been carried out with abacavir, lamivudine and zidovudine in the species of animals used in the toxicity studies. In general, the similarity between the kinetics and metabolism of the three compounds in man and that defined in the animal species used for toxicology indicates that the species used were appropriate for predicting the safety of the compounds and their metabolites. Nonclinical interaction studies showed that there is a very low potential for pharmacokinetic and metabolic interactions between lamivudine and zidovudine and between abacavir and other drugs. Clinical data indicate the lack of a clinically relevant interaction between abacavir, lamivudine and zidovudine administered together.

Single dose toxicity studies in rats and mice indicate that all three compounds have a low acute toxicity following oral or intravenous administration. Repeated dose toxicity studies identified the haemopoietic system as the most sensitive target organ for all three compounds. Other potential target organs included the liver and testis for abacavir, and the gastrointestinal tract for lamivudine.

Reproductive and developmental toxicity studies in rats, but not rabbits, showed that the administration of abacavir or zidovudine at maternally toxic doses resulted in fetal abnormalities. All three compounds showed some evidence of early embryofoetal toxicity. In view of this, the triple combination tablet is not recommended for use in pregnancy.

Lamivudine shows activity in genetic toxicity tests *in vitro* and abacavir and zidovudine in tests *in vitro* and *in vivo*. This activity is consistent with other marketed nucleoside analogues and is considered to reflect the loss of selectivity for viral versus mammalian inhibition of DNA polymerisation at high (toxic) concentrations.

In long-term carcinogenicity studies, lamivudine showed no evidence of carcinogenic potential. In similar studies with zidovudine, treatment-related effects were limited to late-appearing vaginal neoplasms. It is considered that these tumours were the result of chronic local exposure of the vaginal epithelium to high concentrations of zidovudine in the urine. Metabolic, biological and physiological differences between rodents and humans suggest that a similar carcinogenic risk in humans is unlikely. Carcinogenicity studies with abacavir are in progress.

4. Clinical aspects

No specific clinical efficacy studies have been performed with the fixed dose combination tablet, although reference is made to the clinical studies, which are part of the marketing authorisation for

abacavir. Those studies particularly focus on the relevant triple combination of abacavir, lamivudine and zidovudine in the same doses as for the fixed combination (Trizivir) and have been reviewed by the CPMP during the assessment of Trizivir. In addition, the clinical submission comprises pharmacokinetic studies performed with the fixed dose combination tablet (Trizivir) and bioequivalence studies with the fixed combination tablet against single components abacavir, lamivudine and zidovudine.

The approved indication is:
"Trizivir is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults. This fixed combination replaces the three components (abacavir, lamivudine and zidovudine) used separately in similar dosages. The choice of this fixed combination should be based not only on potential adherence criteria, but also mainly on-expected efficacy and risk related to the three nucleoside analogues.

The demonstration of the benefit of Trizivir is mainly based on results of studies performed in treatment naive patients or moderately antiretroviral experienced patients with non-advanced disease. In patients with high viral load (>100,000 copies/ml) choice of therapy needs special consideration (see 5.1. Pharmacodynamic properties)".

Clinical Pharmacology

Pharmacodynamics

Zidovudine, lamivudine and abacavir are potent selective inhibitors of HIV-1 and HIV-2.

The mutation pattern of these three NRTI is well identified *in vitro*.

Substantial genotyping and phenotyping analysis have been performed in clinical trials with patients receiving the 3 NRTI in several studies, through the development program of abacavir. Resistance data obtained from naive patients receiving first line treatment with ABC+ZDV+3TC and in virological failure, are highly suggestive of the main role of M184V, the 3TC associated mutation (approximately 70%) in viral rebound.

According to data from intensification therapy with abacavir in NRTI experienced patients (mainly ZDV+3TC), M184V alone does not seem to have any impact on response to an antiretroviral combination therapy including ABC. However, this response is significantly decreased in patients with viruses harbouring one or more NRTI specific mutations (including M184V). Indeed correlation between genotypes and phenotypes demonstrates that when M184V is present with NRTI associated mutation resistance (frequent in clinical practice), the virus sensitivity to ABC is reduced in more than 50% of patients.

Consequently, virological data from clinical studies favour early use of the NRTI triple combination therapy.

Pharmacokinetics

Abacavir Disposition Summary

Abacavir has excellent bioavailability (~83%) with rapid absorption. The apparent volume of distribution after intravenous administration is approximately 0.8 l/kg. Binding to plasma proteins is moderate (~ 49%). Abacavir is extensively metabolised with less than 2% excreted unchanged in the urine. Metabolism is primarily via two pathways, UDP-glucuronyl transferase and alcohol dehydrogenase resulting in the 5'-glucuronide and the 5'-carboxylic acid which account for about 66% of the metabolites in the urine. The mean plasma elimination half-life of abacavir is about 1.5 hours.

Lamivudine Disposition Summary

Lamivudine absorption is rapid and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. The apparent volume of distribution after intravenous administration is approximately 1.3 l/kg. Binding of lamivudine to human plasma proteins is low (<36% to serum albumin *in vitro*). The observed elimination half-life is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (>70% of unchanged drug) via glomerular filtration and active tubular secretion. Hepatic metabolism of lamivudine is limited (5-10%).

