PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS (Tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS

Each film-coated tablet contains abacavir sulfate equivalent to abacavir 600 mg and lamivudine 300 mg. Contains titanium dioxide.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS

Orange coloured, modified capsule shaped film-coated tablets, debossed with ‘H’ on one side and ‘27’ on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS are indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents from 12 years of age.

4.2 Posology and method of administration

Posology

Patients should be stabilised on individual medicines before being switched over to **AURO ABACAVIR/ LAMIVUDINE 600/300 mg TABLETS.** Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

AURO ABACAVIR/ LAMIVUDINE 600/300 mg TABLETS should not be administered to adults or adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose reduced.

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS can be taken with or without food.

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS is a fixed-dose tablets and should not be prescribed for patients requiring dosage adjustments, such as those with mild hepatic impairment or those with a renal clearance less than 50 mL/min. Separate preparations of abacavir or lamivudine should be administered in cases where discontinuation of dose adjustment is indicated. In these cases the medical practitioner should refer to the individual product information for those medicines.

Adults and adolescents: The recommended dosage is one tablet once daily.

Special populations

Renal Impairment:

Whilst no dosage adjustment of abacavir is necessary for patients with renal dysfunction, a dose reduction of lamivudine is required due to decreased clearance. **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** is not recommended for use in patients with a creatinine clearance < 50 mL/min (see section 5.2 and 4.3).

Hepatic Impairment:

A dose reduction of abacavir is likely to be required for patients with mild hepatic impairment, as dose reduction is not possible with **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** the separate preparations should be used when judged necessary. **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** must not be used on patients with moderate to severe hepatic impairment (see section 5.2).

Paediatric population

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS is not recommended for the treatment of children as the necessary dose adjustment cannot be made. Medical practitioners should refer to the individual package insert for lamivudine and abacavir.

Method of administration

To be taken orally.

4.3 Contraindications

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS are contra-indicated in patients:

- with known hypersensitivity to abacavir or lamivudine or any ingredient of **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** (see section 6.1).
- with moderate to severe liver function impairment.
- who are pregnant and breastfeeding their babies.

As **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** is a fixed-dose tablet, a reduction of the dose is not possible, therefore **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** is contra-indicated in:

- Patients with moderate to severe renal impairment (creatinine clearance < 50mL/min),
- Patients who weigh less than 40 kg,
- Children younger than 12 years old.

4.4 Special warnings and precautions for use

WARNING:

Hypersensitivity: In clinical studies, approximately 5 % of subjects receiving abacavir, contained in AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS, developed a hypersensitivity reaction which in some cases proved 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 a prospective study, use of pre-therapy 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 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.

Screening for carriage of the HLA-B*5701 allele is recommended in any HIV-infected patient without prior exposure to abacavir. Screening is recommended prior to re-initiation of abacavir in patients of HLA-B*5701 status who have previously tolerated

abacavir (see "Special considerations following interruption of AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS").

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.

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. The symptoms of this hypersensitivity reaction can occur at any time during treatment with AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS, but usually appear within the first 6 weeks of initiation of treatment with AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS (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 abacavir such as in AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS.

Clinical Management:

Patients developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed, AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS MUST be discontinued immediately.

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS, 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, AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS 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 medicines).

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS or any other medicine containing abacavir should not be re-started even if a recurrence of symptoms occurs following rechallenge with alternative medicines.

An Alert Card with information for the patient about the hypersensitivity reaction is included in the AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS.

Special considerations following an interruption of AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS therapy:

If therapy with AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS 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 AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS due to possible adverse reactions or illness should be advised to contact their doctor before restarting. If hypersensitivity cannot be ruled out AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS should not be restarted.

There have been infrequent reports of hypersensitivity reactions following reintroduction of abacavir such as in AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS, where the interruption was preceded by a single key symptom (e.g. rash, fever, respiratory or gastrointestinal symptoms).

If a decision is made to restart AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS in these patients this should be done only under direct medical supervision.

Hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no apparent preceding symptoms of a hypersensitivity reaction.

If a decision is made to re-start AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS this must be done only if medical care can be accessed readily by the patient or others.

