

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Finished pharmaceutical product

INN Name: Abacavir and Lamivudine Tablets USP 600/300mg

Trade Name: Abacavir and Lamivudine Tablets USP 600/300mg

Strength: 600/300 mg

Pharmaceutical form: Tablet

2. Qualitative and quantitative composition

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

For Excipients kindly refer to 6.1 list of excipients

3. Pharmaceutical form

Dosage form: Film coated Tablet

Description: Orange, modified capsule shaped, biconvex, film coated tablets, debossed with 'H' on one side and 'AI' on other side.

4. Clinical particulars

4.1 Therapeutic indications

Abacavir Sulfate and Lamivudine Tablets, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

Additional important information on the use of abacavir sulfate and lamivudine tablets for treatment of HIV-1 infection:

- Abacavir sulfate and lamivudine tablets are one of multiple products containing abacavir. Before starting abacavir sulfate and lamivudine tablets, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- As part of a triple-drug regimen, abacavir sulfate and lamivudine tablets are recommended for use with antiretroviral agents from different pharmacological classes and not with other nucleoside/nucleotide reverse transcriptase inhibitors.

4.2 Posology and method of administration

- A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.
- Abacavir sulfate and lamivudine tablets can be taken with or without food.

Adult Patients

The recommended oral dose of abacavir sulfate and lamivudine tablets for adults is one tablet daily, in combination with other antiretroviral agents.

Dosage Adjustment

Because it is a fixed-dose combination, abacavir sulfate and lamivudine tablets should not be prescribed for:

- patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min,
- patients with hepatic impairment.

Use of lamivudine oral solution or tablets and abacavir sulfate oral solution may be considered.

4.3 Contraindications

Abacavir Sulfate and Lamivudine Tablets are contraindicated in patients with:

- previously demonstrated hypersensitivity to abacavir or to any other component of the product. NEVER restart abacavir sulfate and lamivudine tablets or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status.
- hepatic impairment.

4.4 Special warnings and precautions for use

Hypersensitivity Reaction

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate and lamivudine tablets and other abacavir-containing products. Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of a hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. For HLA-B*5701-positive patients, treatment with an abacavir-containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances when the potential benefit outweighs the risk.

HLA-B*5701-negative patients may develop a hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients. Regardless of HLA-B*5701 status, permanently discontinue abacavir sulfate and lamivudine tablets if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

Signs and Symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

Group 1: Fever

Group 2: Rash

Group3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)

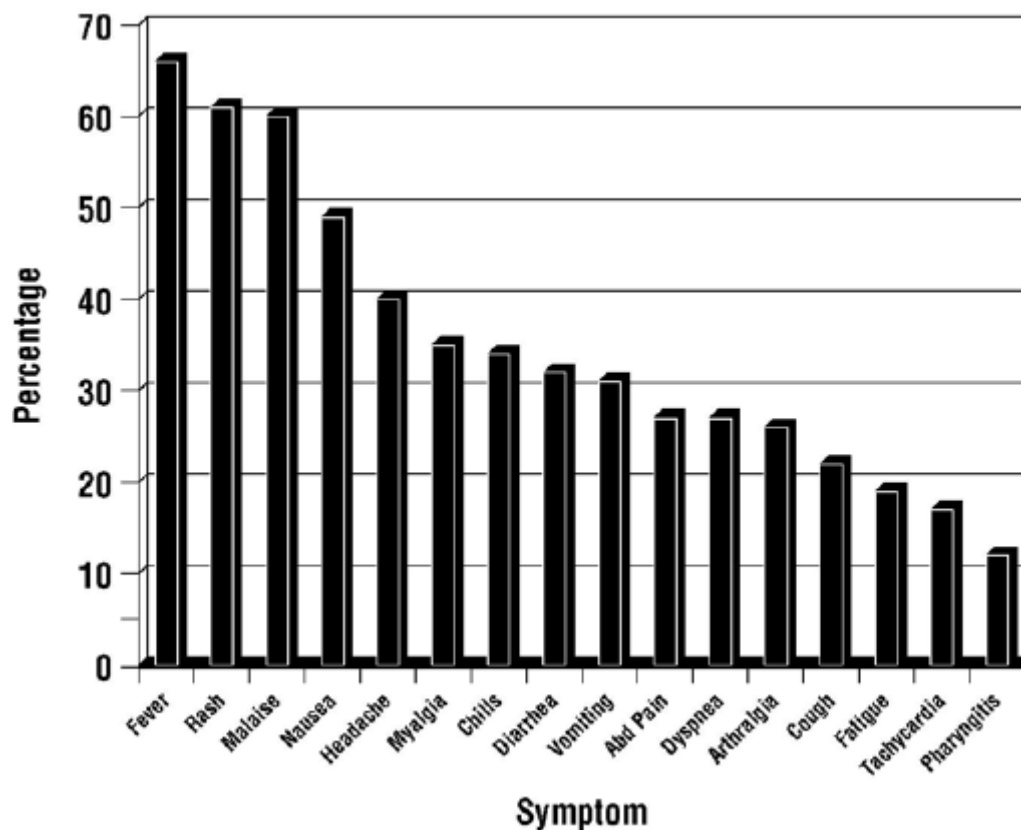
Group 4: Constitutional (including generalized malaise, fatigue, or achiness)

Group 5: Respiratory (including dyspnea, cough, or pharyngitis)

Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 subjects (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. The frequencies of symptoms are shown in below Figure. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first 6 weeks; 95% of subjects reported symptoms from 2 or more of the 5 groups listed above.

Figure: Hypersensitivity-Related Symptoms Reported With $\geq 10\%$ Frequency in Clinical Trials (n = 206 Subjects)



Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. In one trial, 4 subjects (11%) receiving ZIAGEN 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 subjects receiving ZIAGEN 300 mg twice daily.

Physical findings associated with hypersensitivity to abacavir in some subjects include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash. Laboratory abnormalities associated with hypersensitivity to abacavir in some subjects include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity: Discontinue abacavir sulfate and lamivudine tablets as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue abacavir sulfate and lamivudine tablets if hypersensitivity cannot be ruled out, 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).

Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate and lamivudine tablets or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with abacavir sulfate and lamivudine tablets has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of abacavir sulfate and lamivudine tablets or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of abacavir sulfate and lamivudine tablets to ensure that the patient did not have symptoms of a hypersensitivity reaction. If the patient is of unknown HLA-B*5701 status, screening for the allele is recommended prior to reinitiation of abacavir sulfate and lamivudine tablets.

If hypersensitivity cannot be ruled out, DO NOT reintroduce abacavir sulfate and lamivudine tablets or any other abacavir-containing product. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that

a hypersensitivity reaction can occur with reintroduction of abacavir sulfate and lamivudine tablets or any other abacavir-containing product and that reintroduction of abacavir sulfate and lamivudine tablets or introduction of any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

Risk Factor: HLA-B*5701 Allele: Trials have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. CNA106030 (PREDICT-1), a randomized, double-blind trial, evaluated the clinical utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity reaction in abacavir-naïve HIV-1-infected adults (n = 1,650). In this trial, use of pre-therapy screening for the HLA-B*5701 allele and exclusion of subjects with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4% (27/803). Based on this trial, it is estimated that 61% of patients with the HLA-B*5701 allele will develop

a clinically suspected hypersensitivity reaction during the course of abacavir treatment compared with 4% of patients who do not have the HLA-B*5701 allele.

Screening for carriage of the HLA-B*5701 allele is recommended prior to initiating treatment with abacavir. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. For HLA-B*5701-positive patients, initiating or reinitiating treatment with an abacavir-containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances where potential benefit outweighs the risk.

Skin patch testing is used as a research tool and should not be used to aid in the clinical diagnosis of abacavir hypersensitivity.

In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision-making. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

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 alone or in combination, including abacavir sulfate and lamivudine tablets and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering abacavir sulfate and lamivudine tablets to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with abacavir sulfate 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).

Patients With HIV-1 and Hepatitis B Virus Co-Infection

Posttreatment Exacerbations of Hepatitis: In clinical trials in non-HIV-1-infected subjects treated with lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from

lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

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. In non-HIV-1-infected subjects treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see full prescribing information for EPIVIR-HBV[®] [lamivudine] Tablets and Oral Solution for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

Use With Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of abacavir sulfate and lamivudine tablets. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected subjects, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected subjects receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and abacavir sulfate and lamivudine tablets should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of abacavir sulfate 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 >6) (see the complete prescribing information for interferon and ribavirin).

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir sulfate 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.

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.

Myocardial Infarction

In a published prospective, observational, epidemiological trial designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of myocardial infarction (MI).¹ 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).

Use With Other Abacavir-, Lamivudine-, and/or Emtricitabine-Containing Products

Abacavir Sulfate and Lamivudine Tablets contains fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and should not be administered concomitantly with other abacavir-containing and/or lamivudine-containing products, including abacavir sulfate tablets and oral solution, lamivudine tablets and oral solution, EPIVIR-HBV® (lamivudine) tablets and oral solution, lamivudine and zidovudine tablets, or abacavir sulfate, lamivudine, and Zidovudine tablets; or emtricitabine-containing products, including efavirenz/emtricitabine/tenofovir

disoproxil fumarate tablets, emtricitabine capsules and oral solution, TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) tablets, or emtricitabine/rilpivirine/tenofovir disoproxil fumarate tablets.

The complete prescribing information for all agents being considered for use with abacavir sulfate and lamivudine tablets should be consulted before combination therapy with abacavir sulfate and lamivudine tablets is initiated.

4.5 Interaction with other medicinal products and other forms of interaction

- No drug interaction trials have been conducted using abacavir sulfate and lamivudine tablets.

Ethanol

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

Interferon- and Ribavirin-Based Regimens

Lamivudine: Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected subjects, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected subjects receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin.

Methadone

Abacavir: The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy with 600 mg of abacavir sulfate 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.

Trimethoprim/Sulfamethoxazole (TMP/SMX)

Lamivudine: No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

4.6 Pregnancy and lactation

ADDITIONAL INFORMATION ON SPECIFIC POPULATIONS

Pregnancy: *Teratogenic Effects:*

Abacavir Sulfate and Lamivudine Tablets: Pregnancy Category C. There are no adequate and well-controlled studies of abacavir sulfate and lamivudine tablets in pregnant women. Reproduction studies with abacavir and lamivudine have been performed in animals (see Abacavir sulfate and Lamivudine sections below). Abacavir sulfate and lamivudine tablets should be used during

pregnancy only if the potential benefits outweigh the risks.

Abacavir: Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at a half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

Lamivudine: Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryoletality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times those in humans.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to abacavir sulfate and lamivudine tablets or other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Abacavir: Abacavir is secreted into the milk of lactating rats.

Lamivudine: Lamivudine is excreted in human breast milk and into the milk of lactating rats.

Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving abacavir sulfate and lamivudine tablets.

Pediatric Use

Safety and effectiveness of abacavir sulfate and lamivudine tablets in pediatric patients have not been established. Abacavir sulfate and lamivudine tablets are not recommended for use in patients younger than 18 years because it cannot be dose adjusted.

Geriatric Use

Clinical studies of abacavir and lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose

selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients With Impaired Renal Function

Abacavir sulfate and lamivudine tablets are not recommended for patients with impaired renal function (creatinine clearance <50 mL/min) because abacavir sulfate and lamivudine tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted.

Patients With Impaired Hepatic Function

Abacavir sulfate and lamivudine tablets are contraindicated for patients with hepatic impairment because abacavir sulfate and lamivudine tablets are a fixed-dose combination and the dosage of the individual components cannot be adjusted.

4.7 Fertility, pregnancy and lactation

Please refer to 4.6.

4.8 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed.

4.9 Undesirable Effects

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious and sometimes fatal hypersensitivity reaction. In one trial, once-daily dosing of abacavir was associated with more severe hypersensitivity reactions.
- Lactic acidosis and severe hepatomegaly.
- Acute exacerbations of hepatitis B.
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C.
- Immune reconstitution syndrome.
- Fat redistribution.
- Myocardial infarction.

Clinical Trials Experience

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

Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a $\geq 5\%$ frequency during therapy with abacavir sulfate 600 mg once daily or abacavir sulfate 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily, are listed in below Table .

Table. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate

Intensity (Grades 2 to 4, $\geq 5\%$ Frequency) in Therapy-Naive Adults (CNA30021) Through 48 Weeks of Treatment

Adverse Event	Abacavir sulfate 600 mg q.d. plus lamivudine plus Efavirenz (n = 384)	Abacavir sulfate 300 mg b.i.d. plus lamivudine 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 abacavir sulfate 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received abacavir sulfate 300 mg twice daily. Five percent (5%) of subjects receiving abacavir sulfate 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects receiving abacavir sulfate 300 mg twice daily. Two percent (2%) of subjects receiving abacavir sulfate 600 mg once daily had severe diarrhea while none of the subjects receiving abacavir sulfate 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 abacavir sulfate (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily); or zidovudine (300 mg twice daily), lamivudine (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 abacavir sulfate

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.

Post marketing Experience

In addition to adverse reactions reported from clinical trials, the following reactions have been identified during postmarketing use of abacavir, lamivudine, and/or abacavir sulfate and lamivudine tablets. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to abacavir, lamivudine, and/or abacavir sulfate and lamivudine tablets.

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 SULFATE AND LAMIVUDINE TABLETS:

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, post treatment 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.

4.10 Overdose

Abacavir: There is no known antidote for abacavir. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

Lamivudine: One case of an adult ingesting 6 grams of lamivudine was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of Action: *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. The lack of a 3'-OH group in the incorporated nucleotide analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases α , β , and γ .

