PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ADCO ABACAVIR 20 mg/ml ORAL SOLUTION

Hypersensitivity to abacavir

In clinical studies, conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5 % of subjects receiving abacavir developed a hypersensitivity reaction. In some cases, this has proven fatal.

Risk Factors

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 one study, use of pre-therapy screening for the HLA-8*5701 allele and subsequently avoiding abacavir in patients with this allele, reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7,8 % to 3,4 % and the incidence of hypersensitivity reactions confirmed by skin patch testing from 2,7 % to 0,0 %. Based on this study, it

is estimated that 48 % to 61 % of patients with the HLA-8*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0 % to 4 % of patients who do not have the HLA-8*5701 allele. It is recommended that any HIV-infected patient without prior exposure to abacavir, be screened for HLA-B*5701 allele.

Screening is recommended prior to re-initiation of abacavir in patients of unknown HLA- 8*5701 status who have previously tolerated abacavir.

Use of abacavir in patients known to carry the HLA-8*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.

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

In order to avoid restarting abacavir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining ADCO ABACAVIR oral solution.

Clinical Description of abacavir HSR

Abacavir HSR has been well characterised through clinical studies and during post marketing follow-up. The hypersensitivity reaction is characterised by the appearance of symptoms indicating multi-organ involvement. The majority of patients have fever and/or rash as part of the syndrome. Some of the other symptoms of hypersensitivity may include fatigue, malaise, gastrointestinal symptoms such as nausea, vomiting, diarrhoea, or abdominal pain, and respiratory signs and symptoms such as dyspnoea, sore throat, cough and abdominal chest x-ray findings (predominantly infiltrates, which can be localised). Importantly, such symptoms may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis. The symptoms of this hypersensitivity reaction can occur at any time during treatment with abacavir, but usually occur within the first six weeks (median time to onset 11 days) of therapy. The symptoms 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.

Clinical Management

Regardless of their HLA-8*5701 status, any patient developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice.

If a hypersensitivity reaction is diagnosed, ADCO ABACAVIR SOLUTION MUST be discontinued immediately. ADCO ABACAVIR SOLUTION, or any other medical product containing abacavir. MUST NEVER be restarted following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.

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

ADCO ABACAVIR SOLUTION, or any other medicinal product containing abacavir, should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

Special consideration following an interruption of ADCO ABACAVIR SOLUTION therapy

Regardless of a patient's HLA-B*5701 status, if therapy with ADCO ABACAVIR SOLUTION has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction.

If a hypersensitivity reaction cannot be ruled out, ADCO ABACAVIR SOLUTION or any other medicinal product containing abacavir should not be restarted.

There have been infrequent reports of a hypersensitivity reaction following reintroduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made

to restart ADCO ABACAVIR SOLUTION in these patients, this should be done only under direct medical supervision.

Hypersensitivity reactions have been reported in patients who have restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to restart ADCO ABACAVIR SOLUTION, this must be done only if medical care can be accessed readily by the patient or others.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of ADCO ABACAVIR SOLUTION in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Re-initiation of ADCO ABACAVIR SOLUTION in such patients who test positive for the HLA-B*5701 allele is not recommended and should be considered only under exceptional circumstances where potential benefit outweighs the risk and with close medical supervision.

Essential patient information: Prescribers must ensure the following:

- Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in life threatening reactions or death.
- Patients developing signs or symptoms possibly linked with a hypersensitivity reaction MUST CONTACT their doctor IMMEDIATELY.
- Patients who have experienced a hypersensitivity reaction should be asked to return the remainder of the medication to the pharmacy.
- Patients who have stopped taking ADCO ABACAVIR SOLUTION for any reason such as adverse reactions or illness, must be advised to contact their doctor before restarting.
- Each patient should be reminded to read the patient information leaflet included in the ADCO ABACAVIR SOLUTION pack.
- Patients should be reminded of the importance of removing the Alert Card included in the pack and keeping it with them at all times. (Find the Alert Card attached)

PROFESSIONAL INFORMATION

2. QUALITATIVE AND QUANTATIVE COMPOSITION

Each ml of solution contains the equivalent of 20 mg abacavir as abacavir sulphate.

Sugar free

Contains sweetener:

Sorbitol 344,4 mg/ml

Saccharin Sodium 0,150 mg/ml

Preservatives:

Methyl parahydroxy benzoate 0, 15 % m/v & propyl parahydroxy benzoate 0,018 % m/v.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

ADCO ABACAVIR 20 mg/ml ORAL SOLUTION

Clear to opalescent, yellowish , strawberry-banana flavoured liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO ABACAVIR SOLUTION is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children in combination with other antiretroviral agents.

4.2 Posology and method of administration

Before initiating treatment with ADCO ABACAVIR SOLUTION, screening for carriage of the HLA-8*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-8*5701 status who have previously tolerated abacavir. ADCO ABACAVIR SOLUTION should not be used in patients known to carry the HLA-8*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing.

The oral solution is available for use in children and for those patients in whom the tablet dosage form is inappropriate.

Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Adults and children over 12 years:

The recommended dose of ADCO ABACAVIR SOLUTION is 600 mg daily (30 ml).

Paediatric population

Children from 3 months to 12 years:

The recommended dosage is 8 mg/ kg twice daily up to a maximum of 600 mg (30 ml) daily.

Method of administration

Oral

ADCO ABACAVIR SOLUTION can be taken with or without food.

4.3 Contraindications

ADCO ABACAVIR SOLUTION is contra-indicated in:

- Patients with a known hypersensitivity to abacavir or any of the inactive ingredients listed in section 6.1.
- Patients with hepatic impairment (such as those infected with hepatitis B virus) should not use ADCO ABACAVIR SOLUTION.
- ADCO ABACAVIR SOLUTION should not be used in pregnancy or lactation.

4.4 Special warnings and precautions for use

Hypersensitivity reactions (see also section 4.8):

Cases of fatal hypersensitivity reactions (HSR) have occurred in patients receiving ADCO ABACAVIR SOLUTION. This hypersensitivity reaction is characterised by the emergence of symptoms indicating multi-organ/ body-system involvement. Patients should discontinue ADCO ABACAVIR SOLUTION if

they develop a hypersensitivity reaction and MUST not be rechallenged with ADCO ABACAVIR SOLUTION or any other abacavir containing medicinal product (see section 4.8).

Lactic acidosis/severe hepatomegaly with steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral neucloside analogues alone or in combination, including abacavir in the treatment of HIV infection (see section 4.8).

ADCO ABACAVIR SOLUTION should be discontinued immediately if symptoms associated with hypersensitivity occur and should never be recommenced in patients who have stopped therapy due to a hypersensitivity reaction. Patients should be closely monitored for signs of hypersensitivity during the first two months of treatment, although hypersensitivity reactions can occur at any time. Patients restarting therapy after an interruption are at particular risk even if they have not previously shown symptoms of hypersensitivity. Since intermittent therapy may increase the risk of hypersensitivity developing, patients should be advised of the importance of regular dosing. The patients should be reminded to keep the Alert Card with them all the time.

ADCO ABACAVIR SOLUTION should be avoided in patients with end-stage renal disease.
Before initiating treatment with ADCO ABACAVIR SOLUTION, screening for carriage of the HLA-8*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-8*5701 status who have previously tolerated abacavir. ADCO ABACAVIR SOLUTION should not be used in patients known to carry the HLA-8*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing.

Lipodystrophy and metabolic abnormalities
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement [buffalo hump], peripheral wasting, facial wasting , breast enlargement, elevated serum lipid and blood glucose

levels have been observed either separately or together in some patients receiving combination antiretroviral therapy. Whilst all members of the Protease Inhibitor and NRTI classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicate that there are differences in the risk between individual members of the respective therapeutic classes. In addition, the lipodystrophy syndrome has a multi-factorial aetiology with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles. The long-term consequences of these events are currently unknown. Clinical examination should include evaluation to physical signs of fat re-distribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Opportunistic Infections:

Patients receiving ADCO ABACAVIR SOLUTION may still develop opportunistic infections and other complications of HIV infections. Therefore patients should remain under close clinical observation by medical practitioners experienced in the treatment of these associated HIV diseases. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:

Patients should be advised that antiretroviral therapy with ADCO ABACAVIR SOLUTION has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Pancreatitis:

Pancreatitis has been observed in some patients receiving ADCO ABACAVIR SOLUTION. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated

biochemical markers. Discontinue use of ADCO ABACAVIR SOLUTION until diagnosis of pancreatitis is excluded.

Lactic acidosis/ hyperlactataemia:

Use of ADCO ABACAVIR SOLUTION can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LOH) and/or creatine kinase. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal< 2 mmol/litre) and the serum bicarbonate respond as follows:

- Lactate 2-5 mmol/litre with minimum symptoms: switch to agents that are less likely to cause lactic acidosis monitor regularly, and be alert for clinical signs.
- Lactate 5-10 mmol/litre without symptoms: monitor closely.
- Lactate 5-10 mmol/litre with symptoms and/or with reduced standard bicarbonate: STOP NRTIs and change treatment option . Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, (lymphoma) and hyperthyroidism.
- Lactate > 10 mmol/litre: STOP all therapy (80 % mortality in case studies).

The above lactate values may not be applicable to paediatric patients.

Caution should be exercised when administering ADCO ABACAVIR SOLUTION to patients with known risk factors for liver disease.

Treatment with ADCO ABACAVIR SOLUTION should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

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. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behavior). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Immune Reconstitution Inflammatory Syndrome:

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued, and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis:

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), There have been reports of

osteonecrosis, particularly in patients with advanced HIV disease 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.

Excipients

Fructose intolerance:

ADCO ABACAVIR SOLUTION contains 344.4 mg/ml of sorbitol which is metabolised to fructose and is therefore not suitable for patients who have hereditary fructose intolerance. Sorbitol can have a mild laxative effect. The calorific value of sorbitol is 2.6 kcal/g.

ADCO ABACAVIR SOLUTION also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

ADCO ABACAVIR SOLUTION contains 55 mg/ml of propylene glycol. When taken according to the dosage recommendations each 15 ml dose contains approximately 825 mg of propylene glycol.

Ability to drive and use machines:

No currently available data suggest that ADCO ABACAVIR SOLUTION affects the ability to drive or operate machinery.

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 ADCO ABACAVIR SOLUTION, action should be taken to minimize all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidaemia).

Liver disease

Use of ADCO ABACAVIR SOLUTION can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of ADCO ABACAVIR SOLUTION has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant professional information for these medicines.

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. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Patients with HIV and hepatitis B or C virus co-infection

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines.

Patients co-infected with HIV and HBV who discontinue ADCO ABACAVIR SOLUTION should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced

liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interactions

The potential for P450 mediated interactions with other medicinal products involving abacavir is low. *In vitro* studies have shown that abacavir has potential to inhibit cytochrome P450 1A1 (CYP1A1). P450 does not play a major role in the metabolism of abacavir, and abacavir shows limited potential to inhibit metabolism mediated by CYP 3A4. Abacavir has also been shown *in vitro* not to inhibit 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:

Administration of ADCO ABACAVIR SOLUTION with alcohol may result in decreased elimination of abacavir, and an increase in the area under the plasma concentration time curve 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 increases the systemic clearance of oral methadone by 22%. The induction of drug metabolising enzymes cannot therefore be excluded. Patients should be monitored for signs 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.

Riociguat:

In vitro, abacavir inhibits CYP1A1. Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving the combination of abacavir/dolutegravir/lamivudine (600mg/50mg/300mg once daily) led to an approximately three-fold higher riociguat AUC(0- ∞) when compared to historical riociguat AUC(0-∞) reported in healthy subjects. Riociguat dose may need to be reduced. Consult the riociguat prescribing information for dosing recommendations.

4.6 Fertility, pregnancy and lactation

ADCO ABACAVIR SOLUTION is contra-indicated in pregnancy and lactation.

Pregnancy:

ADCO ABACAVIR SOLUTION has not been studied in pregnant women. However, animal studies have shown teratogenicity and other problems. ADCO ABACAVIR SOLUTION must not be used in pregnancy or if planning pregnancy.

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*:**

It is not known whether ADCO ABACAVIR SOLUTION is excreted into breast milk. Due to the potential for adverse events in the infant, patients on ADCO ABACAVIR SOLUTION treatment should not breast feed. In addition, breast-feeding is not recommended for patients with HIV infection due to the risk of passing HIV on to the infant.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

a. Summary of safety profile

Severe hypersensitivity reactions, sometimes fatal, have occurred in about 4 % of patients receiving ADCO ABACAVIR SOLUTION, especially (but not exclusively) during the first six weeks of treatment, or during intermittent therapy. This hypersensitivity reaction is characterised by symptoms of multiorgan involvement. Symptoms of hypersensitivity commonly include fever, rash, cough, dyspnoea, lethargy, malaise, headache, myalgia, elevated liver function tests and gastrointestinal disturbances, particularly nausea and vomiting, diarrhoea, and abdominal pain. Anaphylaxis has been reported. 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.

MedDRA System Organ Class	**Description and frequency**
Immune system disorders	*Frequent*: Hypersensitivity reactions. *Frequency not known*: Anaphylaxis
Metabolism and nutrition disorders	*Frequent:* Anorexia *Less frequent:* Lactic acidosis *Frequency unknown*: Elevated blood glucose and triglyceride concentrations, fat redistribution/accumulation of body fat.
Nervous system disorders	*Frequent*: headache
Gastrointestinal disorders	*Frequent:* Nausea and vomiting, diarrhoea, abdominal pain *Less frequent:* Pancreatitis.
Skin and subcutaneous tissue disorders	*Frequent*: Rash *Less frequent*: Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.
General disorders and administration site conditions	*Frequent*: lethargy, fatigue, fever, malaise

c. 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.

Caution is needed as hypersensitivity may be misdiagnosed as influenza, respiratory disease, or gastroenteritis.

