Professional Information

SCHEDULING STATUS: **S4**

1 NAME OF THE MEDICINE

BAVIR TABLETS 300 mg (Tablet)

BAVIR ORAL SOLUTION 20 mg/ml (Solution)

WARNING:

Hypersensitivity: In clinical studies, approximately 4 % of subjects receiving abacavir developed a hypersensitivity reaction which in rare cases proved fatal.

Description: This 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. The symptoms of this hypersensitivity reaction can occur at any time during treatment with BAVIR, but usually appear within the first 6 weeks of initiation of treatment with BAVIR (median time to onset 11 days), and most often include fever, gastrointestinal symptoms (nausea, vomiting, diarrhoea and abdominal pain), rash and fatigue or malaise. Other symptoms may include myalgia, arthralgia, oedema, paraesthesia and respiratory symptoms such as dyspnoea, sore throat or cough.

The symptoms worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of BAVIR.

Management: To avoid a delay in diagnosis and minimize the risk of a life- threatening hypersensitivity reaction, BAVIR should 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).

BAVIR should not be re-started even if a recurrence of symptoms occurs following re-challenge with alternative medication(s).

An Alert Card with information for the patient about the hypersensitivity reaction is included in the BAVIR pack.

Special considerations following an interruption of BAVIR therapy: If therapy with BAVIR 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. Patients who have stopped BAVIR due to possible adverse reactions or illness should be advised to contact their doctor before restarting. If hypersensitivity cannot be ruled out BAVIR should not be restarted.

There have been infrequent reports of hypersensitivity reaction following reintroduction of BAVIR, where the interruption was preceded by a single key symptom (e.g. rash, fever or gastrointestinal symptoms). When patients who have discontinued BAVIR present with an indeterminate diagnosis of hypersensitivity (single symptom), the doctor should:

• Assess the probability that hypersensitivity preceded the interruption

• Assess the risk: benefit of reinitiating BAVIR

• Select the appropriate medical setting in which to re-introduce BAVIR, if such a decision is made

On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no apparent preceding symptoms of a hypersensitivity reaction. Some of these cases were poorly documented. The clinical significance of these reports is unclear. If a decision is made to re-start BAVIR, this must be done only if medical care can be accessed readily by the patient or others.

Essential patient information: Prescribers must ensure that patients are fully informed regarding the following 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.

• Patients developing signs or symptoms possibly linked with a hypersensitivity reaction MUST CONTACT their doctor IMMEDIATELY.

• In order to avoid restarting BAVIR, patients who have experienced a hypersensitivity reaction should be asked to return the remaining BAVIR tablets or oral solution to the pharmacy.

• Patients who have stopped BAVIR for any reason, and particularly due to adverse reactions

or illness, must be advised to contact their doctor before restarting.

• Each patient should be reminded to read the package insert included in the BAVIR 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

BAVIR TABLETS 300 mg:

Each film-coated tablet contains abacavir sulphate equivalent to 300 mg of abacavir. Sugar free.

BAVIR ORAL SOLUTION 20 mg/ml:

Each 1 ml contains:

Abacavir sulphate equivalent to 20 mg of abacavir.

Preservatives: Methyl paraben……..…..0,15 % m/v

Propyl paraben……..0,018 % m/v

Contains sugar: sorbitol 344.4 mg/mL.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

BAVIR TABLETS 300 mg:

Yellow coloured, biconvex, capsule shaped, coated tablets, debossed with “D” and “88” on either side of the score line on one side and plain with a score line on the other side.

BAVIR ORAL SOLUTION 20 mg/ml:

Clear to opalescent, yellowish, strawberry-banana flavoured liquid, in 300 ml white round HDPE bottle.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

BAVIR 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

Adults and adolescents over 12 years: The recommended dose of **BAVIR** is one tablet of 300 mg or 15 ml twice daily.

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 daily.

Children less than 3 months: There are no data available on the use of **BAVIR** in this age group.

BAVIR can be taken with or without food.

An oral dosing syringe is provided for accurate measurement of the prescribed dose of oral solution.

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

Special populations

Renal impairment: No dosage adjustment of **BAVIR** is necessary in patients with renal dysfunction (see section 5.2).

Hepatic impairment: Abacavir is metabolised primarily by the liver. There is insufficient data to recommend the use of **BAVIR** in patients with impaired hepatic function.

Method of administration

To be taken orally.

4.3 Contraindications

BAVIR is contra-indicated:

- in patients with known hypersensitivity to abacavir or any ingredient of the formulations,
- in patients with a hereditary fructose intolerance,
- in patients with liver function impairment,
- in pregnancy and lactation,
- in infants under 3 months of age.

4.4 Special warnings and precautions for use

Hypersensitivity:

Approximately 4 % of subjects receiving **BAVIR** develop a hypersensitivity reaction which in rare cases has proved fatal. This is characterised by the appearance of symptoms indicating multi-organ/body-system involvement. **Patients who develop a hypersensitivity reaction must discontinue BAVIR and MUST not be re-challenged with BAVIR** (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 nucleoside analogues alone or in combination, including abacavir, in the treatment of HIV infection (see section 4.8). A majority of these cases have been in women.
Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).
Caution should be exercised when administering **BAVIR**, particularly to those with known risk factors for liver disease. Treatment with **BAVIR** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations)

Patients receiving **BAVIR** 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. Patients should be advised that

antiretroviral therapy with **BAVIR** 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 taken.

