Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Abacavir Sulfate and Lamivudine Tablets 600mg/300mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 600 mg of Abacavir as abacavir sulfate USP and 300 mg of Lamivudine USP.

The inactive ingredients are colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The tablets are coated with opadry orange which contains FD & C Yellow #6/Sunset Yellow FCF Aluminum lake, hypromellose, polyethylene glycol, polysorbate 80 and titanium dioxide.

3. PHARMACEUTICAL FORM

Film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abacavir and Lamivudine tablets, in combination with other antiretroviral agents, are indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

4.2 Posology and method of administration

i. Screening for HLA-B*5701 Allele Prior to Starting Abacavir and Lamivudine Tablets

Screen for the HLA-B*5701 allele prior to initiating therapy with abacavir and lamivudine tablets.

ii. Recommended Dosage for Adult Patients

The recommended dosage of abacavir and lamivudine tablets for adults is one tablet taken orally once daily, in combination with other antiretroviral agents, with or without food.

iii. Recommended Dosage for Pediatric Patients

The recommended oral dose of abacavir and lamivudine tablets for pediatric patients weighing at least 25 kg is one tablet daily in combination with other antiretroviral agents.

Before prescribing abacavir and lamivudine tablets, pediatric patients should be assessed for the ability to swallow tablets.

iv. Not Recommended Due to Lack of Dosage Adjustment

Because Abacavir and Lamivudine is a fixed-dose tablet and cannot be dose adjusted, Abacavir and Lamivudine tablets are not recommended for:

- patients with creatinine clearance less than 50 mL per minute.
- patients with mild hepatic impairment. Abacavir and Lamivudine tablets are contraindicated in patients with moderate or severe hepatic impairment.

Use of EPIVIR® (lamivudine) oral solution or tablets and ZIAGEN® (abacavir) oral solution may be considered.

4.3 Contraindications

Abacavir and Lamivudine tablets are contraindicated in patients:

- who have the HLA-B*5701 allele.
- with prior hypersensitivity reaction to abacavir or lamivudine.
- with moderate or severe hepatic impairment.

4.4 Special warnings and special precautions

i. Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir, a component of abacavir and lamivudine tablet. These hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with abacavir (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment. Patients who carry the HLA-B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA-B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with

abacavir-containing products where HLA-B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making.

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with abacavir:

- All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with abacavir and lamivudine or reinitiation of therapy with abacavir and lamivudine, unless patients have a previously documented HLA-B*5701 allele assessment.
- Abacavir and Lamivudine tablets are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
- Before starting abacavir and lamivudine tablet, review medical history for prior exposure to any abacavir-containing product. NEVER restart abacavir and lamivudine tablets or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status.
- To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue abacavir and lamivudine tablets immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).
- If a hypersensitivity reaction cannot be ruled out, do not restart abacavir and lamivudine tablets or any other abacavir-containing products because more severe symptoms, which may include life-threatening hypotension and death, can occur within hours.
- If a hypersensitivity reaction is ruled out, patients may restart abacavir and lamivudine tablet. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of abacavir and lamivudine tablets or any other abacavir-containing product is recommended only if medical care can be readily accessed.
- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

ii. Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. Treatment with abacavir and lamivudine tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

iii. Patients with Hepatitis B Virus Co-infection

Posttreatment Exacerbations of Hepatitis

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

Emergence of Lamivudine-Resistant HBV

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV. Emergence of hepatitis B virus variants associated with resistance to lamivudine has been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

iv. Use with Interferon- and Ribavirin-Based Regimens

Patients receiving interferon alfa with or without ribavirin and abacavir and lamivudine tablets should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of abacavir and lamivudine tablets should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

v. Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir and lamivudine tablets. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

vi. Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

vii. Myocardial Infarction

In a published prospective, observational, epidemiological trial designed to investigate the rate of myocardial infarction (MI) in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of MI. In a sponsor-conducted pooled analysis of clinical trials, no excess risk of MI was observed in abacavir-treated subjects as compared with control subjects. In totality, the available data from the observational cohort and from clinical trials are inconclusive.