Screening for carriage of HLA-B*5701 allele is recommended prior to re-initiation of AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS in patients of unknown HLA-B*5701 status who have previously tolerated AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS. Re-initiation of AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS 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 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.**
- **Patients who are hypersensitive to abacavir should be reminded that they must never take AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS or any abacavir containing medicine again regardless of their HLA-B*5701 status.**

- **In order to avoid restarting AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS, patients who have experienced a hypersensitivity reaction should be asked to return the remaining AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS to the pharmacy.**
- **Patients who have stopped AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS 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 AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS pack.**
- **They should be reminded of the importance of removing the Alert Card included in the pack and keeping it with them at all times.**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination, with other antiretrovirals in the treatment of HIV infection.

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. 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), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS**, 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 **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** 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 **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** to patients with known risk factors for liver disease. Treatment with **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** 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 **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS**. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment (creatinine clearance < 50 mL/min)

In patients with moderate to severe renal impairment, the terminal half-life of **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS**is increased due to decreased clearance. As **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS,** is a fixed-dose tablet, the dose cannot be adjusted, it should therefore not be given to patients with moderate to severe renal impairment (see section 4.3).

Liver disease

Use of **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** 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 lamivudine contained in **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** 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. Discontinuation of **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Hypersensitivity

Patients who develop a hypersensitivity reaction must discontinue **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS and MUST not be rechallenged with AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS (see section 4.4).**

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 **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS**, 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.

Paediatric population

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS is not recommended for the treatment of children as the necessary dose adjustment cannot be made. Medical practitioners should refer to the individual package insert for lamivudine and abacavir (see section 4.2).

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS contains sodium

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

4.5 Interaction with other medicines and other forms of interaction

Interactions relevant to lamivudine:

Zalcitabine:

Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used together. **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** is therefore not recommended to be used in combination with zalcitabine.

Trimethoprim:

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg (co-trimoxazole) results in a 40 % increase in lamivudine exposure, because of the trimethoprim component. However, unless the patient has renal impairment, no dose adjustment of lamivudine is necessary (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis carinii* pneumonia and toxoplamosis has not been studied.

The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance.
Lamivudine is predominately eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is renal. Interactions listed herein should not be considered exhaustive but are representative of the classes of medicinal products where caution should be exercised.

Interactions relevant to abacavir:

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 AUC was unchanged. These 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 dose re-titration may be required.

Ethanol:

The metabolism of abacavir is altered by concomitant consumption of ethanol resulting in increase in AUC if abacavir of about 41 %. Given the safety profile of abacavir, these findings are not considered clinically significant. Abacavir has no effect on the metabolism of ethanol.

Retinoids: Isotretinoin

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

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS contains abacavir and lamivudine therefore any interactions for those individually relate to **AURO ABACAVIR/ LAMIVUDINE 600/300 mg TABLETS**. Clinical studies have shown that there are no clinically significant interactions between abacavir and lamivudine. Abacavir and lamivudine are not significantly metabolised by cytochrome P_{450} enzymes (such as CYP 3A4, CYP 2C9 or CYP 206) nor do they induce or inhibit this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P450 enzymes.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

No information available.

Pregnancy

AURO ABACAVIR/ LAMIVUDINE 600/300 mg TABLETS are contra-indicated in pregnancy. Teratogenicity has been observed with **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS.**

Breastfeeding

AURO ABACAVIR/ LAMIVUDINE 600/300 mg TABLETS are contra-indicated in lactation. Lamivudine is excreted and abacavir may be secreted, in human milk.

Fertility

No fertility data available.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse reaction profile of **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** must be taken into account when considering the patient's ability to drive and operate machines.

4.8 Undesirable effects

a) Summary of the safety profile

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS contains abacavir and lamivudine, therefore the adverse effects associated with the medicines may be expected.

b) Tabulated list of adverse reactions

- Frequency not known- cannot be estimated from the available data.

Lamivudine:

System Organ Class	**Adverse effect**	**Frequency**
Blood and the lymphatic system disorders:	Lymphopenia, leukopenia.	*Frequent*
	Neutropenia, anaemia, thrombocytopenia, pure red cell aplasia.	*Less Frequent*
Metabolism and nutrition disorders:	Hyperlactataemia	*Frequent*
	Lactic acidosis, redistribution/accumulation of body fat.	*Less Frequent*
Nervous system disorders:	Headache, insomnia	*Frequent*
	Peripheral neuropathy (or paraesthesia)	*Less Frequent*
Respiratory, thoracic and mediastinal disorders:	Cough, nasal symptoms	*Frequent*
Gastrointestinal disorders:	Adult respiratory distress syndrome, respiratory failure.	*Frequency not known*

