This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	[HA060 trade name][*]
Manufacturer of Pre Qualified Product:	Cipla Mumbai, India
Active Pharmaceutical Ingredient(s) (API):	Lamivudine Zidovudine
International Nonproprietary Name:	Lamivudine Zidovudine
Pharmaco-therapeutic group (ATC Code):	Lamivudine J05AF05 Zidovudine J05AF01
Therapeutic indication:	[HA060 trade name] is indicated for the treatment of HIV infection, as a part of combination therapy.

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

1. Introduction

The standard of care in Human Immunodeficiency Virus (HIV) infection is the use of a triple drug antiretroviral regimen. The drugs for treatment of HIV infection are categorized as nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The first category of agents acts at an early stage in the HIV life cycle by blocking the activity of reverse transcriptase (RT). This enzyme is essential for conversion of the viral RNA to proviral DNA, which integrates in the host DNA and results in viral replication.

The success of complex antiretroviral regimens is dependent on consistent adherence of patients to the drugs. Patients frequently encounter practical difficulties in adhering to the complex combination due to various reasons like dosing frequency, daily pill burden, food restriction etc. Sub-optimal adherence may reduce the effectiveness of the regimen by allowing viral replication and the emergence of drug resistant strains.

[HA060 trade name] is a fixed dose combination tablet containing 150 mg of lamivudine and 300 mg of zidovudine in each film-coated tablet. [HA060 trade name] has a simple dosing schedule of one tablet, twice daily, with no food restrictions or water requirements.

[HA060 trade name] provides a combination of drugs i.e. lamivudine and zidovudine, that are already established as a backbone of the triple drug regimens.

The development of a fixed dose combination aims to reduce the number of daily tablets, and therefore enhance adherence to therapy and thereby minimizing the risk of emergence of resistance.

[HA060 trade name] tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product (API's lamivudine and zidovudine). It is not indicated for use in paediatric patients less than 12 years of age and patients with renal impairment, since it is a fixed dose combination that cannot e titrated for these patients.

2. Assessment of Quality

Introduction
[HA060 trade name] is a generic version of Combivir®, the first fixed-dose combination containing two known antiretroviral agents belonging to the RT inhibitors class.

Composition
[HA060 trade name] is presented as white, film-coated, oblong, biconvex tablets with "DVR" embossed on one side and plain on the other side.
Other ingredients include colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycollate. The film-coating materials include hydroxy-propylmethyl cellulose E15, propylene glycol, talc and titanium dioxide.
The container is clear PVC/PVDC/Aluminium foil blister units containing 10 tablets per blister card.

Method of preparation
Lamivudine/zidovudine tablets are manufactured by direct compression involving blending, compression and film coating. The in-process controls of tablet cores were considered adequate to ensure batch to batch reproducibility and compliance with standard specifications. Validation data presented on three batches were considered acceptable to demonstrate the consistency of the process and the quality of the product.

Control of starting materials
Lamivudine is official in the USP and its quality is therefore considered as well established. Zidovudine is official in internationally used major pharmacopoeias and its quality is therefore considered as well established.

All excipients in the tablet core and the film-coating materials are described in the monographs of internationally used major pharmacopoeias.

Primary packaging materials, PVC/PVDC and aluminium foils, were shown to comply either with the requirements of internationally used major pharmacopoeias or the requirements for materials used in contact with food.

Control tests on the finished medicinal product
Tablets are tested according to standard methods of internationally used major pharmacopoeias. The specifications and routine tests at release and at the end of shelf life for the Finished Pharmaceutical Product (FPP) are acceptable. Test procedures for the control of the FPP are sufficiently validated.

Stability
Stability data of lamivudine up to 24 months met specifications at all storage conditions, and no degradation was observed.

Stability tests up to 24 months were presented for zidovudine. No significant increase in drug-related substances was observed. The samples exposed to light showed deterioration, indicating the need for protection from light.

FPP stability tests were carried out on batches packed in the proposed commercial containers. A good stability under various proposed storage conditions supports 24-month shelf life.

Conclusions
With regard to chemical and pharmaceutical part of the dossier, the data submitted are acceptable to ensure the quality and the consistency of [HA060 trade name] fixed-dose combination tablets.

3. Assessment of Bio-Equivalence

The following bioequivalence study has been performed in 2004 according to internationally accepted guidelines.