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

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.
Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

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. polymyositis and Guillain-Barre syndrome) 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 and sometimes can be an atypical presentation.

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.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including **BAVIR**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Lactic acidosis / hyperlactataemia

Use of **BAVIR** 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.

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).

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

Caution should be exercised when administering **BAVIR** to patients with known risk factors for liver disease.

Treatment with **BAVIR** 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 behaviour). 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.

Pancreatitis

Pancreatitis has been observed in some patients receiving **BAVIR**.

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **BAVIR** until diagnosis of pancreatitis is excluded.

Liver disease

Use of **BAVIR** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis).

The safety and efficacy of **BAVIR** 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 package inserts 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 package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue **BAVIR** 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.

Sorbitol

BAVIR contains sorbitol which may cause abdominal pains and diarrhoea. **BAVIR** contains sorbitol which is metabolized to fructose and is therefore unsuitable for patients who have hereditary fructose intolerance (see section 4.3).

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

Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in rats in the thyroid gland of males and the liver, urinary bladder, lymph nodes and the sub cutis 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 potential clinical benefit. Mild myocardial degeneration in the heart of mice and rats was observed following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

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 **BAVIR**, action should be taken to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).
In addition, alternative treatment option to the abacavir containing regimen should be considered when treating patients with a high cardiovascular risk.

Therapy experienced patients

In clinical trials patients with prolonged prior NRTI exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients with prolonged prior NRTI exposure, or who have HIV-1 isolates containing multiple mutations conferring resistance to NRTIs.

BAVIR contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet/ml, that is to say essentially ‘sodium free’.

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 limited 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 medicine interactions with antiretroviral protease inhibitors and other medicines metabolised by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine.

Effect of abacavir on the pharmacokinetics of other agents *In vitro,* abacavir demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or Pglycoprotein (Pgp) and minimal inhibition of organic cation transporter 1 (OCT1), OCT2 and multidrug and toxin extrusion protein 2-K (MATE2-K). Abacavir is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters. Abacavir is an inhibitor of MATE1 *in vitro,* however abacavir has low potential to affect the plasma concentrations of MATE1 substrates at therapeutic drug exposures (up to 600 mg).

Effect of other agents on the pharmacokinetics of abacavir *In vitro,* abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, Multidrug resistance-associated protein 2 (MRP2) or MRP4, therefore drugs that modulate these transporters are not expected to affect abacavir plasma concentrations. Although abacavir is a substrate of BCRP and Pgp *in vitro,* clinical studies demonstrate no clinically significant changes in abacavir pharmacokinetics when co-administered with lopinavir/ritonovir (Pgp and BCRP inhibitors).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

BAVIR is contra-indicated in pregnancy.

Breastfeeding

BAVIR is contra-indicated in lactation.

4.7 Effects on ability to drive and use machines

No currently available data suggests that BAVIR affects the ability to drive or operate machinery.

4.8 Undesirable effects

a) Summary of the safety profile

Hypersensitivity: In clinical studies, approximately 4 % of subjects receiving **BAVIR** developed a hypersensitivity reaction which in rare cases proved fatal. This 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.

Symptoms can occur at any time while being treated with **BAVIR**, but usually appear within the first 6 weeks of initiation of treatment with **BAVIR** (median time to onset 11 days).

b) Tabulated list of adverse reactions

The signs and symptoms of this hypersensitivity reaction are tabulated below:

System Organ Class	**Adverse effect**	**Frequency**
Blood and the lymphatic system disorders	Lymphopenia	Frequent
Nervous system disorders	Paraesthesia, headache.	Frequent
Respiratory, thoracic and mediastinal disorders	Dyspnoea, sore throat, cough	Frequent
Gastrointestinal disorders	Mouth ulceration, diarrhoea, abdominal pain	Frequent
	Nausea, vomiting	Frequency unknown
Hepato-biliary disorders	Hepatic failure, elevated liver function tests	Frequent

Skin and subcutaneous tissue disorders:	Rash (usually maculopapular or urticarial)	Frequent
Musculoskeletal, connective tissue and bone disorders	Elevated creatine phosphokinase, myalgia, myolysis, arthralgia	Frequent
Renal and urinary disorders	Elevated creatinine, renal failure	Frequent
General disorders and administration site conditions	Fatigue, fever, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis	Frequent

Some patients with hypersensitivity reactions were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in **BAVIR** being continued or re-introduced, leading to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reactions should be carefully considered for patients presenting with symptoms of these diseases.

Symptoms worsen with continued therapy, and usually resolve upon discontinuation of **BAVIR**. Restarting **BAVIR** following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction may be more severe than on initial presentation, and may include life-threatening hypotension and death. Patients who develop this hypersensitivity reaction MUST discontinue **BAVIR** and MUST NOT be re-challenged.