As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).

4.5 Drug Interactions

i. Methadone

In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased. This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

4.6 Fertility, Pregnancy and lactation

i. Pregnancy: ***Teratogenic Effects:***

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to abacavir and lamivudine during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Available data from the APR show no difference in the overall risk of birth defects for abacavir or lamivudine compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks gestation. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, oral administration of abacavir to pregnant rats during organogenesis resulted in fetal malformations and other embryonic and fetal toxicities at exposures 35 times the human exposure (AUC) at the recommended clinical daily dose. However, no adverse developmental effects were observed following oral administration of abacavir to pregnant rabbits during organogenesis, at exposures approximately 9 times the human exposure (AUC) at the recommended clinical dose. Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the recommended clinical dose.

Data

Human Data: Abacavir: Based on prospective reports to the APR of over 2,000 exposures to abacavir during pregnancy resulting in live births (including over 1,000 exposed in the first trimester), there was no difference between the overall risk of birth defects for abacavir

compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 2.9% (95% CI: 2.0% to 4.1%) following first trimester exposure to abacavir-containing regimens and 2.7% (95% CI: 1.9% to 3.7%) following second/third trimester exposure to abacavir-containing regimens.

Abacavir has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.

Lamivudine: Based on prospective reports to the APR of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.8% (95% CI: 2.5%, 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)–fold greater compared with paired maternal serum concentration (n = 8).

Animal Data: Abacavir: Abacavir was administered orally to pregnant rats (at 100, 300, and 1,000 mg per kg per day) and rabbits (at 125, 350, or 700 mg per kg per day) during organogenesis (on gestation Days 6 through 17 and 6 through 20, respectively). Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) or developmental toxicity (decreased fetal body weight and crown-rump length) were observed in rats at doses up to 1,000 mg per kg per day, resulting in exposures approximately 35 times the human exposure (AUC) at the recommended daily dose. No developmental effects were observed in rats at 100 mg per kg per day, resulting in exposures (AUC) 3.5 times the human

exposure at the recommended daily dose. In a fertility and early embryo-fetal development study conducted in rats (at 60, 160, or 500 mg per kg per day), embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) or toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at doses up to 500 mg per kg per day. No developmental effects were observed in rats at 60 mg per kg per day, resulting in exposures (AUC) approximately 4 times the human exposure at the recommended daily dose. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In pregnant rabbits, no developmental toxicities and no increases in fetal malformations occurred at up to the highest dose evaluated, resulting in exposures (AUC) approximately 9 times the human exposure at the recommended dose.

Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300 and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (Cmax) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at systemic exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (Cmax) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the pre-and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day from gestation Day 6 through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, were not affected by the maternal administration of lamivudine.

ii. Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Abacavir and lamivudine are present in human milk. There is no information on the effects of abacavir and lamivudine on the breastfed infant or the effects of the drug on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a

breastfed infant, instruct mothers not to breastfeed if they are receiving abacavir and lamivudine tablets.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The clinical condition of the patient and the side effect profile of this product should be taken into consideration.

4.8 Undesirable effects

The following adverse reactions are:

- Serious and sometimes fatal hypersensitivity reactions.
- Lactic acidosis and severe hepatomegaly with steatosis.
- Exacerbations of hepatitis B.
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C.
- Immune reconstitution syndrome.
- Fat redistribution.
- Myocardial infarction

i. Clinical Trials Experience in Adult Subjects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Serious and Fatal Abacavir-Associated Hypersensitivity Reactions

In clinical trials, serious and sometimes fatal hypersensitivity reactions have occurred with abacavir, a component of abacavir and lamivudine tablets. These reactions have been characterized by 2 or more of the following signs or symptoms: (1) fever; (2) rash; (3) gastrointestinal symptoms (including nausea, vomiting, diarrhea, or abdominal pain); (4) constitutional symptoms (including generalized malaise, fatigue, or achiness); (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). Almost all abacavir hypersensitivity reactions include fever and/or rash as part of the syndrome.