A randomized, open label, two treatment, four period, two sequence, single dose, fully replicated, crossover bioequivalence study on lamivudine 150 mg + zidovudine 300 mg tablets (Cipla Ltd., India) comparing with Combivir tablets (marketed by GlaxoSmithKline, USA) in 57 healthy, adult, human subjects under fasting conditions (study number 420/04). Bio analytical assays were conducted on the 1st completed 40 volunteers for pharmacokinetic analysis and therefore, bioequivalence evaluation.

The objective of the study was to compare the bioavailability of lamivudine 150 mg + zidovudine 300 mg tablets (test drug) with Combivir tablets (reference drug) containing the same amount of lamivudine and zidovudine in healthy, adult volunteers under fasting conditions. The comparison was performed as a single centre, open label, randomized, four period, fully replicated, crossover study in subjects aged 24±4 years. Each subject was

assigned to receive each of the following two treatments twice during the study in a replicate randomized fashion:

Treatment T: Test – Lamivudine 150 mg + Zidovudine 300 mg tablets (lamivudine 150 mg; zidovudine 300 mg) Batch Nr. G44737

Treatment R: Reference – Combivir tablets (lamivudine 150 mg; zidovudine 300 mg) Batch Nr. 4ZP3632

A five day wash-out period was observed between drug administrations. Serial blood samples (22 samples within 36 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for lamivudine and zidovudine in plasma were analyzed using a validated LC-MS/MS method.

The study recruited 60 participants to perform the replicate study. After an interim analysis based on results of 40 subjects the data generated from a total of 57 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Lamivudine

Pharmacokinetic Parameter	Test formulation (T) Geom.. Mean	Reference Combivir (R) Geom. Mean	ln-transformed parameters	
			Ratio of Least Square Means T/R (%)	Conventional 90% CI (Parametric)
t_{max} (h) *)	1.10	1.14	-	-
C_{max} (µg/ml)	1.7968	1.8092	99.31	93.70 – 105.26
AUC_{0-t} (µg.h/ml)	7.6194	7.9280	96.11	92.30 – 100.07
$AUC_{0-\infty}$ (µg.h/ml)	7.8499	8.1923	95.82	92.17 – 99.62

* *Median*

Zidovudine

Pharmacokinetic Parameter	Test formulation (T) Geom.. Mean	Reference Combivir (R) Geom. Mean	ln-transformed parameters	
			Ratio of Least Square Means T/R (%)	Conventional 90% CI (Parametric)
t_{max} (h) *)	0.50	0.54	-	-
C_{max} (µg/ml)	2.0618	1.9230	107.22	96.89 – 118.64
AUC_{0-t} (µg.h/ml)	2.3938	2.3655	101.20	97.61 – 104.92
$AUC_{0-\infty}$ (µg.h/ml)	2.4596	2.4305	101.20	97.68 – 104.84

* *Median*

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding lamivudine and zidovudine. Accordingly, the test product, Lamivudine 150 mg + Zidovudine 300 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference product, Combivir tablets (containing 150 mg lamivudine and 300 mg zidovudine). It should be noted, that the investigation conducted employing an interim analysis is accepted as presented, because a

large number of subjects were included in the interim analysis (n=40), a fully replicated design was employed, and the intra-subject variability is fairly small.

4. Summary of Product Safety and Efficacy

4.1 Introduction:

Triple antiretroviral therapy is regarded as the optimal approach for the treatment of HIV infection. The combination of zidovudine + lamivudine is one of the preferred 2 NRTI-backbones for antiretroviral therapy (WHO 2003, DHHS Guidelines, 2004) and is one of the standard first line regimens recommended by WHO for resource constrained settings.

[HA060 trade name] is a fixed dose combination tablet containing lamivudine 150 mg and zidovudine 300 mg. [HA060 trade name] is taken as a single tablet, twice daily and is co-formulated so as to reduce pill burden and increase adherence to triple drug regimens.