Zidovudine Disposition Summary

Zidovudine absorption is rapid with a bioavailability of 60-70%. After intravenous zidovudine administration, the mean terminal plasma half-life is 1.1 hours, the mean systemic clearance is 27.1 ml/min/kg (or 1.6 l/h/kg) and the apparent volume of distribution is 1.6 l/kg. Plasma protein binding is low (34 to 38%). Renal clearance of zidovudine exceeds creatinine clearance, indicating that active tubular secretion occurs. The inactive 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50-80% of the administered dose eliminated by renal excretion. 3'-amino-3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

Concurrent Administration of Abacavir, Lamivudine and Zidovudine

There have been several studies of the concurrent administration of abacavir, lamivudine and zidovudine in man.

The pharmacokinetics of abacavir, lamivudine, and zidovudine as single doses administered alone or concurrently has been studied in 15 HIV infected subjects (CNAA1002).

This was a 7-period, crossover, randomized study. The pharmacokinetics of zidovudine, lamivudine and abacavir were assessed after single administration of drugs, alone or 2 drugs combined or coadministration of the 3 drugs. It was demonstrated that abacavir pharmacokinetics remained unchanged when coadministered with either zidovudine, or lamivudine or both. Zidovudine and lamivudine pharmacokinetics remained unchanged when coadministered. In contrast addition of abacavir led to slight alteration of zidovudine and lamivudine concentrations:

decrease in ZDV C_{max} (-20%) and increase in GZDV AUC (+40%)

decrease in lamivudine C_{max} (-35%) and AUC (-15%)

This was considered to be related to interaction at absorption sites and renal excretion and not to be clinically significant.

The lack of interaction between abacavir and zidovudine was also observed in multiple-dose trials (CNAA2001 and CNAB2002, submitted in the abacavir dossier) indicating the lack of interaction between abacavir and compounds that are metabolised by glucuronidation via UDP-glucuronyltransferase. The lack of a clinically significant interaction between abacavir and lamivudine is consistent with their different routes of elimination.

Given the results of these investigations and based on the pharmacokinetic disposition of abacavir, lamivudine, and zidovudine, no dosage adjustment is necessary when the three compounds are administered in combination.

Drug Interactions

As the triple combination tablet contains abacavir, lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur, as detailed in the individual SPCs for Ziagen, Epivir, and Retrovir. A recent study has investigated the potential interaction between abacavir and methadone (CNAA1012). Co-administration of 600 mg abacavir twice daily and methadone showed a 35% reduction in abacavir C_{max} and a 1 hour delay, but AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study, abacavir increased methadone systemic clearance by a median of 22%. This change is not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required. Based on this study, a statement has been added to section 4.5 of the SPC for the triple combination tablet.

Bioequivalence Studies

These studies were performed according to internationally accepted guidelines.

Bioequivalence of a combined formulated tablet compared to Epivir and Retrovir administered concurrently and the effect of food on absorption (Study Protocol Number NZTA1001).

The objectives of this study were to assess: (1) the bioequivalence of a single tablet composed of lamivudine 150 mg and zidovudine 300 mg (Combivir) and the marketed tablets EPIVIR 150 mg (lamivudine) and RETROVIR 300 mg (zidovudine), (2) the effect of food on the absorption of the new combination formulation. This was a single-centre, open-label, randomized, three-way cross-over study in 24 healthy male and female subjects between the ages of 19 and 36 years. Each subject was assigned to receive one of the following three treatments during each study period, and all three treatments during the study, in a randomized fashion:

treatment A: lamivudine 150 mg and zidovudine 300 mg as a combined formulation following an overnight fast,

treatment B: EPIVIR 150 mg tablet + RETROVIR 300 mg tablet swallowed simultaneously and following an overnight fast,

treatment C: lamivudine 150 mg and zidovudine 300 mg as a combined formulation 5 minutes following a standardised breakfast.

Serial blood samples were obtained during each treatment period for evaluation of lamivudine and zidovudine AUC, C_{max} and t_{max}. Plasma samples were assayed for lamivudine by a validated HPLC-UV method and for zidovudine by a validated RIA method.

The mean ± SD (AUC and C_{max}) and median and range (t_{max}) for lamivudine and zidovudine are summarized in the following tables:

lamivudine

Parameter	**Treatment A**	**Treatment B**	**Treatment C**
C_{max} (ng/ml)	1620.3 ± 519.6	1742.2 ± 616.3	1367.6 ± 403.9
$AUC_{0-\infty}$ (ng.h/ml)	6137.6 ± 1234.0	6374.2 ± 1607.4	6035.4 ± 1160.6
t_{max} (h)	0.75 (0.5 - 2.0)	1.0 (0.5 - 2.0)	1.5 (0.5 - 4.05)

zidovudine

Parameter	**Treatment A**	**Treatment B**	**Treatment C**
C_{max} (ng/ml)	2008.3 ± 809.9	1992.6 ± 636.1	1139.2 ± 587.8
$AUC_{0-\infty}$ (ng.h/ml)	2398.2 ± 705.8	2390.9 ± 553.1	2147.6 ± 664.6
t_{max} (h)	0.5 (0.25 - 2.0)	0.5 (0.25 - 2.0)	1.0 (0.25 - 2.0)

The 90% CI for AUC and C_{max} were as follows:

lamivudine

Parameter	**A vs B**	**C vs A**
C_{max}	0.84 - 1.06	0.76 - 0.96
AUC	0.92 - 1.02	0.94 - 1.04

zidovudine

Parameter	**A vs B**	**C vs A**
C_{max}	0.82 - 1.15	0.46 - 0.65
AUC	0.91 - 1.07	0.83 - 0.97

The results of these studies show that:

- the combined lamivudine 150 mg and zidovudine 300 mg tablet is bioequivalent to the EPIVIR 150 mg tablet + RETROVIR 300 mg tablets administered simultaneously to fasting volunteers,
- the extent of absorption of lamivudine and zidovudine is unchanged but the rate of absorption is slowed when the lamivudine 150 mg and zidovudine 300 mg combined formulation is administered with food,

- the combined lamivudine 150 mg and zidovudine 300 mg tablet may be administered with or without food as there was no significant difference in extent of absorption (AUC) following a meal and no clinical significance of the slowed absorption (C_{max}, t_{max}) is expected.