Other signs and symptoms have included lethargy, headache, myalgia, edema, arthralgia, and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress

syndrome, respiratory failure, myolysis, and death have occurred in association with these hypersensitivity reactions. Physical findings have included lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and maculopapular or urticarial rash (although some patients had other types of rashes and others did not have a rash). There were reports of erythema multiforme. Laboratory abnormalities included elevated liver chemistries, elevated creatine phosphokinase, elevated creatinine, and lymphopenia and abnormal chest

x-ray findings (predominantly infiltrates, which were localized).

Additional Adverse Reactions with Use of Abacavir and Lamivudine Tablets:

Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with greater than or equal to 5% frequency during therapy with ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily, both in combination with lamivudine

300 mg once daily and efavirenz 600 mg once daily, are listed in Table 1.

Table 1. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4, Greater than or Equal to 5% Frequency) in Therapy-Naive Adults (CNA30021) through 48 Weeks of Treatment

Adverse Event	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
Drug hypersensitivity[a,b]	9%	7%
Insomnia	7%	9%
Depression/Depressed mood	7%	7%
Headache/Migraine	7%	6%
Fatigue/Malaise	6%	8%
Dizziness/Vertigo	6%	6%
Nausea	5%	6%
Diarrhea[a]	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

[a] Subjects receiving ZIAGEN 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received ZIAGEN 300 mg twice daily. Five percent (5%) of subjects receiving ZIAGEN 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects

receiving ZIAGEN 300 mg twice daily. Two percent (2%) of subjects receiving ZIAGEN 600 mg once daily had severe diarrhea while none of the subjects receiving ZIAGEN 300 mg twice daily had this event.

[b] CNA30024 was a multi-center, double-blind, controlled trial in which 649 HIV-1-infected, therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg twice daily), EPIVIR (150 mg twice daily), and efavirenz (600 mg once daily). CNA30024 used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the trial, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 subjects in the abacavir group and 3% of 325 subjects in the zidovudine group.

Laboratory Abnormalities: Laboratory abnormalities observed in clinical trials of ZIAGEN were anemia, neutropenia, liver function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical trials of EPIVIR were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

The frequencies of treatment-emergent laboratory abnormalities were comparable between treatment groups in CNA30021.

Other Adverse Events: In addition to adverse reactions listed above, other adverse events observed in the expanded access program for abacavir were pancreatitis and increased GGT.

ii. Clinical Trials Experience in Pediatric Subjects

The safety of once-daily compared with twice-daily dosing of abacavir and lamivudine, administered as either single products or as abacavir and lamivudine tablets, was assessed in the ARROW trial (n = 336). Primary safety assessment in the ARROW (COL105677) trial was based on Grade 3 and Grade 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily dosing compared with subjects randomized to twice-daily dosing. One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator. No additional safety issues were identified in pediatric subjects receiving abacavir and lamivudine once-daily compared with historical data in adults.

iii. Postmarketing Experience

The following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Abacavir

Cardiovascular: Myocardial infarction.

Skin: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases. There have also been reports of erythema multiforme with abacavir use.

Abacavir and Lamivudine

Body as a Whole: Redistribution/accumulation of body fat

Digestive: Stomatitis.

Endocrine and Metabolic: Hyperglycemia.

General: Weakness.

Hemic and Lymphatic: Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatic: Lactic acidosis and hepatic steatosis, posttreatment exacerbations 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Abacavir and Lamivudine tablet is an antiretroviral agent

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5'-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue.