4.2 Clinical pharmacology:

Pharmacodynamic properties
Pharmacotherapeutic group: nucleoside analogue, ATC code: JO5A F30

Mechanism of action:
Lamivudine and zidovudine are nucleoside analogues which have activity against human immunodeficiency virus (HIV). Additionally, lamivudine has activity against hepatitis B virus (HBV). Both medicinal products are metabolized intracellularly to their active moieties, lamivudine 5'-triphosphate and zidovudine 5'-triphosphate (TP) respectively. Their main modes of action are as chain terminators of viral reverse transcription. Lamivudine-TP and zidovudine-TP have selective inhibitory activity against HIV-1 and HIV-2 replication *in vitro*; lamivudine is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

Antiviral Activity In Vitro:
The relationship between in vitro susceptibility of HIV to lamivudine or zidovudine and the inhibition of HIV replication in humans has not been established.
Lamivudine Plus Zidovudine: In HIV-1infected MT-4 cells, lamivudine in combination with zidovudine had synergistic antiretroviral activity. Synergistic activity of lamivudine and zidovudine was also shown in a variable-ratio study.
Lamivudine: In vitro activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). IC50 and IC90 values (50% and 90% inhibitory concentrations) for lamivudine were 0.0006 mcg/mL to 0.034 mcg/mL and 0.015 to 0.321 mcg/mL, respectively. Lamivudine had anti-HIV-1 activity in all acute virus-cell infections tested.
Zidovudine: In vitro activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The IC50 and IC90 values for zidovudine were 0.003 to 0.013 mcg/mL and 0.03 to 0.13 mcg/mL, respectively. Zidovudine had anti-HIV-1 activity in all acute virus-cell infections tested. However, zidovudine activity was substantially less in chronically infected cell lines. In cell culture drug combination studies with zidovudine, interferon-alpha demonstrated additive activity and zalcitabine, didanosine, saquinavir, indinavir, ritonavir, nelfinavir, nevirapine, and delavirdine demonstrated synergistic activity.

Drug Resistance:
Lamivudine Plus Zidovudine Administered As Separate Formulations:
In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harbouring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine. HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple mutations, the most essential of which may be at codon 333 (Gly→Glu). The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.
Lamivudine: Lamivudine-resistant isolates of HIV-1 have been selected in vitro and have also been recovered from patients treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of the resistant isolates showed that the resistance was due to mutations in the HIV-1 reverse transcriptase gene at codon 184 from methionine to either isoleucine or valine.
Zidovudine: HIV isolates with reduced susceptibility to zidovudine have been selected in vitro and were also recovered from patients treated with zidovudine. Genotypic analyses of the isolates showed mutations which result in 5 amino acid substitutions (Met41→Leu, Asp67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) in the HIV-1 reverse transcriptase gene. In general, higher levels of resistance were associated with greater number of mutations.

Cross-Resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized.
Lamivudine Plus Zidovudine: Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a mutation at codon 184, which confers resistance to lamivudine. In the presence of the 184 mutation, cross-resistance to didanosine and zalcitabine has been seen in some patients; the clinical significance is unknown. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below).
Lamivudine: See Lamivudine Plus Zidovudine (above).
Zidovudine: HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for .1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of genotypic resistant mutations with such combination therapies was different (Ala62→Val, Val75→Ile, Phe77→Leu, Phe116→Tyr, and Gln151→Met) from the pattern with zidovudine monotherapy, with the 151 mutation being most commonly associated with multidrug resistance. The mutation at codon 151 in combination with the mutations at 62, 75, 77, and 116 results in a
virus with reduced susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine. Multiple-drug resistance has been observed in 2 of 39 (5%) patients receiving zidovudine and didanosine combination therapy for 2 years.

Pharmacokinetic properties

Pharmacokinetics in Adults:
[HA060 trade name]: One [HA060 trade name] tablet contains 150 mg of lamivudine and 300 mg of zidovudine. The pharmacokinetics of lamivudine and zidovudine studied in fasting patients are as follows:-
Lamivudine: The pharmacokinetic properties of lamivudine in fasting patients are

summarized in Table 2. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).
Zidovudine: The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 2. Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is 3′-azido-3′-deoxy-5′-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one fifth of the
zidovudine AUC.

Table 2: Pharmacokinetic Parameters* for Lamivudine and Zidovudine in Adults

Parameter	Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 16	n=12	64 ± 10	n=5
Apparent volume of distribution (L/kg)	1.3 ± 0.4	n = 20	1.6 ± 0.6	n=8
Plasma protein binding (%)	< 36		< 38	
CSF plasma ratio†	0.12 [0.04 to 0.47]	n = 38	0.60 [0.04 to 2.62]	n = 39§
Systemic clearance (L/hr/kg)	0.33 ± 0.06	n = 20	1.6 ± 0.6	n = 6
Renal clearance (L/hr/kg)	0.22 ± 0.06	n = 20	0.34 ± 0.05	n = 9
Elimination half-life (hr)I	5 to 7		0.5 to 3	

* Data presented as mean ± standard deviation except where noted
† Median [range]
§ Adults
I Approximate range

Bioequivalence study
[HA060 trade name] has shown to be bioequivalent to Combivir®.
A study was carried out to assess the bioequivalence between the fixed dose combination tablet to the two marketed formulations being lamivudine 150 mg tablets and zidovudine 300 mg tablets. This open-label, three-way crossover study involved 24 healthy volunteers. The three treatments were as follows:

- Fixed dose combination tablet (lamivudine 150 mg/zidovudine 300 mg) after an overnight fast
- Separate lamivudine 150 mg tablets and zidovudine 300 mg tablets swallowed simultaneously after an overnight fast
- Fixed dose combination tablet (lamivudine 150 mg/zidovudine 300 mg) after a standardized breakfast.

Results from this study confirmed the lack of pharmacokinetic interaction between zidovudine and lamivudine since the properties of both substances in combination are in the range of the respective administration of monotherapy. In addition, the fixed dose combination tablet was shown to be bioequivalent to the two marketed formulations, lamivudine 150 mg tables and zidovudine 300 mg tablets, when co-administered under fasting conditions. The influence of food was also evaluated. When the combined lamivudine/zidovudine fixed dose tablet was administered with food the extent of the absorption of either lamivudine or zidovudine was unchanged in comparison to administration

under fasting conditions. The effect of food to slow the rate of absorption was previously demonstrated with current available separated formulations and was not expected to have clinical consequence. Therefore the combined lamivudine/zidovudine fixed tablet may be administered without regard to meal since there was no significant difference in extent of absorption following a meal and no clinical consequence of slowed absorption is expected.

Special populations

Impaired Renal Function: Because lamivudine and zidovudine require dose adjustment in the presence of renal insufficiency, [HA060 trade name] is not recommended for patients with impaired renal function.

Impaired Hepatic Function: A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Because [HA060 trade name] is a fixed-dose combination that cannot be adjusted for this patient population, [HA060 trade name] is not recommended for patients with impaired hepatic function.

Gender: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in zidovudine exposure (AUC ∞□) or lamivudine (AUC ∞) normalized for body weight.

Race: There are no significant racial differences in lamivudine pharmacokinetics.

Pregnancy and lactation: Currently no special studies have been conducted to demonstrate the safety and efficacy of [HA060 trade name] in pregnant and lactating women or pediatric populations.

Pregnancy:
Zidovudine and lamivudine have been used in combination but not as a fixed-dose combination in pregnant women and have been shown to reduce maternal transmission to the baby. Lamivudine and zidovudine are both passed on to the infants while breast-feeding.

Lactation:
Current guidelines (UK, US and other) do recommend that women taking zidovudine and lamivudine as a part of combination therapy should avoid breast-feeding.

Children: zidovudine and lamivudine have also been used extensively in children but not in a fixed-dose combination.

4.3 Drug Interactions, related side effects and Contraindications

Lamivudine
Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher doses TMP/SMX on lamivudine pharmacokinetics has not been investigated. No data are available regarding the potential for interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of [HA060 trade name] in combination with zalcitabine is not recommended.

Zidovudine
Co-administration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Concomitant use of lamivudine/zidovudine with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated in vitro. In addition, concomitant use of zidovudine with doxorubicin or ribavirin should be avoided because an antagonistic relationship has been demonstrated in vitro.

Lamivudine plus Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr).

The effect of co-administered drugs on the pharmacokinetics of lamivudine and zidovudine are depicted in Table 1.

