Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Abacavir Oral Solution USP 20 mg/mL

2. Qualitative and quantitative composition

Each mL contains Abacavir Sulfate USP equivalent to Abacavir 20 mg.

Excipients of known effect: sorbitol, methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Oral solution.
The solution is a clear to opalescent yellowish, aqueous solution with strawberry-banana flavour. Abacavir oral solution comes in bottles of 240 ml.

4. Clinical particulars

4.1 Therapeutic indications

Abacavir Oral Solution is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in children (see also section 4.4 concerning Abacavir oral solution use and HLA-B*5701 screening).
This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and lactation, to allow full access to all relevant information.

4.2 Posology and method of administration

Therapy should be prescribed by a physician experienced in the management of HIV infection.
6 weeks of age and above: **Children**
Amount of oral solution (ml) by weight band to be taken twice daily (approximately 12 hours apart):

Weight band	Amount of solution (twice daily)
3 - 5.9 kg	3 ml
6 - 9.9 kg	4 ml
10 - 13.9 kg	6 ml

Children weighing 14 kg or more, adolescents and adults:
For these patient groups other formulations with higher amounts of the active substance are available.
Abacavir oral solution can be taken with or without food (see section 6.6 for instructions for use).
Renal impairment: No dose adjustment is necessary in patients with renal impairment (see section 5.2).
Hepatic impairment: No data are available in patients with moderate hepatic impairment, therefore the use of Abacavir oral solution is not

recommended unless judged necessary. In patients with mild and moderate hepatic impairment close monitoring is required (see sections 4.4 and 5.2). Abacavir oral solution is contraindicated in patients with severe hepatic impairment (see section 4.3).

4.3 Contraindications

Abacavir oral solution is contraindicated in patients:
- with known hypersensitivity to abacavir or to any of the excipients (for abacavir hypersensitivity, see section 4.4 and section 4.8);
- with severe hepatic impairment.

4.4 Special warnings and precautions for use

Hypersensitivity reaction

In a clinical study, 3.4% of subjects with a negative HLA-B*5701 status receiving abacavir developed a hypersensitivity reaction.

Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. In a prospective study, use of pre-therapy screening for the HLA-B*5701 allele and subsequently avoiding abacavir in patients with this allele significantly reduced the incidence of abacavir hypersensitivity reactions. In populations similar to that enrolled in this study, it is estimated that 48% to 61% of patients with the HLA-B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0% to 4% of patients who do not have this allele. These results are consistent with those of prior retrospective studies.

As a consequence, screening for carriage of the HLA-B*5701 allele is recommended in any HIV-infected patient without prior exposure to abacavir. Overall frequencies of hypersensitivity reactions have been reported to vary across different racial groups (e.g. lower frequency in African Americans and black Africans). Nevertheless, screening for HLA-B*5701 should be performed in any patient irrespective of race. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see "Management after an interruption of abacavir therapy"). Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

Only in the rare case where no other therapeutic option is available based on the treatment history, drug tolerability and resistance testing, the use of abacavir might be considered. However, such patients must be very closely monitored for signs and symptoms of a hypersensitivity reaction.

In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making. Therefore, 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. This is due to the potential for a severe or even fatal reaction.

Skin patch testing is not a tool for prospectively evaluating abacavir tolerability in abacavir-naïve patients. It has not been thoroughly evaluated for use in routine clinical management of patients, and should not be used as a substitute for genotyping for HLA-B*5701.

Clinical Description

Hypersensitivity reactions are characterised by the appearance of symptoms indicating multi-organ system involvement. Almost all hypersensitivity reactions will have fever and/or rash as part of the syndrome.

Other signs and symptoms may include respiratory signs and symptoms such as dyspnoea, sore throat, cough and abnormal chest x-ray findings (predominantly infiltrates, which can be localised), gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, and may lead to misdiagnosis of hypersensitivity as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis. Other frequently observed signs or symptoms of the hypersensitivity reaction may include lethargy or malaise and musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia).