System Organ Class	Adverse effect	Frequency
	Diarrhoea, abdominal pain, nausea, vomiting	*Frequent*
	Rises in serum amylase, pancreatitis	*Less Frequent*
Hepato-biliary disorders:	Transient rises in liver enzymes (AST, ALT), hepatitis	*Less Frequent*
Skin and subcutaneous tissue disorders:	Rash (usually maculopapular or urticarial), alopecia	*Frequent*
Musculoskeletal, connective tissue and bone disorders:	Arthralgia, muscle disorders	*Frequent*
	Rhabdomyolysis Elevated creatine phosphokinase, myalgia, myolysis.	*Less Frequent*
Renal and urinary disorders:	Elevated creatinine, renal failure	*Frequent*
General disorders and administration site conditions:	Fatigue, fever, malaise.	*Frequent*

Abacavir:

System Organ Class	Adverse effect	Frequency
Immune system disorders	Hypersensitivity, fever, rash (usually maculopapular or urticarial)	*Frequent*
Metabolism and nutrition disorders:	Anorexia, hyperlactataemia	*Frequent*
	Lactic acidosis, redistribution/accumulation of body fat.	*Less frequent*
Nervous system disorders	Headache	*Frequent*
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration	*Frequent*
	Pancreatitis	*Less frequent*
Skin and subcutaneous tissue disorders	Rash (without systemic symptoms)	*Frequent*
	Erythema multiforme, stevens-johnson syndrome and toxic epidermal necrolysis	*Less frequent*

System Organ Class	Adverse effect	Frequency
General disorders and administration site conditions:	Fever, lethargy, fatigue	*Frequent*

c) Description of selected adverse reactions

Abacavir:

Hypersensitivity: In clinical studies, approximately 5 % of subjects receiving **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** developed a hypersensitivity reaction which in some cases proved fatal. This reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever.

Symptoms may occur at any time while being treated with **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** , but usually appear within the first 6 weeks of initiation of treatment with **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** (median time to onset 11 days).

The signs and symptoms of this hypersensitivity reaction are listed below. Those reported **in at least 10 %** of patients with a hypersensitivity reaction are in bold text.

Haematological: lymphopaenia

Neurological/Psychiatry: **headache,** paraesthesia

Respiratory tract: **dyspnoea, cough**, sore throat, adult respiratory distress syndrome, respiratory failure.

Gastrointestinal tract: **nausea, vomiting, diarrhoea, abdominal pain,** mouth ulceration.

Liver/pancreas: **elevated liver function tests**, hepatic failure

Skin: **rash** (usually maculopapular or urticarial)

Miscellaneous: **fever, fatigue malaise,** oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis

Musculoskeletal: **myalgia,** rarely myolysis, arthralgia, elevated creatine phosphokinase

Urology: elevated creatine, renal failure

Some patients with hypersensitivity reactions were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis or reactions to other medicines. This delay in diagnosis of hypersensitivity has resulted in **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** 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. If hypersensitivity reactions cannot be ruled out, **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** or any other medicine containing abacavir should not be restarted.

Symptoms related to this hypersensitivity reaction worsen with continued therapy, and may resolve upon discontinuation of **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS**.

Restarting **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** 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 AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS and MUST NOT be rechallenged with AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS or any other medicine containing abacavir.** There has 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 or a respiratory

symptom). Hypersensitivity reactions have been reported in patients who have restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction.

An Alert Card with information for the patient about the hypersensitivity reaction is included in the **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** pack (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. Health care 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

Symptoms: See section 4.8.

Treatment: If overdosage occurs the patient should be monitored for evidence of toxicity, and standard symptomatic and supportive treatment applied as necessary. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis. Lamivudine is dialysable.

Additional information on special populations

Not applicable.

Paediatric population

Not applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION

A 20.2.8 Antiviral agents

Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HIV infections, combinations

ATC Code: J05AR02

PHARMACOLOGICAL ACTION

Abacavir and lamivudine are nucleoside analogue reverse transcriptase inhibitors (NRTIs) and are potent selective inhibitors of HIV-1 and HIV-2. Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective 5'- triphosphate (TP). Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir), are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates show significantly less affinity for host cell DNA polymerases. Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Abacavir shows synergy *in vitro* in combination with amprenavir, nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, stavudine and lamivudine.
HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral RT. This variant arises both *in vitro* and HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display

greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. Studies *in vitro* indicate that zidovudine- resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the 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 clinically relevant level. Isolates resistant to abacavir might also show reduced sensitivity to lamivudine, zalcitabine, tenofovir, emtricitabine and/or didanosine, but remain sensitive to zidovudine and stavudine.