Antiviral Activity:

Abacavir: The antiviral activity of abacavir against HIV-1 was assessed in a number of cell lines including primary monocytes/macrophages and peripheral blood mononuclear cells (PBMCs). EC_{50} values ranged from 3.7 to 5.8 microM (1 microM = 0.28 mcg per mL) and 0.07 to 1 microM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and the mean EC_{50} value was 0.26 ± 0.18 microM against 8 clinical isolates. The median EC_{50} values of abacavir were 344 nM (range: 14.8 to 676 nM), 16.9 nM (range: 5.9 to 27.9 nM), 8.1 nM (range: 1.5 to 16.7 nM), 356 nM (range: 35.7 to 396 nM), 105 nM (range: 28.1 to 168 nM), 47.6 nM (range: 5.2 to 200 nM), 51.4 nM (range: 7.1 to 177 nM), and 282 nM (range: 22.4 to 598 nM) against HIV-1clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 0.024 to 0.49 microM.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC_{50} values

were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A to G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4) ranged from 0.003 to 0.120 microM in PBMCs. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

The combination of abacavir and lamivudine has demonstrated antiviral activity in cell culture against non-subtype B isolates and HIV-2 isolates with equivalent antiviral activity as for subtype B isolates. Neither abacavir, nor lamivudine, were antagonistic to all tested anti-HIV agents. Ribavirin, used in the treatment of HCV infection, decreased the anti-HIV-1 potency of abacavir/lamivudine reproducibly by 2- to 6-fold in cell culture.

Resistance

HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture with amino acid substitutions K65R, L74V, Y115F, and M184V/I emerging in HIV-1 RT. M184V or I substitutions resulted in high-level resistance to lamivudine and an approximately 2-fold decrease in susceptibility to abacavir. Substitutions K65R, L74M, or Y115F with M184V or I conferred a 7- to 8-fold reduction in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reduction in susceptibility.

Cross-Resistance:

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with a K65R substitution with or without an M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutation substitutions (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

5.2 Pharmacokinetic properties

Pharmacokinetics in Adults

In a single-dose, 3-way crossover bioavailability trial of 1 abacavir and lamivudine tablet versus 2 ZIAGEN tablets (2 x 300 mg) and 2 EPIVIR tablets (2 x 150 mg) administered simultaneously in healthy subjects (n = 25), there was no difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of each component.

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg per mL (mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg·hour per mL. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl transferase to form the 5'-glucuronide.

Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg per mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg·hour per mL. 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).

In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes.

The pharmacokinetic properties of abacavir and lamivudine in fasting subjects are summarized in Table 2.

Table 2. Pharmacokinetic Parameters[a] for Abacavir and Lamivudine in Adults

Parameter	Abacavir		Lamivudine	
Oral bioavailability (%)	86 ± 25	n = 6	86 ± 16	n = 12
Apparent volume of distribution (L/Kg)	0.86 ± 0.15	n = 6	1.3 ± 0.4	n = 20
Systemic clearance (L/h/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20
Renal clearance (L/h/kg)	.007 ± .0008	n = 6	0.22 ± 0.06	n = 20
Elimination half-life (h)	1.45 ± 0.32	n = 20	5 to 7[b]	

[a] Data presented as mean ± standard deviation except where noted.

[b] Approximate range.

Effect of Food on Absorption of Abacavir and Lamivudine:

Abacavir and Lamivudine tablets may be administered with or without food. Administration with a high-fat meal in a single-dose bioavailability trial resulted in no change in AUC_{last}, AUC_{∞}, and C_{max} for lamivudine. Food did not alter the extent of systemic exposure to abacavir (AUC_{∞}), but the rate of absorption (C_{max}) was decreased approximately 24% compared with fasted conditions (n = 25). These results are similar to those from previous trials of the effect of food on abacavir and lamivudine tablets administered separately.

Specific Populations

Renal Impairment: Abacavir and Lamivudine*:* The effect of renal impairment on the combination of abacavir and lamivudine has not been evaluated.

Hepatic Impairment: Abacavir and Lamivudine*:* The effect of hepatic impairment on the combination of abacavir and lamivudine has not been evaluated.