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

Clinical Management

Hypersensitivity reaction symptoms usually appear within the first six weeks of initiation of treatment with abacavir, although these reactions may occur at any time during therapy. Patients should be monitored closely, especially during the first two months of treatment with abacavir, with consultation every two weeks.

Patients who are diagnosed with a hypersensitivity reaction whilst on therapy MUST discontinue Abacavir oral solution immediately.

Abacavir oral solution or any other abacavir-containing product MUST NEVER be restarted in patients who have stopped therapy due to a hypersensitivity reaction. Restarting abacavir following a hypersensitivity reaction results 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.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, abacavir must be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications).

Special care is needed for those patients simultaneously starting treatment with abacavir and other medicinal products known to induce skin toxicity (such as non-nucleoside reverse transcriptase inhibitors - NNRTIs). This is because it is difficult to differentiate between rashes induced by these products and abacavir related hypersensitivity reactions.

Management after an interruption of abacavir therapy

If therapy with abacavir has been discontinued for any reason and restarting therapy is under consideration, the reason for discontinuation must be established to assess whether the patient had any symptoms of a hypersensitivity reaction. If a hypersensitivity reaction cannot be ruled out, abacavir must not be restarted. Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting

abacavir in patients who had only one of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping abacavir. The most common isolated symptom of a hypersensitivity reaction was a skin rash. Since on very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy, and who had no preceding symptoms, the possibility of a hypersensitivity reaction should be borne in mind and these patients should be closely monitored for its signs and symptoms.
Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Re-initiation of abacavir in such patients who test positive for the HLA-B*5701 allele is not recommended and should be considered only under exceptional circumstances where the potential benefit outweighs the risk and with close medical supervision.
Essential patient information
Prescribers must ensure that patients' caregivers are fully informed regarding the following information on the hypersensitivity reaction:
- patients' caregivers must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death.
- caregivers of patients developing signs or symptoms possibly linked to a hypersensitivity reaction MUST CONTACT the patient's doctor IMMEDIATELY.
- the caregivers of patients who are hypersensitive to abacavir should be reminded that the patients must never take Abacavir oral solution or any other medicinal product containing abacavir.
- in order to avoid restarting abacavir, the caregivers of patients who have experienced a hypersensitivity reaction should be asked to return the remaining abacavir-containing product to the pharmacy.
- the caregivers of patients who have stopped abacavir for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact the patient's doctor before restarting.
- each patient's caregiver should be reminded to read the Patient Information Leaflet included in the Abacavir oral solution pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.
Lactic acidosis: Lactic acidosis is a rare but severe, potentially life-threatening complication associated with the use of nucleoside reverse transcriptase inhibitors. Several other agents of this class are known to cause lactic acidosis. Whereas this has not clearly been shown for abacavir, an association cannot be excluded. Lactic acidosis may occur after a few to several months of nucleoside reverse transcriptase inhibitor (NRTI) treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity. Patients

co-infected with hepatitis C and treated with alpha interferon and ribavirin may be at higher risk.
Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs. Lactic acid levels > 10 mmol/l usually are a medical emergency.
Mitochondrial dysfunction: NRTIs 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 postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). 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-infected patients. Whereas for some other antiretrovirals there is considerable evidence for this adverse reaction, the evidence for abacavir as a causative agent is weak; indeed switching from a thymidine analogue to abacavir has been shown to increase limb fat in patients with lipoatrophy. A higher risk of lipodystrophy has been associated e.g. with older age of the patient, longer duration of antiretroviral therapy and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered (see section 4.8).
Pancreatitis: pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain. Treatment with Abacavir oral solution should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur (see section 4.8).
Myocardial infarction: published prospective, observational, epidemiological studies in adults have shown an association between myocardial infarction and the use of abacavir. A pooled analysis of 26 randomised controlled trials with over 5000 patients assigned to abacavir found no association between abacavir use and MI risk. There is no established biological mechanism to explain a potential increase in risk. Hence, the available data is overall inconclusive.
When prescribing Abacavir oral solution, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Combination therapy with abacavir: Abacavir should only be used in combination with zidovudine and lamivudine in the treatment of antiretroviral naïve patients in situations when a regimen based on a protease inhibitor (PI) or NNRTI cannot be used. Abacavir should not be used as part of a triple combination regimen including tenofovir.
Liver disease: the safety and efficacy of abacavir has not been established in patients with significant underlying liver disorders. Clinical safety data available with abacavir in hepatically impaired patients is very limited and pharmacokinetic data show substantial variability of drug exposure in this population. Therefore, close safety 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 (see section 4.3).
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 events. 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).
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.
Immune Reactivation Syndrome: in HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be 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 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 (adult) patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. 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: treatment with Abacavir oral solution has not been shown to eliminate the risk of transmission of HIV infection by sexual contact or by blood transfer. Patients should continue to use appropriate precautions to prevent transmission of HIV.
Excipients: Abacavir oral solution contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).
Abacavir oral solution contains sorbitol. Patients with rare hereditary problems of fructose intolerance may experience symptoms of intolerance.

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.
Potent enzymatic inducers such as rifampicin, phenobarbital and phenytoin may, via their effects on UDP-glucuronyl transferases, decrease the plasma concentrations of abacavir. The magnitude of any such effects, as well as their possible clinical consequences, are unknown.
Ethanol: the metabolism of abacavir is altered by concomitant intake of 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: coadministration of abacavir increased the mean methadone systemic clearance by 22% possibly due to induction of drug metabolising enzymes. Patients being treated with methadone and abacavir should be monitored for evidence of withdrawal symptoms and methadone doses should be adjusted accordingly.
Retinoids: retinoid compounds are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.
Lopinavir and ritonavir: in a pharmacokinetic study, coadministration of 600 mg abacavir once daily with lopinavir/ritonavir 400/100 mg twice daily led to a 32% decrease in abacavir plasma AUC. The clinical relevance of this is unknown.
Tipranavir and ritonavir: co-administration of abacavir and tipranavir + ritonavir decreased the plasma AUC of abacavir by approximately 40%. The clinical relevance is unknown.
Ribavirin: though evidence is conflicting, co-administration of abacavir and ribavirin has been associated with a lower response rate to ribavirin-containing hepatitis C treatment. If possible, abacavir should be substituted by another NRTI (e.g. tenofovir) when co-treating with ribavirin.

4.6 Fertility, pregnancy and lactation

Pregnancy

No increased risk of birth defects has been reported for abacavir. However, risks to the fetus cannot be ruled out. Abacavir oral solution should not be initiated during pregnancy, due to the risk of a hypersensitivity reaction to abacavir. If a patient becomes pregnant during treatment with Abacavir oral solution, however, this Abacavir containing therapy may be continued if the benefit is considered to outweigh the risk.

Breastfeeding

Abacavir is probably excreted into the breast milk of lactating mothers. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility

A fertility study in the rat has shown that abacavir had no effect on male or female fertility (see section 5.3). No data are available on the effect of abacavir on human fertility.

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. Nevertheless, the clinical status of the patient and the adverse reaction profile of Abacavir oral solution should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Abacavir hypersensitivity (see also section 4.4):

In clinical studies, approximately 3.4% of subjects with a negative HLA-B*5701 status receiving abacavir developed a hypersensitivity reaction. Some of these hypersensitivity reactions were life-threatening and resulted in fatal outcome despite taking precautions (see also section 4.4). This reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

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.

The signs and symptoms of this hypersensitivity reaction 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.

System	**Signs and symptoms**
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.

Rash (81% vs 67% respectively) and **gastrointestinal manifestations** (70% vs 54% respectively) were **more frequently** reported in **children** compared to adults.

Some patients with hypersensitivity reactions were initially thought to have gastroenteritis, respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. This delay in diagnosis of hypersensitivity has resulted in abacavir being continued or re-introduced, leading to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reaction should always be considered for patients that have recently initiated abacavir treatment and that present with symptoms of these diseases.

Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir. Close medical supervision is necessary during the first two months, with consultations every two weeks.

It has been suggested that intermittent therapy may increase the risk of developing clinically significant hypersensitivity reactions. Consequently, patients should be advised of the importance of taking abacavir regularly.

Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction was usually more severe than on initial presentation, and may include life-threatening hypotension and death.

Regardless of their HLA-B*5701 status, patients who develop this hypersensitivity reaction must discontinue Abacavir oral solution and must never be rechallenged with Abacavir oral solution or any other medicinal product containing abacavir.

Hypersensitivity reactions have occurred after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity prior to stopping abacavir. The most common isolated symptom of a hypersensitivity reaction was a skin rash.

On very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy and who had no preceding symptoms of a hypersensitivity reaction.

In both cases, if a decision is made to restart abacavir this must be done in a setting where medical assistance is readily available.

For many of the other adverse reactions reported, it is unclear whether they are related to abacavir, to other medicinal products used in the management of HIV infection, or are a result of the disease process.

Many of those 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 a hypersensitivity reaction. If abacavir has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart therapy with an abacavir-containing product, the possibility of a hypersensitivity reaction should be borne in mind and these patients should be closely monitored for signs and symptoms (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.
The following convention has been used for the classification of adverse reactions: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (frequency cannot be estimated from the available data).

System Organ Class	**Frequency**	**Adverse Reaction(s)**
Metabolism and nutrition disorders	Common	Anorexia
Metabolism and nutrition disorders	Not known	Lipodystrophy, hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia, lactic acidosis, usually associated with severe hepatomegaly and hepatic steatosis
Musculoskeletal and connective tissue disorders	Not known	Osteonecrosis
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Nausea, vomiting, diarrhoea
Gastrointestinal disorders	Rare	Pancreatitis
Skin and subcutaneous tissue disorders	Common	Rash
Skin and subcutaneous tissue disorders	Very rare	Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
General disorders and administration site conditions	Common	Fever, lethargy, fatigue
General disorders and administration site conditions	Not known	Immune reconstitution syndrome

Laboratory abnormalities
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. See also section 4.4.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Single doses up to 1200 mg and daily doses up to 1800 mg of abacavir (i.e. two to three times the normal adult dose) have been administered to adult 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. The rate of removal of abacavir by haemodialysis is low.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside reverse transcriptase inhibitors, ATC Code: J05AF06

Mechanism of action: Abacavir is a NRTI. It is a 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, resulting in chain termination and interruption of the viral replication cycle.

Clinical efficacy:

Adults:

In antiretroviral therapy-naïve adult patients treated with abacavir 300 mg twice daily, together with lamivudine and efavirenz, the proportion of patients with plasma HIV-1 RNA ≤50 copies/ml by Week 48 was 70%, by intention-to-treat analysis. The 600 mg once daily abacavir regimen has been shown to be non-inferior to the 300 mg twice daily regimen in treatment-naïve as well as moderately treatment-experienced patients. Though the clinical benefit of abacavir has otherwise mainly been demonstrated in combination with lamivudine and zidovudine, this triple nucleoside regimen is not longer recommended as a preferred treatment option, due to inferior efficacy compared to NNRTI- or PI-containing regimens (see section 4.4).

Children:

Among 45 antiretroviral therapy-naïve children aged 3 months to 16 years receiving abacavir/lamivudine in combination with nelfinavir (except 6 patients who received only the dual NRTI combination) 56% had viral load <50 copies after 48 weeks of treatment. Among 43 patients receiving abacavir/zidovudine in combination with nelfinavir (except 12 patients who received only the dual NRTI combination), 44% had viral load < 50 copies/mL at 48 weeks.

Resistance:

In the pivotal clinical trials, the most common mutation emerging in patients failing on abacavir containing regimens (also including lamivudine) was M184V/I. Other key mutations appearing, though more rarely, include L74V and K65R. When occurring together with M184V/I, either of these mutations substantially reduce the activity of abacavir. The presence of M184V with K65R gives rise to cross-resistance between

abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. A further mutation selected for and reducing the activity of abacavir is Y115F. Though TAMs (M41L, D67N/G, K70R, L210W, T215F/Y, K219E/Q/N/R) are generally not selected for when failing on abacavir-containing regimens in the absence of thymidine analogues, the presence of two or more together with M184V will substantially reduce the activity of abacavir. In addition, the 69 insertion complex or the Q151M mutation cause a high level of resistance to abacavir.

5.2 Pharmacokinetic properties

Absorption:

Abacavir is rapidly absorbed following oral administration. The absolute bioavailability of oral abacavir in adults is about 83%.

Food delayed absorption and decreased Cmax but did not affect overall plasma concentrations (AUC). Therefore Abacavir oral solution can be taken with or without food.

Distribution:

Following intravenous administration, the apparent volume of distribution was about 0.8 l/kg.

Plasma protein binding to human plasma proteins at therapeutic concentrations is ~49%. 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%.

Metabolism:

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.

Elimination:

The mean plasma 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 adult 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 (AUC24,ss +32%, Cmax24,ss +99% and Ctrough +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 adult patients.

Special populations

Hepatic impairment: 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 in the abacavir AUC, and 1.58-fold in the elimination half-life. No recommendation on dosage adjustments can be given for this patient population due to the substantial variability of abacavir exposure. No pharmacokinetic data are available for patients with moderate to severe hepatic impairment (see section 4.2 and 4.4).

Renal impairment: 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.

Children: Abacavir is rapidly and well absorbed from an oral solution administered to children. The overall pharmacokinetic parameters in children are comparable to adults, with greater variability in plasma concentrations. The recommended dose for children less than 16 years (weighing less than 37.5 kg) is 8 mg/kg twice daily. This will provide slightly higher mean plasma concentrations in children, ensuring that the majority will achieve therapeutic concentrations equivalent to 300 mg twice daily in adults.

Dosing according to weight bands is recommended for abacavir based primarily on pharmacokinetic modelling. Higher exposures of abacavir can occur in some paediatric patients since accurate dosing can not be achieved with this approach. Therefore, children should be closely monitored for abacavir toxicities (see section 4.2).

There are insufficient data to recommend the use of abacavir in infants less than six weeks old.

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. These results indicate that abacavir has a weak potential to cause chromosomal damage, both in vitro and in vivo, at high 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 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.

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 decreased foetal body weight, foetal oedema, and an increase in skeletal variations/malformations, early intra-uterine deaths and stillbirths have been observed in rats but not in rabbits. 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

Sorbitol
Sodium citrate
Citric acid anhydrous
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Propylene glycol
Saccharin sodium
Strawberry flavour
Banana flavour
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

After first opening the container: 3 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Abacavir oral solution is supplied in high density polyethylene bottles containing 240 ml of oral solution. An oral dosing syringe with adaptor is included in the pack.

6.6 Special precautions for disposal and other handling

An oral dosing syringe with adaptor is provided for accurate measurement of the prescribed dose of oral solution. The adapter is placed in the neck of the bottle and the syringe attached to this. The bottle is inverted and the correct volume withdrawn. Instructions for use are included in the package leaflet.

7. Marketing authorisation holder

M/s Aurobindo Pharma Ltd
Plot No.: 2, Maitrivihar, Ameerpet,
Hyderabad-500 038, India.

8. Marketing authorisation number

H2009/19904/937/R1

9. Date of first authorisation/renewal of the authorisation

1st March 2026

10. Date of revision of the text

26th August 2026