National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

[Instructions in this font/colour are from the World Health Organisation Public Assessment Report WHOPAR guidelines.]

[Additional instructions and examples]

{<example text>}

Abacavir Tablets USP
300 mg

1. NAME OF THE MEDICINAL PRODUCT

Abacavir tablets USP 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Abacavir sulfate USP equivalent to Abacavir 300 mg

3. PHARMACEUTICAL FORM

A Peach, film–coated, capsule shaped, biconvex, beveled edge tablet debossed with "M" on one side of the score and "120" on the other side of the score on one side of the tablet and blank on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abacavir Tablets is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children (see sections 4.4 and 5.1).

The demonstration of the benefit of Abacavir Tablets 300 mg is mainly based on results of studies performed with a twice daily regimen, in treatment-naïve adult patients on combination therapy (see section 5.1).

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin (see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

4.2 Posology and method of administration

Abacavir should be prescribed by physicians experienced in the management of HIV infection.

Abacavir can be taken with or without food.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing.

Abacavir is available as an oral solution for use in children over three months of age and weighing less than 14 kg and for those patients for whom the tablets are inappropriate.

Alternatively, for patients who are unable to swallow tablets, the tablet(s) may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see section 5.2).

Adults, adolescents and children (weighing at least 25 kg): The recommended dose of Abacavir tablets is 600 mg daily. This may be administered as either 300 mg (one tablet) twice daily or 600 mg (two tablets) once daily (see sections 4.4 and 5.1).

Children (weighing less than 25 kg):
Dosing according to weight bands is recommended for Abacavir tablets.
Children weighing ≥20 kg to <25 kg: The recommended dose is 450 mg daily. This may be administered as either one 150 mg (one half of a tablet) taken in the morning and 300 mg (one whole tablet) taken in the evening, or 450 mg (one and a half tablets) taken once daily.
Children weighing 14 to <20 kg: The recommended dose is 300 mg daily. This may be administered as either 150 mg (one half of a tablet) twice daily or 300 mg (one whole tablet) once daily.
Children less than three months of age: The clinical experience in children aged less than three months is limited and are insufficient to propose specific dosage recommendations (see section 5.2).
Patients changing from the twice daily dosing regimen to the once daily dosing regimen should take the recommended once daily dose (as described above) approximately 12 hours after the last twice daily dose, and then continue to take the recommended once daily dose (as described above) approximately every 24 hours. When changing back to a twice daily regimen, patients should take the recommended twice daily dose approximately 24 hours after the last once daily dose.

Special populations

Renal impairment: No dosage adjustment of Abacavir is necessary in patients with renal dysfunction. However, Abacavir is not recommended for patients with end-stage renal disease (see section 5.2).

Hepatic impairment: Abacavir is primarily metabolised by the liver. No dose recommendation can be made in patients with mild hepatic impairment. In patients with moderate hepatic impairment, no data are available, therefore the use of abacavir is not recommended unless judged necessary. If abacavir is used in patients with mild or moderate hepatic impairment, then close monitoring is required, and if feasible, monitoring of abacavir plasma levels is recommended (see section 5.2). Abacavir is contraindicated in patients with severe hepatic impairment (see section 4.3 and 4.4).

Elderly: No pharmacokinetic data is currently available in patients over 65 years of age.

4.3 Contraindications

Hypersensitivity to abacavir or to any of the excipients listed in section 6.1. See sections 4.4 and 4.8.
Patients with severe hepatic impairment.

4.4 Special warning and precautions for use

Hypersensitivity Reaction (see also section 4.8):

Abacavir is associated with a risk for hypersensitivity reactions (HSR) (see section4.8) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSRs have been observed with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately.

The risk for abacavir HSR to occur is high for patients who test positive for the HLA-B*5701 allele.

However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.

Therefore the following should be adhered to:

- HLA-B*5701 status must always be documented prior to initiating therapy.
- Abacavir should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen.
- Abacavir must be stopped without delay, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with Abacavir after the onset of hypersensitivity may result in a life-threatening reaction.
- After stopping treatment with Abacavir for reasons of a suspected HSR, Abacavir or any other medicinal product containing abacavir must never be re-initiated.
- Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.
- In order to avoid restarting abacavir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining Abacavir oral solution.

Clinical description of abacavir HSR

Abacavir HSR has been well characterised through clinical studies and during post marketing follow-up. Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, although these reactions may occur at any time during therapy.

Almost all HSR to abacavir include fever and/or rash. Other signs and symptoms that have been observed as part of abacavir HSR are described in detail in section 4.8 (Description of selected

adverse reactions), including respiratory and gastrointestinal symptoms. Importantly, such symptoms may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis.

The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Rarely, patients who have stopped abacavir for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re- initiating abacavir therapy (see Section 4.8 Description of selected adverse reactions). Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

Lactic acidosis: Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

Mitochondrial dysfunction: Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect

current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Pancreatitis: Pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain.

Triple nucleoside therapy: In patients with high viral load (>100,000 copies/ml) the choice of a triple combination with abacavir, lamivudine and zidovudine needs special consideration (see section 5.1).

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when abacavir was combined with tenofovir disoproxil fumarate and lamivudine as a once daily regimen.

Liver disease: The safety and efficacy of abacavir has not been established in patients with significant underlying liver disorders. Abacavir is contraindicated in patients with severe hepatic impairment (see section 4.3). Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

A pharmacokinetic study has been performed in patients with mild hepatic impairment. However, a definitive recommendation on dose reduction is not possible due to substantial variability of drug exposure in this patient population (see section 5.2). The clinical safety data available with abacavir in hepatically impaired patients is very limited. Due to the potential increases in exposure (AUC) in some patients, close monitoring is required. No data are available in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to substantially increase in these patients. Therefore, the use of abacavir in patients with moderate hepatic impairment is not recommended unless judged necessary and requires close monitoring of these patients. For patients with severe hepatic impairment, abacavir is contraindicated.

Patients co-infected with chronic hepatitis B or C virus: Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially

fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.
Caution should be exercised when abacavir and ribavirin are co-administered (see section 4.5).

Renal disease: Abacavir should not be administered to patients with end-stage renal disease (see section 5.2).

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections: Patients receiving abacavir or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission: While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Myocardial Infarction: Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing Abacavir, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

4.5 Interaction with other medicinal products and other forms of interaction

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for P450 mediated interactions with other medicinal products involving abacavir is

low. P450 does not play a major role in the metabolism of abacavir, and abacavir does not inhibit metabolism mediated by CYP 3A4. Abacavir has also been shown *in vitro* not to inhibit CYP 3A4, CYP2C9 or CYP2D6 enzymes at clinically relevant concentrations. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for interactions with antiretroviral PIs and other medicinal products metabolised by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine.

Potent enzymatic inducers such as rifampicin, phenobarbital and phenytoin may via their action on UDP-glucuronyltransferases slightly decrease the plasma concentrations of abacavir.

Ethanol: The metabolism of abacavir is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41%. These findings are not considered clinically significant. Abacavir has no effect on the metabolism of ethanol.

Methadone: In a pharmacokinetic study, co-administration of 600 mg abacavir twice daily with methadone showed a 35% reduction in abacavir C_{max} and a one hour delay in t_{max} but the AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study abacavir increased the mean methadone systemic clearance by 22%. The induction of drug metabolising enzymes cannot therefore be excluded. Patients being treated with methadone and abacavir should be monitored for evidence of withdrawal symptoms indicating under dosing, as occasionally methadone re-titration may be required.

Retinoids: Retinoid compounds are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

Ribavirin: As abacavir and ribavirin share the same phosphorylation pathways, a possible intracellular interaction between these drugs has been postulated, which could lead to a reduction in intracellular phosphorylated metabolites of ribavirin and, as a potential consequence, a reduced chance of sustained virological response (SVR) for Hepatitis C (HCV) in HCV co-infected patients treated with pegylated interferon plus ribavirin. Conflicting clinical findings are reported in literature on co-administration between abacavir and ribavirin. Some data suggest that HIV/HCV co-infected patients receiving abacavir-containing anti-retroviral therapy may be at risk of a lower response rate to pegylated interferon/ribavirin therapy. Caution should be exercised when both drugs are co-administered.

4.6 Fertility, pregnancy and lactation

Pregnancy:
As a general rule, when deciding to use antiretroviral agents for the treatment HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, both animal data as well as clinical experience in pregnant women should be taken into account.
Animal studies have shown toxicity to the developing embryo and foetus in rats, but not in rabbits (see section 5.3). Abacavir has been shown to be carcinogenic in animal models (see section 5.3). Clinical relevance in human of these data is unknown. Placental transfer of abacavir and/or its related metabolites has been shown to occur in human.

In pregnant women, more than 800 outcomes after first trimester exposure and more than 1000 outcomes after second and third trimester exposure indicate no malformative and foetal/neonatal effect of abacavir. The malformative risk is unlikely in humans based on those data.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues (see section 4.4).

Breast-feeding
Abacavir and its metabolites are excreted into the milk of lactating rats. Abacavir is also excreted into human milk. There are no data available on the safety of abacavir when administered to babies less than three months old. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility
Studies in animals showed that abacavir had no effect on fertility (see section 5.3).

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

4.8 Undesirable effects

For many adverse reactions reported, it is unclear whether they are related to Abacavir, to the wide range of medicinal products used in the management of HIV infection or as a result of the disease process. Many of the adverse reactions listed below occur commonly (nausea, vomiting, diarrhoea, fever, lethargy, rash) in patients with abacavir hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity (see section 4.4). Very rarely cases of erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported where abacavir hypersensitivity could not be ruled out. In such cases medicinal products containing abacavir should be permanently discontinued.
Many of the adverse reactions have not been treatment limiting. The following convention has been used for their classification: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1,000 to <1/100), rare (>1/10,000 to <1/1,000) very rare (<1/10,000).

Metabolism and nutrition disorders

Common: anorexia

Nervous system disorders

Common: headache

Gastrointestinal disorders

Common: nausea, vomiting, diarrhoea

Rare: pancreatitis

Skin and subcutaneous tissue disorders

Common: rash (without systemic symptoms)

Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

General disorders and administration site conditions

Common: fever, lethargy, fatigue

Description of Selected Adverse Reactions

Abacavir hypersensitivity reactions

The signs and symptoms of this HSR are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported in at least 10% of patients with a hypersensitivity reaction are in bold text.

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

Skin	**Rash** (usually maculopapular or urticarial)
Gastrointestinal tract	**Nausea, vomiting, diarrhoea, abdominal pain**, mouth ulceration
Respiratory tract	**Dyspnoea, cough**, sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous	**Fever, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry	**Headache**, paraesthesia
Haematological	Lymphopenia
Liver/pancreas	**Elevated liver function tests,** hepatitis, hepatic failure
Musculoskeletal	**Myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology	Elevated creatinine, renal failure

Symptoms related to this HSR worsen with continued therapy and can be life- threatening and in rare instance, have been fatal.

Restarting abacavir following an abacavir HSR results in a prompt return of symptoms within hours. This recurrence of the HSR is usually more severe than on initial presentation, and may include life-threatening hypotension and death. Similar reactions have also occurred infrequently after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (see

above) prior to stopping abacavir; and on very rare occasions have also been seen in patients who have restarted therapy with no preceding symptoms of a HSR (i.e., patients previously considered to be abacavir tolerant).

Lactic acidosis
Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).

Lipodystrophy
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Metabolic abnormalities
CART has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Immune reactivation syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART) an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Changes in laboratory chemistries
In controlled clinical studies laboratory abnormalities related to Abacavir treatment were uncommon, with no differences in incidence observed between Abacavir treated patients and the control arms.

Paediatric population
1206 HIV-infected paediatric patients aged 3 months to 17 years were enrolled in the ARROW Trial (COL105677), 669 of whom received abacavir and lamivudine either once or twice daily (see section 5.1). No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 1200 mg and daily doses up to 1800 mg of Abacavir Tablets have been administered to patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known. If overdose occurs the patient should be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleoside reverse transcriptase inhibitors, ATC Code: J05A F06

Mechanism of action: Abacavir is a NRTI. It is a potent selective inhibitor of HIV-1 and HIV-2. Abacavir is metabolised intracellularly to the active moiety, carbovir 5'- triphosphate (TP). *In vitro* studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, an event which results in chain termination and interruption of the viral replication cycle. The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Resistance

In vitro resistance: Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro*, requiring multiple mutations for a clinically relevant increase in EC_{50} over wild-type virus.