Table 1: Effect of Co-administered Drugs on Lamivudine and Zidovudine AUC
Note: Routine Dose Modification of lamivudine and Zidovudine is not warranted with co-administration of the following drugs

Drugs That May Alter Lamivudine Blood Concentrations					
Co-administered Drug and Dose	**Lamivudine Dose**	**n**	**Lamivudine Concentrations**		**Concentration of Co-administered Drug**
			AUC	**Variability**	
Nelfinavir 750 mg q 8 hour x 7 to 10 days	Single 150 mg	11	↑ AUC 10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg / Sulfamethoxazole 800 mg daily x 5 days	Single 300 mg	14	↑ AUC 43%	90% CI: 32% to 55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Co-administered Drug and Dose	**Zidovudine Dose**	**n**	**Zidovudine Concentrations**		**Concentration of Co-administered Drug**
			AUC	**Variability**	
Atovaquone 750 mg q 12 hr with f00d	200 mg q 8 hr	14	↑ AUC 31%	Range 23% to 78%†	↔
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑ AUC 74%	95% CI: 54% to 98%	Not Reported
Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑ AUC 43%	Range 16% to 64%†	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	Single 200 mg	11	↓ AUC 35%	Range 28% to 41%	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑ AUC 106%	Range 100% to 170%†	Not assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓ AUC 25%	95% CI: 15% to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑ AUC 80%	Range 64% to 130%†	Not assessed

↑ = Increase; ↓ = Decrease; ↔ = no significant change, AUC = area under the concentration versus time curve, CI = confidence interval, †=Estimated range of percent difference

4.4 Clinical efficacy

The use of lamivudine and zidovudine as either monotherapy or in combination for the treatment of HIV-1 infection has been extensively studied. For the development of the fixed-dose formulation, the properties of each substance, the administration of lamivudine with zidovudine and the bioequivalence of the compounds were reviewed. The development of the fixed-dose combination tablet was based on the recommendations of the existing CPMP Guideline on fixed combination products.

Various studies have demonstrated the clinical safety of zidovudine and lamivudine administered as separate tablets as a part of 2 NRTI backbone triple drug antiretroviral therapy. Additionally, one study has demonstrated the non-inferiority of the fixed-dose combination tablet versus the same drugs given separately, when administered as a part of triple drug regimen. One observational cohort study has reported the safety, tolerability and effectiveness of the generic antiretroviral regimens in South India. Finally there is one study that has reported using the commercial product [HA060 trade name].

One study (AIDS 2000; 14: 671-81) has established the clinical equivalence (non-inferiority) of a regimen employing a lamivudine 150 mg/zidovudine 300 mg combination tablet administered twice daily, plus a protease inhibitor, compared with a conventional regimen of 150 mg lamivudine twice daily, 600 mg zidovudine daily and a protease inhibitor, in antiretroviral-experienced patients infected with HIV-1. patients were randomized to the conventional reigimen (n=113) or combination tablet regimen (n=110) for 16 weeks. The primary srudy end point was treatment failure, defined as an increase in HIV-1 RNA $\geq$0.5 $\log_{10}$ above baseline in patients in patients with viral load greater than the lower limit of quantitation (LLOQ) (<400 copies/mL) at randomization and as HIV-1 RNA increasing to $\geq$1250 copies/mL in patients with viral load < LLOQ at randomization.

The combination tablet regimen was associated with 3.5% greater success rate than the conventional regimen (96.4 versus 92.9%), with four and eight patients failing treatment due to increases in HIV-1 RNA levels respectively the lower limit of the associated confidence interval for the difference was –2.4%, which was well within the –10% margin predefined as clinically important. This establishes the clinical equivalence (non-inferiority) of the combination tablet regimen to the conventional regimen regarding virologic response. The combination tablet and conventional regimens were similar with respect to percentage of patients maintaining HIV-1 RNA levels < LLOQ at the end of study or improving from baseline to undetectability (94 versus 91%; 0.063), overall incidence of drug related adverse events (21 versus 19%) (p=0.0868), and mean area under the curve for the CD4 cell counts [treatment difference, 5.9 cells (95% confidence interval, -15.8 to 27.6 x 10^6 cells/L)]. A self-reported adherence questionnaire indicated that the patients in the combination tablet group were less likely to miss doses of nucleoside analogue medication at weeks 8 (p=0.007) and 16 (p=046).

The study concluded that the combination of lamivudine/zidovudine tablet and protease inhibitor regimen is clinically equivalent (non-inferior) to the conventional regimen with respect to virologic response and may offer adherence advantages.

An observational study on the cohort study on the safety, tolerability and effectiveness of generic antiretroviral drug regimens in South India has been reported by Kumaraswamy et al in the Journal AIDS (AIDS 2003; 17(15): 2267-69). From 1 May 2000 until 1 January, 2003, 333 patients began on generic HAART, containing nevirapine in combination with

zidovudine/lamivudine (n=110), stavudine/lamivudine (n=190) or stavudine/didanosine (n=33), reflecting 279 persons-years experience.