An evaluation of the bioequivalence of a combined formulated tablet (300/150/300 mg abacavir/lamivudine/ zidovudine) compared to Ziagen (abacavir) 300 mg tablet, Epivir (lamivudine) 150 mg tablet, and Retrovir (zidovudine) 300 mg tablet administered concurrently and the effect of food on absorption in healthy volunteers (Protocol No. AZL10001).

The primary objective of this study was to demonstrate bioequivalence between a single tablet composed of 300 mg abacavir, 150 mg lamivudine and 300 mg zidovudine (Trizivir) versus the reference formulations ZIAGEN (abacavir) 300 mg tablet, EPIVIR (lamivudine) 150 mg tablet and RETROVIR (zidovudine) 300 mg tablet swallowed sequentially. A secondary objective was to evaluate the effect of food on the absorption of the new combination formulation. This was a single-centre, open-label, randomized, three-way cross-over study in 24 healthy subjects. Each subject was assigned to receive one of the following three treatments during each study period, and all three treatments during the study, in a randomized fashion:

treatment A: triple combination tablet containing abacavir 300 mg, lamivudine 150 mg and zidovudine 300 mg following an overnight fast,
treatment B: ZIAGEN (abacavir) 300 mg tablet, EPIVIR (lamivudine) 150 mg tablet and RETROVIR (zidovudine) 300 mg tablet swallowed sequentially and following an overnight fast,
treatment C: triple combination tablet containing abacavir 300 mg, lamivudine 150 mg and zidovudine 300 mg 5 minutes following a standardised (high fat) breakfast.

Serial blood samples were obtained during each treatment period for evaluation of abacavir, lamivudine and zidovudine AUC, C_{max} and t_{max}. Plasma samples were assayed for abacavir by HPLC-UV, and for lamivudine and zidovudine by LC-MS-MS.

The mean ± SD (median and range for t_{max}) AUC and C_{max} values are summarized in the tables below:

<u>abacavir</u>

Parameter	Treatment A	Treatment B	Treatment C
C_{max} (µg/ml)	3.29 ± 1.24	3.23 ± 0.96	2.28 ± 0.84
$AUC_{0-\infty}$ (µg.h/ml)	7.31 ± 2.71	7.39 ± 2.81	6.57 ± 2.11
t_{max} (h)	0.75 (0.5 - 3.0)	0.75 (0.25 - 2.0)	2.0 (0.75 - 4.0)

<u>lamivudine</u>

Parameter	Treatment A	Treatment B	Treatment C
C_{max} (µg/ml)	1.57 ± 0.49	1.78 ± 0.73	1.27 ± 0.36
$AUC_{0-\infty}$ (µg.h/ml)	6.04 ± 1.36	6.42 ± 1.76	5.60 ± 1.34
t_{max} (h)	1.25 (0.75 - 3.0)	1.0 (0.75 - 4.0)	2.5 (1.0 - 4.0)

<u>zidovudine</u>

Parameter	Treatment A	Treatment B	Treatment C
C_{max} (µg/ml)	1.36 ± 0.74	1.43 ± 0.68	0.99 ± 0.51
$AUC_{0-\infty}$ (µg.h/ml)	2.07 ± 0.72	2.17 ± 0.73	2.05 ± 0.54
t_{max} (h)	0.75 (0.5 - 3.0)	0.75 (0.25 - 2.0)	1.5 (0.5 - 4.0)

The 90% CI for AUC and C_{max} were as follows:

abacavir

Parameter	A vs B	C vs A
C_{max}	0.90 - 1.11	0.62 - 0.76
AUC	0.96 - 1.03	0.88 - 0.95

lamivudine

Parameter	A vs B	C vs A
C_{max}	0.82 - 0.99	0.75 - 0.90
AUC	0.91 - 0.99	0.88 - 0.97

zidovudine

Parameter	A vs B	C vs A
C_{max}	0.80 - 1.15	0.60 - 0.87
AUC	0.89 - 1.02	0.94 - 1.08

The results of these studies show that:

1. The abacavir/lamivudine/zidovudine combination tablet is bioequivalent to the reference formulations of ZIAGEN 300 mg tablet, EPIVIR 150 mg tablet, RETROVIR 300 mg tablet administered simultaneously with respect to AUC and C_{max},
2. Administration of the abacavir/lamivudine/zidovudine combination tablet with food results in slightly lower C_{max} and slightly longer t_{max} values; these changes are not clinically relevant, thus the abacavir/lamivudine/ zidovudine combination tablet may be administered without food restrictions.

Steady-state pharmacokinetics of abacavir, lamivudine and zidovudine following administration of a combined formulated tablet (300/150/300 mg abacavir/lamivudine/zidovudine) versus Ziagen (abacavir) (300 mg tablet) and Combivir (150/300 mg lamivudine/zidovudine) administered in subjects with HIV-1 infection (Protocol no. AZL10002).