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. CBV-TP and 3TC-TP are weak inhibitors of cellular DNA polymerases α , β , and γ .

Antiviral Activity: *Abacavir:* The antiviral activity of abacavir against HIV-1 was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to effect viral replication by 50 percent (EC₅₀) ranged from 3.7 to 5.8 μ M (1 μ M = 0.28 mcg/mL) and 0.07 to 1.0 μ M against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was $0.26 \pm 0.18 \mu$ M against 8 clinical isolates. The EC₅₀ values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015 to 1.05 μ M, and against HIV-2 isolates, from 0.024 to 0.49 μ M. Ribavirin (50 μ M) had no effect on the anti-HIV-1 activity of abacavir in cell culture.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC₅₀ values were in the range of 0.003 to 15 μ M (1 μ M = 0.23 mcg/mL). HIV-1 from therapy-naïve subjects with no amino acid substitutions associated with resistance gave median EC₅₀ values of 0.429 μ M (range: 0.200 to 2.007 μ M) from Virco (n = 92 baseline

samples from COLA40263) and 2.35 μM (1.37 to 3.68 μM) from Monogram Biosciences ($n = 135$ baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 μM , and against HIV-2 isolates from 0.003 to 0.120 μM in peripheral blood mononuclear cells. Ribavirin (50 μM) 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. Abacavir/lamivudine had additive to synergistic activity in cell culture in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) emtricitabine, stavudine, tenofovir, zalcitabine, zidovudine; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine, efavirenz, nevirapine; the protease inhibitors (PIs) amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir; or the fusion inhibitor, enfuvirtide. Ribavirin, used in combination with interferon for 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 and have also been obtained from subjects failing abacavir/lamivudine-containing regimens. Genotypic characterization of abacavir/lamivudine-resistant viruses selected in cell culture identified amino acid substitutions M184V/I, K65R, L74V, and Y115F in HIV-1 RT.

Genotypic analysis of isolates selected in cell culture and recovered from abacavir-treated subjects demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in HIV-1 RT contributed to abacavir resistance. Genotypic analysis of isolates selected in cell culture and recovered from lamivudine-treated subjects showed that the resistance was due to a specific amino acid substitution in HIV-1 RT at codon 184 changing the methionine to either isoleucine or valine (M184V/I). In a trial of therapy-naïve adults receiving abacavir sulfate 600 mg once daily ($n = 384$) or 300 mg twice daily ($n = 386$) in a background regimen of lamivudine 300 mg and efavirenz 600 mg once daily (CNA30021), the incidence of virologic failure at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic ($n = 38$) and phenotypic analyses ($n = 35$) of virologic failure isolates from this trial showed that the RT substitutions that emerged during abacavir/lamivudine once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The abacavir- and lamivudine-associated resistance substitution M184V/I was the most commonly observed substitution in virologic failure isolates from subjects receiving abacavir/lamivudine once daily (56%, 10/18) and twice daily (40%, 8/20).

Thirty-nine percent (7/18) of the isolates from subjects who experienced virologic failure in the abacavir once-daily arm had a >2.5 -fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range: 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-

daily arm with a median-fold decrease of 0.92 (range: 0.7 to 13). Fifty-six percent (10/18) of the virologic failure isolates in the once-daily abacavir group compared with 41% (7/17) of the failure isolates in the twice-daily abacavir group had a >2.5-fold decrease in lamivudine susceptibility with median-fold changes of 81 (range: 0.79 to >116) and 1.1 (range: 0.68 to >116) in the once-daily and twice-daily abacavir arms, respectively.

Cross-Resistance: Cross-resistance has been observed among NRTIs. Viruses containing abacavir and lamivudine resistance-associated amino acid substitutions, namely, K65R, L74V, M184V, and Y115F, exhibit cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in cell culture and in subjects. The K65R substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V substitution can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V substitution can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine.

The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the substitutions K65R with or without the M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/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: *Abacavir Sulfate and Lamivudine Tablets:* In a single-dose, 3-way crossover bioavailability trial of 1 abacavir sulfate and lamivudine tablet versus 2 abacavir sulfate Tablets (2 x 300 mg) and 2 lamivudine 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/mL (mean $\pm$ SD) and AUC_{∞} was 11.95 ± 2.51 mcg·hr/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/mL (mean $\pm$ SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg·hr/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).

The steady-state pharmacokinetic properties of the lamivudine 300-mg tablet once daily for 7 days compared with the lamivudine 150-mg tablet twice daily for 7 days were assessed in a crossover trial in 60 healthy subjects. EPIVIR 300 mg once daily resulted in lamivudine exposures that were similar to lamivudine 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

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 below Table.

Table. pharmacokinetic properties^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/hr/kg)	0.80 ± 0.24	n = 6	0.33 ± 0.06	n = 20
Renal clearance (L/hr/kg)	0.007 ± 0.008	n = 6	0.22 ± 0.06	n = 20
Elimination half-life (hr)	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 tablets: Abacavir Sulfate 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.

Special Populations: Renal Impairment: Abacavir Sulfate and Lamivudine Tablets: Because

lamivudine requires dose adjustment in the presence of renal insufficiency, abacavir and lamivudine tablets is not recommended for use in patients with creatinine clearance <50 mL/min.

Hepatic Impairment: Abacavir Sulfate and Lamivudine Tablets: Abacavir Sulfate and Lamivudine Tablets is contraindicated for patients with hepatic impairment because abacavir sulfate and lamivudine tablets is a fixed-dose combination and the dosage of the individual components cannot be adjusted. Abacavir is contraindicated in patients with moderate to severe hepatic impairment, and dose reduction is required in patients with mild hepatic impairment.

Pregnancy: See Use in Specific Populations (8.1).

Abacavir and Lamivudine: No data are available on the pharmacokinetics of abacavir or lamivudine during pregnancy.

Nursing Mothers: See Use in Specific Populations (8.3).

Abacavir: No data are available on the pharmacokinetics of abacavir in nursing mothers.

Lamivudine: Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Pediatric Patients: Abacavir Sulfate and Lamivudine Tablets: The pharmacokinetics of abacavir sulfate and lamivudine tablets in pediatric subjects are under investigation. There are insufficient data at this time to recommend a dose.

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

Gender: Abacavir: A population pharmacokinetic analysis in HIV-1-infected male (n = 304) and female (n = 67) subjects showed no gender differences in abacavir AUC normalized for lean body weight.

Lamivudine: A pharmacokinetic trial in healthy male (n = 12) and female (n = 12) subjects showed no gender differences in lamivudine AUC_∞ normalized for body weight.

Race: Abacavir: There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

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

Drug Interactions: The drug interactions described are based on trials conducted with the individual nucleoside analogues. 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 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.

Methadone: In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir sulfate twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%).

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 q 12 hr).

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.

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

Table . Effect of Coadministered Drugs on Abacavir and lamivudine AUC

Note: ROUTINE DOSE MODIFICATION OF ABACAVIR AND LAMIVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.

Drugs That May Alter Abacavir Blood Concentrations

Coadministered Drug and Dose	Abacavir Dose	n	Abacavir Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Ethanol 0.7 g/kg	Single 600 mg	24	↑41%	90% CI: 35% to 48%	↔
Drugs That May Alter Lamivudine Blood Concentrations					
Coadministered Drug and Dose	Lamivudine Dose	n	Lamivudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Nelfinavir 750 mg q 8 hr x 7 to 10 days	Single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x 5 days	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.

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.

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) those observed in humans at the recommended therapeutic dose for HIV-1 infection.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

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 or lamivudine induced no adverse effects on the mating performance or fertility of male and female rats at doses producing systemic exposure levels approximately 8 or 130 times, respectively, higher than those in humans at the recommended dose based on body surface area comparisons.

Animal Toxicology and/or Pharmacology

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose, USP-NF (Ceolus KG 802), Purified Water, IHS/USP/Ph.Eur, Sodium Starch Glycolate, USP-NF (Primojel), Colloidal Silicon Dioxide, USP-NF (Aerosil 200), Magnesium Stearate, USP-NF (LIGAMED MF-2-V) and Opadry Orange YS-1-13065-A, IHS.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30° C

6.5 Nature and contents of container

HDPE Container pack: 30's count

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder and Manufacturing Site Addresses

Supplier	Manufacturer
Hetero Labs Limited 7-2-A2, Hetero Corporate Industrial Estates Sanath Nagar, Hyderabad-500 018 Telangana, India Tel. No.: +91 40 23704923/ 24/25 Fa:+91 40 23704035, 23813359 Email: contact@heterodrugs.com	Hetero Labs Limited Unit-V, TSIIC Formulation SEZ, Survey No. 411, 425, 435 & 458, Polepally village, Jadcherla Mandal, Mahaboob Nagar (Dist) – 509301, Telangana. India.

8. MARKETING AUTHORIZATION NUMBER

H2015/CTD1811/027

9. DATE OF FIRST REGISTRATION / RENEWAL OF THE REGISTRATION

RENEWAL OF THE REGISTRATION-June 2026

10. DATE OF REVISION OF THE TEXT

Not applicable