An Alert Card with information for the patient about the hypersensitivity reaction is included in the **BAVIR** pack (see section 4.4).

The adverse events reported during therapy for HIV disease with **BAVIR** were similar in adults and children.

System Organ Class	Adverse effect	Frequency
Metabolism and nutrition disorders	Anorexia, hyperlactataemia	Frequent
	Elevated blood glucose and triglyceride concentrations	Unknown
	lactic acidosis	Less frequent
Nervous system disorders	Headache	Frequent
Gastrointestinal disorders	Diarrhoea, nausea, vomiting	Frequent
	Pancreatitis	Less frequent
Skin and subcutaneous tissue disorders	Skin rash (without systemic symptoms)	Frequent
	Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	Less frequent
General disorders and administration site conditions	Lethargy and fatigue, fever	Frequent

c) Description of selected adverse reactions

Gastrointestinal disorders: Pancreatitis has been reported but a causal relationship to **BAVIR** treatment is uncertain. In general, adverse events have been transient and not treatment-limiting.

Hepatobiliary disorders: Lactic acidosis/severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including abacavir, in the treatment of HIV infection. A majority of these cases have been in women. Caution should be exercised when administering **BAVIR** to any patient, and particularly to those with known risk factors for liver disease. Treatment with **BAVIR** should be suspended in any patient who

develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

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

Pharmacological Classification:

A 20.2.8 Antivirals

Pharmacotherapeutic group: Nucleoside reverse transcriptase inhibitors

ATC Code: J05AF06

Pharmacological Action:

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 HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo,* requiring multiple mutations to reach an eight-fold increase in IC_{50} 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 **BAVIR** to nucleoside reverse transcriptase inhibitors provides additional benefit in reducing viral load, and increasing CD_4 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 1.0 hour for the solution 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 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.

Metabolism: Abacavir is primarily metabolised by the liver with less than 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 dose in the urine.

Elimination: The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant 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 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 contra-indicated 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.

Children:

Abacavir is well absorbed from an oral solution administered to children. The overall pharmacokinetic parameters in children are comparable to adults, with slightly greater variability in plasma concentrations. The recommended dose for children from 3 months to 12 years 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 a day in adults.
There are insufficient safety data to recommend the use of abacavir in infants less than 3 months old.

Elderly:

The pharmacokinetics of abacavir has 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 and cardiac function, and concomitant disease or other drug therapy.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

BAVIR TABLETS 300 mg:

Colloidal silicon dioxide (Aerosil 200), Magnesium stearate, microcrystalline cellulose (Avicel PH 102), Opadry Yellow 13K52177 (comprised of Hypromellose 6 cp, Iron Oxide Yellow (C.I. No: 77492), Polysorbate 80, Titanium Dioxide (C.I. No: 77891) and Triacetin), Sodium starch glycolate (Primogel).

BAVIR ORAL SOLUTION 20 mg/ml:

Banana flavour 85509H $, Citric acid anhydrous, Methyl paraben, Non crystallizing sorbitol solution (Neosorb 70/70B), Propylene glycol, Propyl paraben, Saccharin sodium, Sodium citrate dihydrate, Strawberry cream flavour (11407-33 $).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

BAVIR TABLETS 300 mg: 36 months

BAVIR ORAL SOLUTION 20 mg/ml: 24 months

6.4 Special precautions for storage

BAVIR TABLETS 300 mg:

Store at or below 30 ºC.

BAVIR ORAL SOLUTION 20 mg/ml:

Store at or below 30 ºC. Keep well closed.

Discard oral solution two months after first opening.

6.5 Nature and contents of container

BAVIR TABLETS 300 mg:

1. Tablets are packed in a white round 110 ml HDPE container with 38 mm polypropylene closure with induction sealing wad.

Pack size: Each container contains 60 tablets.

2. Tablets are packed in 100 ml HDPE container with 38 mm closure with induction sealing wad.

Pack size: Each container contains 60 tablets.

BAVIR ORAL SOLUTION 20 mg/ml:

1. White, round 330 ml HDPE container with 28 mm polypropylene closure with screw cap with expanded polyethylene wad and pilfer proof skirt.

Pack size: 240 ml in a HDPE bottle.

2. White opaque 250 ml HDPE bottle with 28 mm closure.

Pack size: 240 ml in a HDPE bottle.

3. White opaque 250 ml HDPE bottle with 28 mm polypropylene child resistant closure with induction sealing wad

Pack size: 240 ml in a HDPE bottle.

A syringe is included in the pack.

6.6 Special precautions for disposal and other handling

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Aurobindo Pharma (Pty) Ltd

Woodhill Office Park, Building 1,

53 Phillip Engelbrecht Avenue,

Meyersdal, Ext. 12,

1448, Johannesburg,

South Africa.

8 REGISTRATION NUMBERS:

BAVIR TABLETS 300 mg: 41/20.2.8/0917

BAVIR ORAL SOLUTION 20 mg/ml: 41/20.2.8/0387

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration:

BAVIR TABLETS 300 mg: 30 April 2010

BAVIR ORAL SOLUTION 20 mg/ml: 19 March 2010

10 DATE OF REVISION OF THE TEXT

11 April 2024