The objectives of the study were to examine the pharmacokinetics of abacavir, lamivudine and zidovudine at steady-state following administration of a combination tablet composed of 300 mg abacavir, 150 mg lamivudine and 300 mg zidovudine (Trizivir) versus treatment with 300 mg ZIAGEN (abacavir) tablets and COMBIVIR (lamivudine 150 mg, zidovudine 300 mg) tablets in HIV infected patients. This was an open-label, multiple dose, and descriptive study. Twelve subjects were enrolled in the study. They all received both treatments:

treatment A: current treatment including COMBIVIR and ZIAGEN,

followed by

treatment B: triple combination tablet bid for at least 7 days.

Steady-state pharmacokinetic evaluations were obtained during each treatment. Abacavir serum concentrations were determined using a validated HPLC-UV method. Lamivudine and zidovudine serum concentrations were determined by HPLC-MS-MS.

The results are summarized in the following tables (mean ± SD for AUC_{ss}, C_{maxss} and t1/2, median and range for t_{maxss}):

abacavir

Parameter	Treatment A COMBIVIR + ZIAGEN	Treatment B triple combination tablet
AUC_{ss} (ng.h/ml)	6110 ± 1719	6388 ± 1997
C_{maxss} (ng/ml)	3469 ± 1737	3493 ± 1577
t_{maxss} (h)	0.75 (0.25 - 1.5)	0.75 (0.5 - 1.5)
t1/2 (h)	1.61 ± 0.35	1.75 ± 0.45

lamivudine

Parameter	Treatment A COMBIVIR + ZIAGEN	Treatment B triple combination tablet
AUC_{ss} (ng.h/ml)	5763 ± 1781	5734 ± 1790
C_{maxss} (ng/ml)	1456 ± 399	1333 ± 441
t_{maxss} (h)	1.24 (0.5 - 3.0)	1.5 (0.75 - 6.0)

zidovudine

Parameter	Treatment A COMBIVIR + ZIAGEN	Treatment B triple combination tablet
AUC_{ss} (ng.h/ml)	1594 ± 753	1502 ± 703
C_{maxss} (ng/ml)	1590 ± 1754	1555 ± 1294
t_{maxss} (h)	0.75 (0.25 – 1.5)	0.75 (0.5 - 1.0)
t1/2 (h)	2.10 ± 0.28	2.35 ± 0.49

Steady-state pharmacokinetic parameters of abacavir, lamivudine and zidovudine were similar following multiple dose administration of the reference formulations COMBIVIR/ZIAGEN, administered simultaneously, and the administration of the triple combination product.

Based on the results of these three studies it can be concluded that:

- the abacavir (300 mg)/lamivudine (150 mg)/zidovudine (300 mg) combination tablet (Trizivir) is bioequivalent to the reference formulations ZIAGEN 300 mg tablets, EPIVIR 150 mg tablets and RETROVIR 300 mg tablets administered simultaneously,
- administration of the abacavir/lamivudine/zidovudine combination tablet with food results in slightly lower C_{max} and slightly longer t_{max} values; these changes are not clinically relevant and the combination tablet can therefore be administered without food restrictions,
- steady-state-plasma concentrations of abacavir, lamivudine and zidovudine are similar following multiple dose administration of the combination product compared to the multiple dose administration of ZIAGEN (abacavir 300 mg) and COMBIVIR (lamivudine 150 mg, zidovudine 300 mg) tablets in 12 patients with HIV-1 infection.

Clinical Efficacy

No specific clinical efficacy studies have been performed with the fixed dose combination tablet, although reference is made to the clinical studies which are part of the marketing authorisation for abacavir. Those studies particularly focus on the relevant triple combination of abacavir, lamivudine and zidovudine in the same doses as for the fixed combination (Trizivir) and have been reviewed by the CPMP during the assessment of Trizivir. In addition, the clinical submission comprises pharmacokinetic studies performed with the fixed dose combination tablet (Trizivir) and bioequivalence studies with the fixed combination tablet against single components abacavir, lamivudine and zidovudine.

The approved indication is: "Trizivir is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults. This fixed combination replaces the three components (abacavir, lamivudine and zidovudine) used separately in similar dosages. The choice of this fixed combination should be based not only on potential adherence criteria, but mainly on expected efficacy and risk related to the three nucleoside analogues.

The demonstration of the benefit of Trizivir is mainly based on results of studies performed in treatment naive patients or moderately antiretroviral experienced patients with non-advanced disease. In patients with high viral load (>100,000 copies/ml) choice of therapy needs special consideration (see 5.1. Pharmacodynamic properties)".

Data from a total of 9 clinical studies using the combination of abacavir, zidovudine and lamivudine and supportive of the triple combination tablet are available; Combivir was used in six of the studies. Studies CNAAB3003, CNAAB3005 and CNAB3002 are considered pivotal to the submission whilst the remainder of the studies are considered supportive. The studies were conducted in Europe, North

America and Australia and all except CNAB2002, CNAB3002 and CNAB3009 are currently ongoing. Details of the individual studies are summarised in the table:

Summary of the Clinical Studies

Protocol No (Report No or source of data)	Design	Population	Reported Period W=weeks	Initial Treatment Arms	Enrolled or randomised/ treated (n)
CNAB2002 (GM1998/00318/01 and GM/1999/00269/00)	Randomised, double-blind, dose-ranging	ART naïve HIV-1 RNA>30,000c/ml	72W report and 120W Summary	100 mg BID ABC 300 mg BID ABC 600 mg BID ABC	20 (18 ABC/3TC/ZDV) 20 (19 ABC/3TC/ZDV) 20 (18 ABC/3TC/ZDV)
CNAB3002 (GM1999/00250/00) PIVOTAL	Randomised, double-blind comparative	ART experienced CD4+≥100cells/mm^3 HIV-1 RNA 400-50,000c/ml	48W	300 mg BID ABC/SBG SBG	92/91 (40 ABC/3TC/ZDV) 93/93 (39 3TC/ZDV)
CNAAB3003 (RM1997/00702/01) PIVOTAL	Randomised, double-blind comparative	ART naïve CD4+ ≥100cells/mm^3	48W	300 mg BID ABC/3TC/ZDV 3TC/ZDV	87/83 86/81
CNAAB3005 (GM/1999/00189/00) PIVOTAL	Randomised, double-blind comparative	ART naïve CD4+≥100cells/mm^3 HIV-1 RNA≥10,000c/ml	48W	300 mg BID ABC/Combivir 800 mg TID IDV/Combivir	282/262 280/265
CNAB3009 (GM/1999/00267/00)	Open-label	ART experienced	48W	300 mg BID ABC/Combivir	52/52
CNAF3007 (GM1999/00291/00)	Randomised, open-label comparative	ART naïve HIV-1 RNA 1000-500,000c/ml	16W	300 mg BID ABC/Combivir 250 mg TID NFV/Combivir	100/98 101/97
CNAF3008 (GM1999/00292/00)	Open-label	ART naïve CD4+> 100cells/mm^3 HIV-1 RNA≥ 500c/ml	24W	300 mg BID ABC/Combivir/ 600 mg OD EFZ	31/31
Simplified Maintenance Study (CH-96-06) GM1999/00288/00)	Randomised, open-label comparative	ART experienced PI-experienced HIV RNA <20c/ml	Up to 31 Aug 1999	300 mg BID ABC/Combivir Continue current PI containing regimen	82/82 79/79
NZTA4005 (Target) (AA1999/00364/00)	Open-label	ART experienced PI naive CD4+≥ 50cells/mm^3 HIV-1 RNA≤50,000c/ml	48W	300 mg BID ABC/Combivir	87/87

Dose-response studies and Main Clinical studies

Main studies

Antiretroviral naive patients

The demonstration of the antiviral activity of the triple combination (abacavir+zidovudine+lamivudine) has been clearly established through the development program of abacavir. The CPMP has previously concluded on a potent and sustained antiviral activity of abacavir in combination with zidovudine and lamivudine.

This conclusion has been mainly drawn from results of two pivotal studies performed in naive patients (CNAAB 3003 and CNAAB 3005).

CNAAB 3003

In this study patients were randomized in a double-blinded way into 2 treatment arms, either ABC/3TC/ZDV or ABC placebo/3TC/ZDV, to compare safety and efficacy. Superiority of the triple combination was shown in terms of durability of the plasma HIV RNA response following 48 weeks of treatment using the Kaplan-Meier methodology (74% vs. 31% respectively remained event free).

Due to the fact that change to open label ABC was not analysed similarly in the 2 groups, no clear conclusions can be drawn from the ITT, switch=failure analysis. The switch included analysis shows similar reductions in HIV RNA levels and a similar CD4 cell response at week 48 for those in the 3TC/ZDV arm who added ABC from week 16 onwards and those originally assigned to ABC/3TC/ZDV, showing that the response is not impacted by the delay in addition of ABC. According to results expressed by baseline viral load strata, the impact on viral load was limited in patients with viral load > 5 log copies/ml.

An open label triple combination arm was also added during the study period

CNAAB 3005

This study is of particular interest since it compares the triple NRTI combination with an HAART therapy including indinavir (a PI regimen).

This phase III, randomized, double blind, parallel group study performed in 562 patients, compared the antiviral effect at 24 and 48 weeks of ABC+ZDV+3TC versus IDV+ZDV+3TC.

- At 24 weeks, abacavir had a quite similar antiviral impact with indinavir (respectively for ABC and IDV percentage of patients with undetectable viral load: ITT: 66% versus 65%; as treated 85% versus 86%/ and viral load median change from baseline (-2.06 versus –2.04 log copies/ml).
- At 48 weeks, the antiviral impact of these two combinations was of the same magnitude (ITT missing=failure; percentage of patients with undetectable viral load 47% (ABC) versus 49% (IDV); As treated population: 86% (ABC) versus 94%(IDV). This is also supported by the results expressed in terms of viral load median change from baseline (-2.04 (ABC) versus –2.02 log copies/ml (IDV) with a threshold limit at 400 copies/ml).

However, the impact of abacavir as compared to indinavir is lower in the subset of patients with high viral load at baseline (>100 000 copies/ml) and when using the ultrasensitive method with lower detection threshold (<50 copies/ml).

Moreover, although the confidence interval of the difference, in terms of percentage of patients with undetectable viral load between both regimens, was in accordance with the initial equivalence hypothesis (12%) for the ITT population, it was not the case for the “as treated population” (both are required to demonstrate equivalence).

It is important to emphasise that the interpretation of these long-term data is difficult especially considering the particular design of this equivalence study allowing the possibility of switch. Indeed, patients were allowed to change their randomised treatment if they met the virological endpoint, therefore 42% of patients discontinued study prior to week 48.

Hence, no formal conclusion could be drawn at long term on the equivalence between these two regimens at 48 weeks. These findings are reflected in the pharmacodynamic section 5.1 of the SPC.

The rate of clinical disease progression was also lower in the IDV containing arm compared to ABC (3% vs. 6%). Hence, it could be anticipated that the durability of the antiviral effect may be less marked than with a protease inhibitor regimen.

On the other hand, the criteria of adherence, which is a crucial factor when considering benefit of treatment, should be taken into account when comparing these two regimens. It is worth noting that the triple NRTI combination given as TRIZIVIR will only require administration of one tablet twice daily without dietary requirement in comparison with HAART including indinavir, which involves a three times daily regimen, the intake of at least 8 tablets and dietary requirements.

Antiretroviral experienced patients

Study CNAB 3002 was designed as a double blind study to compare ABC versus placebo as an intensification therapy on top of stable background therapy (SBG). A significantly higher proportion of subjects in the ABC-containing group achieved HIV RNA levels ≤400 copies/ml at week 48 (25% vs.5%, respectively) and this effect was independent of prior 3TC use and duration of prior ART. Although median plasma HIV-1 RNA AAUCMB over 48 weeks was significantly better in the ABC-containing group (-0.49 vs.0.05 $\log_{10}$ copies/ml) this effect was modest. Median change of viral load from baseline was also modest (-0.64 $\log_{10}$ copies/ml) and not different from the control group (–0.59 $\log_{10}$ copies/ml). There was no difference in CD4 cell count response between the 2 groups.

Patients in this study were only moderately antiretroviral experienced (more than 90% having had less than 18 months prior ART of whom more than 75% only received a combination of 2 NRTI's) and had to be stable under their SBG for at least 16 weeks. Besides, virological response was better in patients with a low viral load. Therefore, results of this study do not allow conclusions to be drawn for a different population where ABC would serve as part of a salvage regimen

It is important to note that clinical studies are currently planned or ongoing with the triple combination tablet:

. AZL 30002: this 48 week, randomised, open label study performed in 200 patients is designed to compare the antiviral effect and the durability of response of patients with undetectable viral load (<50 copies/ml) who remain on their current first antiretroviral combination regimen (2NRTI+1PI or 2NRTI+1 NNRTI or 3NRTI) with those in patients who switch to the triple combination tablet.

. ESS 40005: this open label study will enrol 230 patients who are currently receiving therapy with regimens that include abacavir, lamivudine and zidovudine and have undetectable viral load (<400 copies/ml). Patients will be randomised to remain on abacavir plus Combivir (plus a PI or NNRTI if part of their baseline regimen) or receive the triple combination tablet.

. Simplified Maintenance therapy (CH-96-06): the study protocol is being amended to allow patients currently in the Combivir and abacavir arm to be treated with the triple combination tablet.

Clinical studies in special populations

It is recommended that the separate preparations of abacavir, lamivudine, and zidovudine be administered rather than the triple combination tablet when any of the components are contraindicated or dose adjustments are necessary, as detailed in the individual Summaries of Product Characteristics (SPCs) for Ziagen, Epivir, and Retrovir.

Renal dysfunction

Whilst no dosage adjustment of abacavir is necessary in patients with renal dysfunction, lamivudine and zidovudine concentrations are increased in patients with renal impairment due to decreased clearance. Therefore as dosage adjustments of these agents may be necessary it is recommended that separate preparations of abacavir, zidovudine and lamivudine be administered to patients with reduced renal function (creatinine clearance ≤ 50 ml/min).

Hepatic dysfunction

There are no data available on the use of the triple combination tablet in hepatically impaired patients. Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur because of decreased glucuronidation. Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Abacavir is

primarily metabolised by the liver. Analysis of safety data supports the use of abacavir 300 mg twice a day in patients with mild impairment. However, as there is limited data available on administration of abacavir to hepatically impaired patients, the triple combination tablet is not recommended for use in patients with moderate hepatic impairment and is contraindicated in severe hepatic impairment.

Supportive studies

In treatment naive patients

- The Marketing Authorisation Holder to further address the comparability of the triple NRTI combination with HAART has implemented **CNAF3007**. This currently ongoing open label study performed in 195 antiretroviral naive patients aims to compare Combivir+ABC with Combivir + nelfinavir (NFV). Preliminary 16 weeks results of this study are in favour of a comparability of both regimens in terms of antiviral impact (ITTswitch = failure; threshold 400/50 copies/ml: 65%/54% of patients had undetectable viral load in ABC versus 63%/51% in the NFV group). The median change from baseline was approximately – 2 log copies/ml in both groups Forty eight weeks data are awaited.
- Study **CNAF 3008** is an open label pilot study evaluating safety and efficacy of the quadruple regimen ABC/CBV/EFV. This quadruple combination therapy without protease inhibitor shows an important effect on viral load after 24 weeks of treatment. However, due to the non-comparative design of the study and the small number of patients included, it will be difficult to draw substantial conclusions.
- Study **CNAB 2002** which was initially a blinded dose-ranging study, amended afterwards to switch to open label ABC 300mg BID in combination with 3TC and ZDV, for a total duration of 120 weeks. The results of this study show that the durability of the antiviral effect of this ABC-containing regimen is sustained after 120 weeks of therapy, despite initially having received ABC monotherapy.