Misdiagnosis may lead to continued or re-introduction of ADCO ABACAVIR SOLUTION which may lead to a more severe hypersensitivity reaction and even death. Symptoms worsen with continued therapy, and will usually resolve once therapy is discontinued. Restarting ADCO ABACAVIR SOLUTION after a hypersensitivity reaction has occurred will result in a return of the symptoms within hours. This return of the hypersensitivity reaction may be more severe than the initial reaction and it is possible that it may result in life-threatening hypotension and death.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (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 and autoimmune hepatitis) 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Refer to undesirable effects (section 4.8) for symptoms of overdose.

Treatment is symptomatic and supportive.

No additional adverse reactions to those reported for normal doses 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

A.20.2.8 Antiviral agents

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

Mechanism of action

Abacavir sulphate is a nucleoside reverse transcriptase inhibitor (NRTIs) analogue. The active metabolite of abacavir, carbovir 5'- triphosphate, is an HIV-1 reverse transcriptase inhibitor. Abacavir undergoes intracellular phosphorylation by enzymes. It is monophosphorylated by a pathway involving adenosine phosphotransferase and is then di-and triphosphorylated. *In vitro* passage of HIV-1 in the presence of abacavir selects for modest resistance with mutations at reverse transcriptase codons. Resistance in clinical isolates from patients who had received prior therapy with nucleoside reverse transcriptase inhibitors is associated with multiple mutations. Strains that are resistant to all other nucleoside reverse transcriptase inhibitors also are resistant to abacavir.

5.2 Pharmacokinetics properties

Absorption

Abacavir is rapidly absorbed following oral administration with a bioavailability of about 83 %. Absorption is delayed by food but the extent is unaffected. Abacavir crosses the blood-brain barrier. It is about 50 % bound to plasma proteins. The mean

time (t_{max}) to maximal serum concentrations of abacavir is about 1,5 hours following a single dose.

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. The metabolites are excreted mainly in the urine. There is no significant metabolism by hepatic cytochrome P450 isoenzymes.

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.

Special Populations:

Hepatically impaired:

Metabolism of abacavir is primarily by the liver. Pharmacokinetics of abacavir in patients with mild hepatic impairment show a mean increase of 1,89 - fold in the abacavir AUC, and 1,58 fold in the half-life of abacavir. The AUCs of metabolites are not modified by the liver disease, yet, the rates of formation and elimination of these were decreased. The pharmacokinetics has not been studied in patients with moderate or severe hepatic impairment, therefore ADCO ABACAVIR SOLUTION is contra-indicated in these patient groups.

Renally impaired:

Metabolism of abacavir is primarily by the liver and approximately 2 % of abacavir is excreted in the urine. Pharmacokinetics of abacavir in patients with end-stage renal disease is similar to that in patients with normal renal function. Thus no dosage reduction is required in patients with renal impairment.

Elderly:

Pharmacokinetics of abacavir in patients over 65 years of age have not been studied.
Consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, and concomitant disease or other drug therapy when treating elderly patients.

5.3 Preclinical safety data

No data available.

6. Pharmaceutical particulars

6.1 List of excipients

Other ingredients in the solution:

Methyl parahydroxy benzoate

Propyl parahydroxy benzoate

Citric acid, anhydrous (Powder, EMPROVE)

Propylene glycol

Purified water

Saccharin sodium

Sodium citrate

Sorbitol, liquid (Noncrystallizing) (Neosorb 70/70B)

Strawberry flavour FL N&A WILD TYPE No. 958[4]

Banana flavour ART No. 11090 K[4]

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

The bottles must be tightly closed.

6.5 Nature and contents of container

250 ml white opaque HDPE bottles with white, ribbed, plastic cap. The bottle is packed in a cardboard carton.

(a) Immediate container

Container: 250 ml White opaque HDPE bottles with 28 mm neck

Closure:

Child Resistant Plastic Caps with induction sealing (FSE wad), 28 mm:

Outer cap: White, ribbed, plastic cap with opening illustrations embossed on top.

Inner cap: Translucent child resistant plastic cap with a pulp liner in between the heat seal liner and inner cap.

Child Resistant Plastic Caps with Expanded (PE wad), 28 mm:

Outer cap: White, ribbed, plastic cap with opening illustrations embossed on top.

Inner cap: Translucent child resistant plastic cap with Expanded PE wad.

b) Outer container

The outer container is a cardboard carton.

c) Bulk container

Stainless steel vessel

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand, Johannesburg,1685,

Gauteng,

South Africa.

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER (S):

43/20.2.8/0910

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 July 2014

10. DATE OF REVISION OF THE TEXT

30 January 2025

Botswana	
Product name	**Registration number**
Adco-Abacavir oral solution	BOT1903603