In vivo resistance (Therapy naïve patients): Isolates from most patients experiencing virological failure with a regimen containing abacavir in pivotal clinical trials showed either no NRTI-related changes from baseline (45%) or only M184V or M184I selection (45%). The overall selection frequency for M184V or M184I was high (54%), and less common was the selection of L74V (5%), K65R (1%) and Y115F (1%). The inclusion of zidovudine in the regimen has been found to reduce the frequency of L74V and K65R selection in the presence of abacavir (with zidovudine: 0/40, without zidovudine: 15/192, 8%).

Therapy	Abacavir + FDC Lamivudine+Zidovudine	Abacavir + lamivudine + NNRTI	Abacavir + lamivudine + PI (or PI/ritonavir)	Total
Number of Subjects	282	1094	909	2285
Number of Virological Failures	43	90	158	306
Number of On-Therapy	40 (100%)	51 (100%)[1]	141 (100%)	232 (100%)

Genotypes				
K65R	0	1 (2%)	2 (1%)	3 (1%)
L74V	0	9 (18%)	3 (2%)	12 (5%)
Y115F	0	2 (4%)	0	2 (1%)
M184V/I	34 (85%)	22 (43%)	70 (50%)	126 (54%)
TAMs[2]	3 (8%)	2 (4%)	4 (3%)	9 (4%)

[1]Includes three non-virological failures and four unconfirmed virological failures.
[2]Number of subjects with ≥1 Thymidine Analogue Mutations (TAMs).

TAMs might be selected when thymidine analogs are associated with abacavir. In a meta-analysis of six clinical trials, TAMs were not selected by regimens containing abacavir without zidovudine (0/127), but were selected by regimens containing abacavir and the thymidine analogue zidovudine (22/86, 26%).

In vivo resistance (Therapy experienced patients): Clinically significant reduction of susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors. In a meta-analysis of five clinical trials where abacavir was added to intensify therapy, of 166 subjects, 123 (74%) had M184V/I, 50 (30%) had T215Y/F, 45 (27%) had M41L, 30 (18%) had K70R and 25 (15%) had D67N. K65R was absent and L74V and Y115F were uncommon (≤3%). Logistic regression modelling of the predictive value for genotype (adjusted for baseline plasma HIV-1 RNA [vRNA], CD4+ cell count, number and duration of prior antiretroviral therapies), showed that the presence of 3 or more NRTI resistance-associated mutations was associated with reduced response at Week 4 (p=0.015) or 4 or more mutations at median Week 24 (p≤0.012). In addition, the 69 insertion complex or the Q151M mutation, usually found in combination with A62V, V75I, F77L and F116Y, cause a high level of resistance to abacavir.

Baseline Reverse Transcriptase Mutation	**Week 4 (n = 166)**		
	n	**Median Change vRNA (log_{10} c/mL)**	**Percent with <400 copies/mL vRNA**
None	15	-0.96	40%
M184V alone	75	-0.74	64%
Any one NRTI mutation	82	-0.72	65%
Any two NRTI associated mutations	22	-0.82	32%
Any three NRTI associated mutations	19	-0.30	5%
Four or more NRTI associated mutations	28	-0.07	11%

Phenotypic resistance and cross-resistance: Phenotypic resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple TAMs. Phenotypic cross-resistance to other NRTIs with M184V or M184I mutation alone is limited. Zidovudine, didanosine, stavudine and tenofovir maintain their antiretroviral activities against such HIV-1 variants. The presence of M184V with K65R does give rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between

abacavir, didanosine and lamivudine. The presence of M184V with Y115F gives rise to cross-resistance between abacavir and lamivudine. Appropriate use of abacavir can be guided using currently recommended resistance algorithms.

Cross-resistance between abacavir and antiretrovirals from other classes (e.g. PIs or NNRTIs) is unlikely.

Clinical efficacy and safety: The demonstration of the benefit of abacavir is mainly based on results of studies performed in adult treatment-naïve patients using a regimen of abacavir 300 mg twice daily in combination with zidovudine and lamivudine.

Twice daily (300 mg) administration:

Therapy naïve adults

In adults treated with abacavir in combination with lamivudine and zidovudine the proportion of patients with undetectable viral load (<400 copies/ml) was approximately 70% (intention to treat analysis at 48 weeks) with corresponding rise in CD4 cells.

One randomised, double blind, placebo controlled clinical study in adults has compared the combination of abacavir, lamivudine and zidovudine to the combination of indinavir, lamivudine and zidovudine. Due to the high proportion of premature discontinuation (42% of patients discontinued randomised treatment by week 48), no definitive conclusion can be drawn regarding the equivalence between the treatment regimens at week 48. Although a similar antiviral effect was observed between the abacavir and indinavir containing regimens in terms of proportion of patients with undetectable viral load (≤ 400 copies/ml; intention to treat analysis (ITT), 47% versus 49%; as treated analysis (AT), 86% versus 94% for abacavir and indinavir combinations respectively), results favoured the indinavir combination, particularly in the subset of patients with high viral load >100,000 copies/ml at baseline; ITT, 46% versus 55%; AT, 84% versus 93% for abacavir and indinavir respectively).

In a multicentre, double-blind, controlled study (CNA30024), 654 HIV-infected, antiretroviral therapy-naïve patients were randomised to receive either abacavir 300 mg twice daily or zidovudine 300 mg twice daily, both in combination with lamivudine 150 mg twice daily and efavirenz 600 mg once daily. The duration of double-blind treatment was at least 48 weeks. In the intent-to-treat (ITT) population, 70% of patients in the abacavir group, compared to 69% of patients in the zidovudine group, achieved a virologic response of plasma HIV-1 RNA ≤50 copies/ml by Week 48 (point estimate for treatment difference: 0.8, 95% CI -6.3, 7.9). In the as treated (AT) analysis the difference between both treatment arms was more noticeable (88% of patients in the abacavir group, compared to 95% of patients in the zidovudine group (point estimate for treatment difference: -6.8, 95% CI -11.8; -1.7). However, both analyses were compatible with a conclusion of non-inferiority between both treatment arms.

ACTG5095 was a randomised (1:1:1), double-blind, placebo-controlled trial performed in 1147 antiretroviral naïve HIV-1 infected adults, comparing 3 regimens: zidovudine (ZDV), lamivudine (3TC), abacavir (ABC), efavirenz (EFV) vs ZDV/3TC/EFV vs ZDV/3TC/ABC. After a median follow-up of 32 weeks, the tritherapy with the three nucleosides ZDV/3TC/ABC was shown to be virologically inferior to the two other arms regardless of baseline viral load (< or > 100 000 copies/ml) with 26%

of subjects on the ZDV/3TC/ABC arm, 16% on the ZDV/3TC/EFV arm and 13% on the 4 drug arm categorised as having virological failure (HIV RNA >200 copies/ml). At week 48 the proportion of subjects with HIV RNA <50 copies/ml were 63%, 80% and 86% for the ZDV/3TC/ABC, ZDV/3TC/EFV and ZDV/3TC/ABC/EFV arms, respectively. The study Data Safety Monitoring Board stopped the ZDV/3TC/ABC arm at this time based on the higher proportion of patients with virologic failure. The remaining arms were continued in a blinded fashion. After a median follow-up of 144 weeks, 25% of subjects on the ZDV/3TC/ABC/EFV arm and 26% on the ZDV/3TC/EFV arm were categorised as having virological failure. There was no significant difference in the time to first virologic failure (p=0.73, log-rank test) between the 2 arms. In this study, addition of ABC to ZDV/3TC/EFV did not significantly improve efficacy.

		ZDV/3TC/ABC	ZDV/3TC/EFV	ZDV/3TC/ABC/EFV
Virologic failure (HIV RNA >200 copies/ml)	32 weeks	26%	16%	13%
	144 weeks	-	26%	25%
Virologic success (48 weeks HIV RNA < 50 copies/ml)		63%	80%	86%

Therapy experienced adults: In adults moderately exposed to antiretroviral therapy the addition of abacavir to combination antiretroviral therapy provided modest benefits in reducing viral load (median change 0.44 $\log_{10}$ copies/ml at 16 weeks).

In heavily NRTI pretreated patients the efficacy of abacavir is very low. The degree of benefit as part of a new combination regimen will depend on the nature and duration of prior therapy which may have selected for HIV-1 variants with cross-resistance to abacavir.

Once daily (600 mg) administration:

Therapy naïve adults

The once daily regimen of abacavir is supported by a 48 weeks multi-centre, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. These were primarily asymptomatic HIV infected patients (CDC stage A). They were randomised to receive either abacavir 600 mg once daily or 300 mg twice daily, in combination with efavirenz and lamivudine given once daily. Similar clinical success (point estimate for treatment difference -1.7, 95% CI -8.4, 4.9) was observed for both regimens. From these results, it can be concluded with 95% confidence that the true difference is no greater than 8.4% in favour of the twice daily regimen. This potential difference is sufficiently small to draw an overall conclusion of non-inferiority of abacavir once daily over abacavir twice daily.

There was a low, similar overall incidence of virologic failure (viral load>50 copies/ml) in both the once and twice daily treatment groups (10% and 8% respectively). In the small sample size for genotypic analysis, there was a trend toward a higher rate of NRTI-associated mutations in the once daily versus the twice daily abacavir regimens. No firm conclusion could be drawn due to the limited data derived from this study. Long term data with abacavir used as a once daily regimen (beyond 48 weeks) are currently limited.

Therapy experienced adults: In study CAL30001, 182 treatment-experienced patients with virologic failure were randomised and received treatment with either the fixed-dose combination of abacavir/lamivudine (FDC) once daily or abacavir 300 mg twice daily plus lamivudine 300 mg once daily, both in combination with tenofovir and a PI or an NNRTI for 48 weeks. Results indicate that the FDC group was non-inferior to the abacavir twice daily group, based on similar reductions in HIV-1 RNA as measured by average area under the curve minus baseline (AAUCMB, -1.65 $\log_{10}$ copies/ml versus -1.83 $\log_{10}$ copies/ml respectively, 95% CI -0.13, 0.38). Proportions with HIV-1 RNA < 50 copies/ml (50% versus 47%) and < 400 copies/ml (54% versus 57%) were also similar in each group (ITT population). However, as there were only moderately experienced patients included in this study with an imbalance in baseline viral load between the arms, these results should be interpreted with caution.

In study ESS30008, 260 patients with virologic suppression on a first line therapy regimen containing abacavir 300 mg plus lamivudine 150 mg, both given twice daily and a PI or NNRTI, were randomised to continue this regimen or switch to abacavir/lamivudine FDC plus a PI or NNRTI for 48 weeks. Results indicate that the FDC group was associated with a similar virologic outcome (non-inferior) compared to the abacavir plus lamivudine group, based on proportions of subjects with HIV-1 RNA < 50 copies/ml (90% and 85% respectively, 95% CI -2.7, 13.5).

Additional information:
The safety and efficacy of Abacavir Tablets in a number of different multidrug combination regimens is still not completely assessed (particularly in combination with NNRTIs).
Abacavir penetrates the cerebrospinal fluid (CSF), and has been shown to reduce HIV-1 RNA levels in the CSF. However, no effects on neuropsychological performance were seen when it was administered to patients with AIDS dementia complex.

Paediatric population:
A randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. Of note, from this study clinical data were not available for children under one year old. The results are summarised in the table below:

Virological Response Based on Plasma HIV-1 RNA less than 80 copies/mL at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)

	Twice Daily N (%)	**Once Daily N (%)**
Week 0 (After ≥36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/mL	250/331 (76)	237/335 (71)

Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA <80 c/mL	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA <80 c/mL	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

The abacavir + lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200c/mL, <400c/mL, <1000c/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.
In a separate study comparing the unblinded NRTI combinations (with or without blinded nelfinavir) in children, a greater proportion treated with abacavir and lamivudine (71%) or abacavir and zidovudine (60%) had HIV-1 RNA ?400 copies/mL at 48 weeks, compared with those treated with lamivudine and zidovudine (47%)[p=0.09, intention to treat analysis]. Similarly, greater proportions of children treated with the abacavir containing combinations had HIV-1 RNA ?50 copies/mL at 48 weeks (53%, 42% and 28% respectively, p=0.07).
In a pharmacokinetic study (PENTA 15), four virologically controlled subjects less than 12 months of age switched from abacavir plus lamivudine oral solution twice daily to a once daily regimen. Three subjects had undetectable viral load and one had plasmatic HIV-RNA of 900 copies/mL at Week 48. No safety concerns were observed in these subjects.

5.2 Pharmacokinetic properties

Absorption: Abacavir is rapidly and well absorbed following oral administration. The absolute bioavailability of oral abacavir in adults is about 83%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations of abacavir is about 1.5 hours for the tablet formulation and about 1.0 hour for the solution formulation.

At therapeutic dosages a dosage of 300 mg twice daily, the mean (CV) steady state C_{max} and C_{min} of abacavir are approximately 3.00 µg/ml (30%) and 0.01 µg/ml (99%), respectively. The mean (CV) AUC over a dosing interval of 12 hours was 6.02 µg.h/ml (29%), equivalent to a daily AUC of approximately 12.0 µg.h/ml. The C_{max} value for the oral solution is slightly higher than the tablet. After a 600 mg abacavir tablet dose, the mean (CV) abacavir C_{max} was approximately 4.26 µg/ml (28%) and the mean AUC was 11.95 µg.h/ml (21%).

Food delayed absorption and decreased C_{max} but did not affect overall plasma concentrations (AUC). Therefore Abacavir tablets can be taken with or without food.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data, assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Distribution*:* Following intravenous administration, the apparent volume of distribution was about 0.8 l/kg, indicating that abacavir penetrates freely into body tissues.

Studies in HIV infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44%. The observed values of the peak concentrations are 9 fold greater than the IC_{50} of abacavir of 0.08 µg/ml or 0.26 µM when abacavir is given at 600 mg twice daily**.**

Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (~49%) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for interactions with other medicinal products through plasma protein binding displacement.

Biotransformation: Abacavir is primarily metabolised by the liver with approximately 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. The metabolites are excreted in the urine.

Elimination: The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant accumulation of abacavir. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83% of the administered abacavir dose in the urine. The remainder is eliminated in the faeces.

Intracellular pharmacokinetics

In a study of 20 HIV-infected patients receiving abacavir 300 mg twice daily, with only one 300 mg dose taken prior to the 24 hour sampling period, the geometric mean terminal carbovir-TP intracellular half-life at steady-state was 20.6 hours, compared to the geometric mean abacavir plasma half-life in this study of 2.6 hours. In a crossover study in 27 HIV-infected patients, intracellular carbovir-TP exposures were higher for the abacavir 600 mg once daily regimen ($AUC_{24,ss}$ + 32%, $C_{max24,ss}$ + 99% and C_{trough} + 18 %) compared to the 300 mg twice daily regimen. Overall, these data support the use of abacavir 600 mg once daily for the treatment of HIV infected patients. Additionally, the efficacy and safety of abacavir given once daily has been demonstrated in a pivotal clinical study (CNA30021- See section 5.1 Clinical experience).

Special populations

Hepatically impaired: Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose. The results showed that there was a mean increase of 1.89 fold [1.32; 2.70] in the abacavir AUC, and 1.58 [1.22; 2.04] fold in the elimination half-life. No recommendation on dosage reduction is possible in patients with mild hepatic impairment due to the substantial variability of abacavir exposure.

Renally impaired: Abacavir is primarily metabolised by the liver with approximately 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Therefore no dosage reduction is required in patients with renal impairment. Based on limited experience Abacavir tablets should be avoided in patients with end-stage renal disease.

Paediatric population: According to clinical trials performed in children abacavir is rapidly and well absorbed from an oral solution administered to children. Plasma abacavir exposure has been shown to be the same for both formulations when administered at the same dose. Children receiving abacavir oral solution according to the recommended dosage regimen achieve plasma abacavir exposure similar to adults. Children receiving abacavir oral tablets according to the recommended dosage regimen achieve higher plasma abacavir exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation.
There are insufficient safety data to recommend the use of Abacavir tablets in infants less than three months old. The limited data available indicate that a dose of 2 mg/kg in neonates less than 30 days old provides similar or greater AUCs, compared to the 8 mg/kg dose administered to older children.

Pharmacokinetic data were derived from 3 pharmacokinetic studies (PENTA 13, PENTA 15 and ARROW PK substudy) enrolling children under 12 years of age. The data are displayed in the table below:

Summary of Stead-State Plasma Abacavir AUC (0-24) (µg.h/mL) and Statistical Comparisons for Once and Twice-Daily Oral Administration Across Studies

Study	Age Group	Abacavir 16 mg/kg Once-Daily Dosing Geometric Mean (95% CI)	Abacavir 8 mg/kg Twice-Daily Dosing Geometric Mean (95% CI)	Once-Versus Twice-Daily Comparison GLS Mean Ratio (90% CI)
ARROW PK Substudy Part 1	3 to 12 years (N=36)	15.3 (13.3-17.5)	15.6 (13.7-17.8)	0.98 (0.89, 1.08)
PENTA 13	2 to 12 years (N=14)	13.4 (11.8-15.2)	9.91 (8.3-11.9)	1.35 (1.19-1.54)
PENTA 15	3 to 36 months (N=18)	11.6 (9.89-13.5)	10.9 (8.9-13.2)	1.07 (0.92-1.23)

In PENTA 15 study, the geometric mean plasma abacavir AUC(0-24) (95% CI) of the four subjects under 12 months of age who switch from a twice daily to a once daily regimen (see section 5.1) are 15.9 (8.86, 28.5) µg.h/mL in the once-daily dosing and 12.7 (6.52, 24.6) µg.h/mL in the twice-daily dosing.

Elderly: The pharmacokinetics of abacavir have not been studied in patients over 65 years of age.

5.3 Preclinical safety data

Abacavir was not mutagenic in bacterial tests but showed activity *in vitro* in the human lymphocyte chromosome aberration assay, the mouse lymphoma assay, and the *in vivo* micronucleus test. This is consistent with the known activity of other nucleoside analogues. These results indicate that abacavir has a weak potential to cause chromosomal damage both *in vitro* and *in vivo* at high test concentrations.

Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in rats in the thyroid gland of males and the liver, urinary bladder, lymph nodes and the subcutis of females.

The majority of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg in mice. The systemic exposure at the no effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy. While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

In pre-clinical toxicology studies, abacavir treatment was shown to increase liver weights in rats and monkeys. The clinical relevance of this is unknown. There is no evidence from clinical studies that abacavir is hepatotoxic. Additionally, auto induction of abacavir metabolism or induction of the metabolism of other medicinal products hepatically metabolised has not been observed in man.

Mild myocardial degeneration in the heart of mice and rats was observed following administration of abacavir for two 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.

In reproductive toxicity studies, embryo and foetal toxicity have been observed in rats but not in rabbits. These findings included decreased foetal body weight, foetal oedema, and an increase in skeletal variations/malformations, early intra-uterine deaths and still births. No conclusion can be drawn with regard to the teratogenic potential of abacavir because of this embryo-foetal toxicity.

A fertility study in the rat has shown that abacavir had no effect on male or female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose, Colloidal anhydrous silica, Magnesium Stearate, Sodium Starch Glycolate,

Film coating

Hypromellose, Titanium dioxide, Polyethylene glycol 400, Iron oxide yellow, Iron oxide red.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 Months

6.4 Special precautions for storage
Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container
HDPE bottle of 60's.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

Marketing Authorization Holder

HEALTHLINE LIMITED

Reference:
SmPC of Ziagen Tablets (Glaxo SmithKline, UK)

Mfd by:
Mylan Laboratories Limited
F-4 & F-12, MIDC, Malegaon, Sinnar,
Nashik - 422 113, Maharashtra, INDIA

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