In treatment experienced patients

- In the open label study **CNAB 3009** the addition of ABC to previous limited ZDV/3TC use was evaluated. Intensification with ABC showed an extra benefit in terms of viral load and CD4 cells. However, patients had already a low baseline viral load and a high CD4 cell count before entering this study, which on one hand might underestimate the effect of ABC but on the other hand does not allow extrapolation of these results to a more advanced population.
- In another open label study **NZTA 4005** ABC in combination with CBV was used as a switch/intensification therapy in previously NRTI-experienced but PI-naive subjects. Subjects only received prior single or double NRTI therapy with no concurrent ZDV. There was a sustained suppression of viral load at 48 weeks in this population where one third had already <400 copies/ml at baseline, and a rather modest change in viral load (-0.52 $\log_{10}$ copies/ml) and in CD4 cells (+66 cells/mm^3). Results in this study were only descriptive.
- The design of study **CH-96-06** is interesting because it evaluates if a simplified combination therapy of ABC in combination with CBV can maintain the viral load below the limit of quantification in patients with already undetectable plasma HIV RNA as a result of a previous PI-containing regimen. Interim results show a similar proportion of subjects with <50 copies/ml in both groups (90% vs 87% in the PI-containing arm and CBV/ABC arm, respectively) and a similar proportion of failure (4% vs 6%, respectively). However, failures occurred earlier in the CBV/ABC arm than in the PI-containing arm. Long-term results in a larger patient group are warranted before conclusions can be made.

Discussion on clinical efficacy

Globally, the durability of the antiviral affect of the ABC/3TC/ZDV combination has been shown in antiretroviral naive patients, with a response that is not impacted if the addition of ABC is delayed (as shown in study CNAAB3003) or conversely, if ABC has been given as monotherapy for a while (as shown in study CNAB2002). Although no formal conclusion at long term on the equivalence could be drawn, results of the pivotal trial CNAAB3005 indicate a similar effect between this triple nucleoside regimen and a regimen containing the protease inhibitor indinavir,although the impact of abacavir as

compared to indinavir is lower in patients with high viral load at baseline (>100 000 copies/ml) and when using the ultrasensitive method with lower detection threshold (<50 copies/ml).

The experience in antiretroviral experienced patients is more limited since patients in the submitted studies, except in study CH-96-06, were only moderately pre-treated with prior therapy consisting mainly of double NRTI therapy for a short period. It is important to realise that the modest changes in viral load which were found in these studies after addition of ABC or switching to ABC+CBV cannot be extrapolated to heavily pre-treated patients at an advanced stage of their HIV infection. Therefore the role of ABC (+CBV) as part of a salvage treatment is not defined yet. In study CH-96-06 preliminary results show a possible role of ABC/CBV in maintaining an aviremic status in patients who became aviremic as a result of a protease inhibitor containing regimen, which could be beneficial for improved compliance.

However, it should be underlined that except for preliminary data in study CNAF 3008, no data are available of ABC/3TC/ZDV in combination therapy with other drug categories, namely NNRTI and PI, and therefore neither the efficacy nor the safety of these combinations is currently known.

Clinical Safety

Patient exposure

Safety data are available for 972 subjects from the nine studies including subjects who switched therapy to the triple combination. The safety population includes all subjects who received at least one dose of the triple combination ABC/3TC/ZDV and CNAAB 3003 group B subjects who received open label ABC/3TC/ZDV. A total of 495 of these subjects have received the triple combination for over 48 weeks. Analyses focus primarily on the three pivotal studies CNAAB 3003, CNAAB 3005 and CNAB 3002 because they include comparative data. In addition, an estimated 3174 subjects have received the triple combination regimen in the market support studies and expanded access programmes. Serious adverse event data is available for all subjects enrolled in ongoing studies, both Marketing Authorisation Holder sponsored and collaborations with external agencies and investigators. To date the safety profile of the combination product Trizivir has not been assessed in clinical trials.

Adverse events and serious adverse events/deaths

The most common adverse events of the triple combination of ABC/3TC/ZDV were gastrointestinal symptoms (nausea with or without vomiting, and diarrhoea) together with malaise and fatigue, and headache. A pooled analysis of data from the 3 pivotal comparative studies showed no difference in incidence of adverse events between the ABC/3TC/ZDV arm and control groups, except for a higher incidence of fever and/or chills in the triple therapy arm, probably related to the hypersensitivity reaction to ABC. The incidence of most common AE did not seem to increase with increasing exposure to study drugs but is on the contrary more likely to diminish with time (as shown in study CNAB 2002).

The most important safety problem with this triple combination tablet is -as expected- the hypersensitivity reaction (HSR) to abacavir, with a safety profile that is consistent with the current profile in ABC hypersensitivity cases. In all these studies the incidence of HSR was around the previously described 3%, except for study CNAAB 3005 where the incidence was much higher (7.3%). It is important to remain vigilant because it is possible that it will become clear that more symptoms may be involved in the HSR (e.g. the recently reported respiratory symptoms) and that the true incidence therefore has been underestimated so far.

During the post-marketing phase of Ziagen (abacavir) 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 containing regimen. 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.

Strong measures have been taken regarding the risk of fatal rechallenge after the occurrence of HSR due to ZIAGEN. The overall measures concerning HSR due to ZIAGEN (recommendation, information of prescribers and patients, committments of the Marketing Authorisation Holder) should be applied for TRIZIVIR. 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 is conveyed in the SPC.