Pregnancy: Abacavir: Abacavir pharmacokinetics were studied in 25 pregnant women during the last trimester of pregnancy receiving abacavir 300 mg twice daily. Abacavir exposure (AUC) during pregnancy was similar to those in postpartum and in HIV-infected non-pregnant historical controls. Consistent with passive diffusion of abacavir across the placenta, abacavir concentrations in neonatal plasma cord samples at birth were essentially equal to those in maternal plasma at delivery.

Lamivudine: Lamivudine pharmacokinetics were studied in 36 pregnant women during 2 clinical trials conducted in South Africa. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Pediatric Patients: Abacavir and Lamivudine*:* The pharmacokinetic data for abacavir and lamivudine following administration of abacavir and lamivudine tablets in pediatric subjects weighing 25 kg and above are limited. The dosing recommendations in this population are based on the safety and efficacy established in a controlled trial conducted using either the combination of EPIVIR and ZIAGEN or abacavir and lamivudine tablets..

Geriatric Patients: The pharmacokinetics of abacavir and lamivudine have not been studied in subjects over 65 years of age.

Gender: There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components (abacavir or lamivudine) based on the available information that was analyzed for each of the individual components.

Race: There are no significant or clinically relevant racial differences in pharmacokinetics of the individual components (abacavir or lamivudine) based on the available information that was analyzed for each of the individual components.

Drug Interactions

The drug interactions described are based on trials conducted with abacavir or lamivudine as single entities; no drug interaction trials have been conducted with abacavir and lamivudine.

Cytochrome P450 Enzymes: In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes nor do they inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Abacavir: Lamivudine and/or Zidovudine: Fifteen HIV-1-infected subjects were enrolled in a crossover-designed drug interaction trial evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC

decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

Lamivudine: Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 h).

Other Interactions

Ethanol: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure.

Methadone: In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%). The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects.

Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects.

The effects of other coadministered drugs on abacavir or lamivudine are provided in Table 3.

Table 3. Effect of Coadministered Drugs on Abacavir or Lamivudine

Coadministered Drug and Dose	Drug and Dose	n	Concentrations of Abacavir or Lamivudine		Concentration of Coadministered Drug
			AUC	Variability	
Ethanol 0.7 g/kg	Abacavir Single 600 mg	24	↑41%	90% CI: 35% to 48%	↔[a]
Nelfinavir 750 mg every 8 h x 7 to 10 days	Lamivudine Single 150 mg	11	↑10%	95%CI: 1% to 20%	↔
Trimethoprim 160 mg/Sulfamethoxazole 800 mg daily x 5 days	Lamivudine Single 300 mg	14	↑43%	90% CI: 32% to 55%	↔

↑ = Increase; ↔ = No significant change; AUC = Area under the concentration versus time curve; CI = Confidence interval.

[a] The drug-drug interaction was only evaluated in males.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Abacavir: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose of 600 mg.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) the human exposures at the recommended dose of 300 mg.

Mutagenicity

Abacavir: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility

Abacavir: Abacavir did not affect male or female fertility in rats at a dose associated with exposures (AUC) approximately 3.3 times (male) or 4.1 times (female) those in humans at the clinically recommended dose.

Lamivudine: Lamivudine did not affect male or female fertility in rats at doses up to 4,000 mg per kg per day, associated with concentrations approximately 42 times (male) or 63 times (female) higher than the concentrations (C_{max}) in humans at the dose of 300 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:

colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The tablets are coated with opadry orange which contains FD & C Yellow #6/Sunset Yellow FCF Aluminum lake, hypromellose, polyethylene glycol, polysorbate 80 and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30^{o}C.

6.5 Nature and contents of pack

HDPE Container: 30's Count.

6.6 Instructions for use, handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

M/s. HETERO LABS LIMITED

Unit-V, TSIIC SEZ, Polepally Village,

Jadcherla Mandal, Mahaboob Nagar - 509 301,

Telangana,India.

8. NUMBER'S IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCT

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT