Proposed Professional Information

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

SONKE ABACAVIR 300 Film-coated tablets

Hypersensitivity to abacavir (see section 4.8)

Abacavir is associated with a risk for hypersensitivity reactions (HSR) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSR can be life-threatening, and may be fatal, when not managed appropriately. The risk for abacavir HSR to occur is significantly increased 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.

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 proved fatal.

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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 the prospective study CNA106030 (PREDICT-1), use of pretherapy screening for the HLA B*5701 allele and subsequently avoiding

abacavir in patients with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7,8 % (66 of 847) to 3,4 % (27 of 803) ($p < 0,0001$) and the incidence of hypersensitivity reactions confirmed by skin patch testing from 2,7 % (23 of 842) to 0,0 % (0 of 802) ($p < 0,0001$). Based on 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 the HLA B*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-B*5701 status who have previously tolerated abacavir (see Special considerations following an interruption of **Sonke Abacavir 300** therapy below).

Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended.

Clinical description:

The hypersensitivity reaction is characterised by the appearance of symptoms indicating multi-organ/body-system 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, and abdominal pain and respiratory signs and symptoms such as dyspnoea, sore throat, cough, and abnormal chest X-ray findings (predominantly infiltrates, which can be localised).

The symptoms of this hypersensitivity reaction can occur at any time during treatment with abacavir, but usually occur within the first six weeks of therapy. The symptoms worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Clinical management:

Regardless of their HLA-B*5701 status, any patients developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed **Sonke Abacavir 300** MUST be discontinued immediately. **Sonke Abacavir 300**, or any

other medicine 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 diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, **Sonke Abacavir 300** should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastro-enteritis or reactions to other medications).

Sonke Abacavir 300, or any other medicine containing abacavir, should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

An Alert Card with information for the patient about the hypersensitivity reaction is included in the **Sonke Abacavir 300** pack.

Special considerations following an interruption of Sonke Abacavir 300 therapy:

Regardless of a patient's HLA-B*5701 status, if therapy with **Sonke Abacavir 300** 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, Sonke Abacavir 300 or any other medicine containing abacavir should not be restarted.**

There have been infrequent reports of hypersensitivity reactions following re-introduction 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 **Sonke Abacavir 300** 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 **Sonke Abacavir 300**, this must be done only if medical care can be readily accessed by the patient or others.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of **Sonke Abacavir 300** in patients of unknown HLA-B*5701 status who have previously tolerated **Sonke Abacavir 300**. Re-initiation of Sonke Abacavir 300 in such patients who test positive for the HLA-B*5701 allele is not recommended.

Essential patient information:

Prescribers must ensure that patients are fully informed regarding the following information on the hypersensitivity reaction:

Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased if they are HLA-B*5701-positive.

Patients must also be informed that HLA-B*5701-negative patients can also experience abacavir hypersensitivity reactions. Therefore, ANY patient who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir **MUST CONTACT their doctor IMMEDIATELY**.

Patients who are hypersensitive to abacavir should be reminded that they must never take **Sonke Abacavir 300** or any other medicine containing abacavir again, regardless of their HLA-B*5701 status.

In order to avoid restarting **Sonke Abacavir 300**, patients who have experienced a hypersensitivity reaction to abacavir should be asked to return the remaining **Sonke Abacavir 300** tablets to the pharmacy.

Patients who have stopped **Sonke Abacavir 300** for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.

Each patient should be reminded to read the professional information included in the **Sonke Abacavir 300** 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.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains: Abacavir sulphate equivalent to abacavir 300 mg.

Sugar Free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated Tablets

Peach coloured, capsule shaped, biconvex, film coated tablets, debossed with 'RA72' on one side and plain on the other side with intact coating.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sonke Abacavir 300 is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV)-infected adults and children.

4.2 Posology and method of administration

Posology

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

Sonke Abacavir 300 can be taken with or without food.

Adults, adolescents and children weighing at least 25 kg:

The recommended dose of **Sonke Abacavir 300** is one tablet of 300 mg twice daily. This may be administered as either 300 mg (one tablet) twice daily or 600 mg (two tablets) once daily.

Children weighing at least 25 kg: the adult dosage of 300 mg twice daily or 600 mg once daily should be taken.

Special populations

Renal impairment:

No dosage adjustment of **Sonke Abacavir 300** is necessary in patients with renal dysfunction (see s section 5.2).

Hepatic impairment

Abacavir is metabolised primarily by the liver. Pharmacokinetic and safety data on the use of **Sonke Abacavir 300** in patients with moderate and severe hepatic impairment are not available (see section 5.2). Therefore, the use of **Sonke Abacavir 300** is contraindicated in patients with moderate or severe hepatic impairment, unless the benefit of use outweighs the risk.

Method of administration

For oral use.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing. For patients who are unable to swallow tablets, the tablets 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).

4.3 Contraindications

Sonke Abacavir 300 is contra-indicated:

- In patients with known hypersensitivity to abacavir or to any of the excipients listed in section 6.1.
- In patients with moderate or severe liver function impairment.
- In pregnancy and lactation (see section 4.6)
- In patients under 3 months of age.

4.4 Special warnings and precautions for use

Hypersensitivity to abacavir: Refer to section 1 Boxed warning and section 4.8: Description of Selected Adverse Reactions. Approximately 5 % of subjects receiving **Sonke Abacavir 300** develop a hypersensitivity reaction which in rare cases has proved fatal. This is characterized by the appearance of symptoms indicating multi-organ/body-system involvement. **Patients who develop a hypersensitivity reaction must discontinue Sonke Abacavir 300 and MUST not be re-challenged with Sonke Abacavir 300 or any other product containing abacavir.**

Lactic acidosis/severe hepatomegaly with steatosis: Long- term use of **Sonke Abacavir 300** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Symptomatic hyperlactataemia and lactic acidosis are uncommon. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea and tachypnoea, fatigue and weight loss. Suspicious biochemical features include raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/L with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/L 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 and hyperthyroidism).
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality).

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any patient with a raised lactate level. Blood for lactate assay should be heparinised and stored on ice. After recovery, NRTIs should be avoided. Seek expert advice on medicine selection.

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

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of **Sonke Abacavir 300** alone or in combination. Caution should be exercised when administering **Sonke Abacavir 300** to any patient and particularly to those with known risk factors for liver disease. Treatment with **Sonke Abacavir 300** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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 behaviour). It is not known whether these 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 signs and symptoms.

Pancreatitis: Pancreatitis has been observed in some patients receiving **Sonke Abacavir 300**. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **Sonke Abacavir 300** until diagnosis of pancreatitis is excluded.

Liver disease: Use of **Sonke Abacavir 300** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **Sonke Abacavir 300** 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. If **Sonke Abacavir 300** is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Lipodystrophy and metabolic abnormalities: Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome (IRIS): In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections 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 ART. Relevant examples are tuberculosis, cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci pneumonia* (often referred to as PCP).

Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Opportunistic infections: Patients receiving **Sonke Abacavir 300** 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. Regular monitoring of viral load and CD4 counts needs to be done.

Transmission of infection: 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.

Cardiovascular events

Although the available data from clinical and observational studies with abacavir show inconsistent results, several studies suggest an increased risk of cardiovascular events (notably myocardial infarction) in patients treated with abacavir. Therefore, when prescribing **Sonke Abacavir 300**, action should be taken to minimize all modifiable risk factors (e.g.smoking, hypertension, and hyperlipidaemia). In addition, alternative treatment options to the abacavir containing regimen should be considered when treating patients with a high cardiovascular risk.

Osteonecrosis

Although the aetiology 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.

4.5 Interaction with other medicines and other forms of interaction

Based on the results of in vitro experiments and the known major metabolic pathways of abacavir, the potential for drug interactions involving abacavir is low. Abacavir shows no potential to inhibit metabolism mediated by the cytochrome P450 3A4 enzyme. It has also been shown in vitro not to interact with medicines that are metabolized by CYP3A4, CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for drug interactions with antiretroviral protease inhibitors and other medicines by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine and lamivudine.

Interactions relevant to abacavir:

Ethanol: The metabolism of abacavir is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41 %. No dose reduction of abacavir is necessary. 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 %. This change is not considered clinically relevant for the majority of patients, however occasionally methadone re-titration may be required.

Retinoids: Retinoid compounds such as isotretinoin 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 (600 mg/50 mg/300 mg 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 product labelling for dosing recommendations.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of **Sonke Abacavir 300** in human pregnancy has not been established. **Sonke Abacavir 300** is contraindicated in pregnancy. **Sonke Abacavir 300** should not be used during pregnancy and lactation since teratogenicity and/or foetal toxicity cannot be excluded (see section 4.3).

Breastfeeding

Sonke Abacavir 300 is contraindicated in lactation. It is expected that abacavir will be secreted into human milk. Mothers on treatment with **Sonke Abacavir 300** should not breastfeed their babies (see section 4.3). HIV-infected women should not breastfeed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, the local official lactation and treatment guidelines should be followed when considering breastfeeding during antiretroviral therapy.

4.7 Effects on ability to drive and use machines

No currently available data suggest that **Sonke Abacavir 300** affects the ability to drive or operate machinery.

4.8 Undesirable effects

The majority of the adverse reactions listed below have not been treatment limiting. The adverse events reported during therapy for HIV disease with **Sonke Abacavir 300** were similar in adults and children. Many of the adverse events listed 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 reaction. If **Sonke Abacavir 300** has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart abacavir, this must be done only under direct medical supervision (see Special considerations following an interruption of **Sonke Abacavir 300** therapy in section 1 - Boxed warning).

Clinical Trial Data

Metabolism and nutrition disorders:

Frequent: anorexia

Nervous system disorders:

Frequent: headache

Gastrointestinal disorders:

Frequent: nausea, vomiting, diarrhoea

General disorders and administrative site conditions:

Frequent: fever, lethargy, fatigue.

Paediatric population

No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Post marketing Data

Metabolism and nutrition disorders:

Hyperlactataemia

Lactic acidosis (see section 4.4 Special warnings and precautions for use)

Gastrointestinal disorders:

Pancreatitis has been reported

Skin and subcutaneous tissue disorders:

Rash (without systemic symptoms)

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Description of Selected Adverse Reactions

Hypersensitivity (see also section 1 - Boxed warning):

Abacavir hypersensitivity reaction (HSR) has been identified as a frequent adverse reaction with abacavir therapy. The signs and symptoms of this hypersensitivity reaction are listed below. These have been identified either from clinical studies or postmarketing 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 and subcutaneous tissue disorders:	**Rash** (usually maculopapular or urticarial)
Gastrointestinal disorders:	**Nausea, vomiting, diarrhoea, abdominal pain,** mouth ulceration
Respiratory, thoracic and mediastinal disorders:	**Dyspnoea, cough,** sore throat, adult respiratory distress syndrome, respiratory failure
General disorders and administrative site conditions:	**Fever, fatigue, malaise,** oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Nervous system disorders:	**Headache,** paraesthesia
Blood and the lymphatic system disorders	Lymphopenia
Hepato-biliary disorders:	**Elevated liver function tests,** hepatic failure
Musculoskeletal, connective tissue and bone disorders:	**Myalgia**, less frequently myolysis, arthralgia, elevated creatine phosphokinase
Renal and urinary disorders:	Elevated creatinine, renal failure

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.** Reactions have also occurred infrequently after restarting 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).

For details of clinical management in the event of a suspected abacavir HSR see section 1 – Boxed warning.

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

Single doses up to 1 200 mg and daily doses up to 1 800 mg of abacavir have been administered to patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known. If overdosage 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

Class & Category: A 20.2.8 Antivirals.