Cross-resistance between abacavir or lamivudine and antiretrovirals from other classes e.g. protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI), is unlikely. Reduced susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors.

Clinical isolates with three or more mutations associated with NRTIs are unlikely to be susceptible to abacavir. Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral medicines. Zidovudine, stavudine, abacavir and tenofovir maintain their antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation.

5.2 Pharmacokinetic properties

Absorption:

Abacavir and lamivudine are well absorbed from the gastro-intestinal tract following oral administration. The absolute bioavailability of oral abacavir and lamivudine in adults is about 83 % and 80 % – 85 % respectively. The mean time to maximal serum concentrations (t_{max}) is about 1,5 hours and 1,0 hour for abacavir and lamivudine respectively. Following a single dose of 600 mg of abacavir, the mean C_{max} is 4,26 µg/mL and the mean AUC is 11,95 µg.h/mL. Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days, the mean steady-state C_{max} is 2,04 µg/mL (26 %) and the mean AUC24 is 8,87 µg.h/mL.

Distribution:

Intravenous studies with abacavir and lamivudine showed that the mean apparent volume of distribution is 0,8 and 1,3 L/kg respectively. Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (≈49 %) to human plasma proteins at therapeutic concentrations. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited plasma protein binding *in vitro* (< 36 %). This indicates a low likelihood for interactions with other medicines through plasma protein binding displacement. Data show that abacavir and lamivudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). Studies with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44 %. The observed values of the peak CSF concentrations are 9-fold greater than the IC_{50} of abacavir of 0,08 µg/mL or 0, 26 µm when abacavir is given at 600 mg twice daily. The mean ratio of CSF/serum lamivudine concentrations 2 – 4 hours after oral administration was approximately 12 %. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Metabolism:

Abacavir is primarily metabolised by the liver with approximately 2 % of the administered dose being renally excreted as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce 5'-carboxylic acid and 5'- glucuronide which account for about 68 % of the administered dose. These metabolites are excreted in the urine. Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared by renal excretion of unchanged lamivudine. The likelihood of metabolic interactions with lamivudine is low due to the small extent of hepatic metabolism (less than 10 %).

Elimination:

The mean half-life of abacavir is 1,5 hours. Following multiple 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 dose in the urine. The remainder is eliminated in the faeces. The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 L/h/kg, predominately by renal clearance (>70 %) via the organic cationic transport system.

Special populations:

Hepatically impaired:

Pharmacokinetic data have been obtained for abacavir and lamivudine alone. 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 liver disease. However, the rates of formation and elimination of these were decreased.

Dosage reduction of abacavir is likely to be required in patients with mild hepatic impairment. A separate preparation of abacavir should therefore be used to treat these patients.

The pharmacokinetics of abacavir have not been studied in patient with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to be variable and substantially increased in these patients. **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** is therefore contra-indicated in patients with moderate to severe hepatic impairment.

Data obtained for lamivudine in patients with mild to severe hepatic impairment show that the pharmacokinetics are not significantly affected by hepatic dysfunction.

Renally Impaired:

Pharmacokinetic data have been obtained for lamivudine and abacavir alone. Abacavir is primarily metabolised by the liver and 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. Studies with lamivudine show the plasma concentrations (AUC) are increased with patients with renal dysfunction due to decreased clearance. Dose reduction of lamivudine is required for patients with creatinine clearance of < 50 mL/min therefore a separate preparation of lamivudine should be used to treat these patients as **AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS** is a fixed dose preparation.

Paediatric population

Not applicable.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients of the formulation are:

- microcrystalline cellulose,
- titanium dioxide,
- sodium starch glycolate,
- magnesium stearate,
- opadry orange and,
- purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 ℃. Keep the container tightly closed.

6.5 Nature and contents of container

AURO ABACAVIR/LAMIVUDINE 600/300 mg TABLETS

HDPE Container Pack:

Tablets are packed in white HDPE containers with a white closure with an induction sealing wad. Each container contains 30 tablets.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Aurobindo Pharma (Pty) Ltd

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Johannesburg

South Africa

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10 DATE OF REVISION OF THE TEXT

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