As a result of the high cost per CD4 cell count test, only 109 patients had a follow-up CD4 cell count within the first 6 months of initiating therapy. The median increase in CD4 cell count from baseline for this group was 173 cells/mm3 (p=0.001). only 75 patients had a follow up CD4 count between 6-12 months of initiating therapy. The median increase in CD4 cell count from baseline was greater in patients who were antiretroviral naïve than in patients who had previous dual nucleoside therapy (p=0.01).

In another poster presentation by Kumaraswamy et al the 15th International AIDS Conference 2004 (Abstract no ThPeB7137), viral load suppression was evaluated using a combination of [HA060 trade name] (zidovudine 300 + lamivudine 150) + EFAVIR (efavirenz 600 mg) (Drugs supplied by Cipla Ltd). 39 subjects completed three months on study. During this period, CD4 counts rose from 171 cell/µL to 314 cells/µL (p<0.0001). At baseline, median viral load was 259,000 copies/mL and at 3 months, 95% of the subjects had undetectable viral load (p<0.0001). 26 subjects completed six months follow up. At the 6th month, CD4 rose from 163 to 319 (p<0.0001), and all subjects had undetectable viral load. The investigators concluded that generic HAART was effective at suppressing viral load while increasing CD4 counts.

4.5 Clinical Safety

A study by Pujari et al was presented at 9th Conference on Retrovirus and Opportunistic Infections, February 2002. 347 patients initiated therapy with 2 NRTIs (zidovudine + lamivudine or stavudine + lamivudine) + nevirapine. They were followed up to a minimum period of 6 months. Rash was documented in 10.5% of patients, and sub-clinical hepatitis in 4.7% of patients. Skin rashes developed within 1 month of initiation, and female gender was significantly associated with the development of rash.

Additional post-marketing surveillance data indicate the following:

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of lamivudine, zidovudine, and/or lamivudine/zidovudine as a fixed-dose combination. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine, zidovudine, and/or lamivudine / zisovudine as fixed-dose combination.
Body as a Whole: Redistribution/accumulation of body fat
Cardiovascular: Cardiomyopathy.
Endocrine and Metabolic: Gynecomastia, hyperglycemia.
Gastrointestinal: Oral mucosal pigmentation, stomatitis.
General: Vasculitis, weakness.
Hemic and Lymphatic: Anemia, (including pure red cell aplasia and anemias progressing on therapy), lymphadenopathy, splenomegaly.
Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B.
Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy, seizures.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

4.6 Benefit risk assessment

The combination of lamivudine plus zidovudine has been proven to be effective and well tolerated and is widely used in combination therapy. Pharmacodynamic and pharmacokinetic interactions between zidovudine and lamivudine have shown no differences in zidovudine or lamivudine exposure when co-administered. Additionally, in vitro experiments have found no intracellular interaction with respect to zidovudine triphosphate or lamivudine triphosphate as expected, since different enzyme systems are required for their phosphorylation. Lastly, synergy between these compounds has been observed both *in vitro* and clinically. Hence, taking into account the bioequivalence between the fixed dose combination tablet and the two individual marketed formulations, and the results of the study NUCB 3027, [HA060 trade name] is expected to provide similar efficacy and safety profile as that observed with the two separate formulations.

The combined lamivudine / zidovudine fixed dose tablet may improve patient's compliance and minimize the risk of emergence of resistance. In populations requiring dosage adjustment the use of this fixed dose combination tablet will not be appropriate.

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 Summary of Product Characteristics. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence
[HA060 trade name] has shown to be bioequivalent to Combivir.

Clinical Efficacy and Safety
Regarding clinical efficacy and safety, this double fixed drug combination is considered effective and safe to use when taking into consideration the guidance and restrictions presented in the Summary of Product Characteristics.

Benefit Risk Assessment
Based on the WHO assessment of data on quality, safety and efficacy the team of assessors considered by consensus that the benefit risk profile of [HA060 trade name] was acceptable for the following indication: "as a part in antiretroviral combination therapy for the treatment of HIV infected adults and adolescents over 12 years of age" and have demonstrated adequate tolerability to lamivudine and zidovudine and has advised to include [HA060 trade name] in the list of pre-qualified medicinal products and manufacturers.