Abacavir is a nucleoside analogue reverse transcriptase inhibitor. It is an antiviral agent against HIV-1 and HIV-2, including HIV-1 isolates that are resistant to zidovudine, lamivudine, zalcitabine, didanosine or nevirapine. *In vitro* studies have demonstrated that its mechanism of action in relation

to HIV is inhibition of the HIV reverse transcriptase enzyme, an event that results in chain termination and interruption of the viral replication cycle. Abacavir shows synergy *in vitro* in combination with nevirapine and zidovudine.

It has been shown to be additive in combination with didanosine, zalcitabine, lamivudine and stavudine. Abacavir -resistant isolates of the HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the reverse trancriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo*, requiring multiple mutations to reach an eight-fold increase in IC50 over wild-type virus, which may be a clinically relevant level. Isolates resistant to abacavir may also show reduced sensitivity to lamivudine, zalcitabine and/or didanosine, but remain sensitive to zidovudine and stavudine. Cross-resistance between abacavir and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is unlikely.

Treatment failure following initial therapy with abacavir, lamivudine and zidovudine is mainly associated with the M184V alone, thus maintaining many therapeutic options for a second line regimen. In therapy experienced patients, limited data show that the addition of **Sonke Abacavir 300** to nucleoside reverse transcriptase inhibitors provide additional benefit in reducing viral load and increasing CD4 cell count. The degree of benefit will depend on the nature and duration of prior therapy which may have been selected for cross-resistance to abacavir.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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 %. In a Phase 1 pharmacokinetic study, the penetration of abacavir into the CSF was investigated following administration of abacavir 300 mg twice a day. The mean concentration of abacavir achieved in the CSF 1, 5 hours post dose was 0, 14 µg/mL. In a further pharmacokinetic study of 600 mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0,13 µg/mL at 0,5 to 1 hour after dosing, to approximately 0,74 µg/mL after 3 to 4 hours. While peak concentrations may not have been attained by 4 hours, the observed values are 9 fold greater than the IC_{50} of abacavir of 0,08 µg/ml or 0,26 µM.
Plasma protein binding studies in vitro indicate that abacavir binds only moderately (~49 %) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for drug interactions through plasma protein binding displacement.

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 drug accumulation. 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:

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). The results showed that there was a mean increase of 1,89-fold in the abacavir AUC and a 1,58-fold in the half-life of abacavir. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased. The pharmacokinetics have not been studied in patients with moderate or severe hepatic impairment, therefore, abacavir is contraindicated in these patient groups.

Renal impairment

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.

Elderly population

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

5.3 Preclinical safety data:

Carcinogenicity: 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 female rats.

The majority of these tumours occurred at the highest dose levels equivalent to 24 to 32 times the expected systemic exposure in humans. The exception was the preputial gland tumour which occurred at a dose equivalent to 6 times the expected human systemic exposure. There is no structural counterpart of this gland in humans. While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the clinical benefit.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate

Film-coat:

Hypromellose

Iron oxide red

Iron oxide yellow

Macrogol/polyethylene glycol 400

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Keep out of reach of children.

Store at or below 25 ºC in the original package, protected from moisture. Keep the bottle well closed.

6.5 Nature and contents of container

Cartons containing 10, 30, 60 or 100 tablets packed in PVdC coated PVC blister strips of 10's with a backing of hard tempered aluminium foil coated with a heat seal lacquer on the inner side.

Carton containing 60 tablets packed in white, opaque HDPE bottle or alternatively 60 tablets are packed in a securitainer.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (Pty) LTD

a Sun Pharma company

14 Lautre Road, Stormill Ext 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER:

A40/20.2.8/0777

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 June 2009

10. DATE OF REVISION OF THE TEXT

14 June 2022

Marketed by Sonke Pharmaceuticals (Pty) Ltd

This product is for use only in South Africa, Namibia, Botswana, Swaziland and Lesotho, is not for resale and any other use is not authorised.

Namibia only: NS2 Reg. no.: 07/20.2.8/0178
Botswana only: NS2 Reg. no.: BOT0801201