Furthermore, when this triple NRTI combination will be associated with drugs from other classes (NNRTI or PI), which can give similar side effects as an HSR, extra caution will be necessary to distinguish these side effects from a true HSR. Appropriate recommendations for the use of ABC (alone or combined) should be provided by the Marketing Authorisation Holder to avoid or clarify such clinical situations.

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.

Another particular concern is that of mitochondrial toxicity of this triple NRTI combination. Considering that mitochondrial toxicity is a NRTI class effect, the Marketing Authorisation Holder has explored this particular issue through a review of the literature. The mitochondrial toxicity of this triple NRTI combination is difficult to assess through this literature review of *in vitro* studies consisting of a ranking of NRTIs. No specific *in vitro* study with the fixed triple NRTI combination has been performed by the Marketing Authorisation Holder, which could have been much more contributive to address this issue. The mitochondrial toxicity of NRTI is a complex topic, which is currently the subject of an active research to better understand the mechanism, to propose an appropriate clinical monitoring and therapeutic management. The recommendation of a close monitoring of patients (clinical and biological) should be reinforced. The Marketing Authorisation Holder should be asked to further explore this topic through *in vitro* and *in vivo* data (in view of a better understanding of this toxicity and a better monitoring of patients).

5. Overall Conclusion 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. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

The Marketing Authorisation Holder will provide stability data including the 24-month time point and demonstrate the specificity of the HPLC method used for the determination of the related substances in the finished product with regard to the impurities of abacavir.

- Preclinical pharmacology and toxicology

The extensive non-clinical evaluations carried out on abacavir, lamivudine and zidovudine provide sufficient evidence to support the use in a triple combination tablet. This is in line with the approved uses of Combivir and Ziagen.

The Marketing Authorisation Holder has committed to further explore the issue of mitochondrial toxicity for this triple combination by performing both *in vitro* and *in vivo* studies

- **Efficacy and Safety**

Regarding efficacy, this triple drug combination has demonstrated a significant antiviral effect after 48 weeks of treatment in antiretroviral naive patients. The experience in antiretroviral-experienced patients is rather limited with only modest results at 48 weeks. The efficacy of the combination tablet

in heavily pre-treated and in failing patients or in patients with advanced disease (<50 CD_4 cells/mm^3) has not been documented. There are also insufficient data on combination therapy with NNRTI and PI. This is highlighted in the SmPC. The Marketing Authorisation Holder has committed to submit final reports of studies currently ongoing with the triple combination tablet

Regarding safety, the profile is considered acceptable with the exception of hypersensitivity reactions to abacavir, which remain important safety concerns. The same strict conditions already required for the marketing authorisation of Ziagen will be fully implemented.

Benefit/Risk Assessment

During an oral explanation before the CPMP in June 200 the applicant addressed the issues relating to the wording of the indication highlighting that Trizivir replaces the individual components. It was argued that this triple NRTI fixed dose combination has a substantial antiviral impact and facilitates the dosage administration (only one tablet twice daily); patient's adherence to appropriate and effective HIV/AIDS drug regimen is a central factor in predicting long term benefit of treatment. The CPMP pointed out that the choice of this fixed combination should be based not only on potential adherence criteria, but mainly on expected efficacy and risk related to the three nucleoside analogues.

The results of the antiviral effect as demonstrated in study CNAAB 3005 were discussed. The high dropout rate did not allow definitive conclusions on equivalence between the abacavir and indinavir containing regimens. Although a similar antiviral effect was observed between the abacavir and indinavir containing regimens in terms of proportion of patients with undetectable viral load (≤400 copies/ml), results favoured the indinavir combination, particularly in the subset of patients with high viral load (> 100 000 copies/ml) at baseline. Information on this pivotal trial is made available in relevant parts of the SPC.

Following the urgent safety restriction for Ziagen (abacavir) on 10 August 2000, the applicant (i.e., the marketing authorisation holder for Ziagen) gave an oral explanation before the CPMP at the September CPMP meeting. This again related to the risk of hypersensitivity reactions and the proper management of patients treated with the triple combination.

The CPMP recommended that due to uncertainties on the optimal use of Trizivir in relation to the risk for hypersensitivity reactions and to help ensure that physicians and patients were aware that Trizivir contains abacavir, starting treatment with Trizivir should be delayed 6-8 weeks until some reassurance of the safe use of the combination of the individual components alone had been achieved. This recommendation is conveyed in section 4.1. of the SPC. The CPMP thus revised its previous opinion giving considerations to the new safety information on Ziagen as relevant for the opinion on Trizivir.

Relevant parts of the product information were thus revised.

The overall benefit/risk assessment is considered positive since:

- This triple NRTI fixed dose combination has a substantial antiviral impact and facilitates the dosage administration (only one tablet twice daily).
- Patient's adherence to appropriate and effective HIV/AIDS drug regimens is a central factor in predicting long-term benefit of treatment.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Trizivir was favorable for the following indication "Trizivir is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults. This fixed combination replaces the three components (abacavir, lamivudine and zidovudine) used separately in similar dosages. It is recommended that treatment is started with abacavir, lamivudine, and zidovudine separately for the first 6-8 weeks (see section 4.4. Special Warnings and Precautions). The choice of this fixed combination should be based not only on potential adherence criteria, but also mainly on-expected efficacy and risk related to the three nucleoside analogues. The demonstration of the benefit of Trizivir is mainly based on results of studies performed in treatment naive patients or moderately antiretroviral experienced patients with non-advanced disease. In patients with high viral load (>100.000 copies/ml) choice of therapy needs special consideration (see 5.1. Pharmacodynamic properties)."