Professional Information for ADCO-LAMIVUDINE 300 mg TABLETS

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ADCO-LAMIVUDINE 300 mg TABLETS, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains: 300 mg lamivudine.

Sugar free

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

A white film-coated, oval shaped tablet debossed with 'H' on one side and '31' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO-LAMIVUDINE 300 mg TABLETS is indicated as part of antiretroviral combination therapy for the treatment of HIV infected adults and children. This formulation is not suitable for children below the age of 12 years and patients less than 50 kg in weight.

4.2 Posology and method of administration

Adults and adolescents more than 12 years of age:

The recommended dose of **ADCO-LAMIVUDINE 300 mg TABLETS** is 300 mg daily.

The professional information for zidovudine must be consulted for information on its dosage and administration. This formulation is not suitable for children below 12 years of age and in patients weighing less than 50 kg.

ADCO-LAMIVUDINE 300 mg TABLETS can be taken with or without food.

Special populations

Renal and Hepatic Impairment:

Renal impairment, whether disease- or age-related, affects lamivudine elimination. In patients with a creatinine clearance below 50 ml/min, lower dosage is required. Therefore, this formulation is not suitable for patients with renal impairment.

4.3 Contraindications

Hypersensitivity to lamivudine or to any of the components listed in section 6.1.

4.4 Special warnings and precautions for use

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 **ADCO-LAMIVUDINE 300 mg TABLETS** and other antiretroviral agents may continue to develop opportunistic infections and other complications of HIV infection. Patients should therefore remain under close observation by healthcare professionals experienced in the treatment of patients with HIV-associated diseases. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including **ADCO-LAMIVUDINE 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 **ADCO-LAMIVUDINE 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 to 5 mmol/L with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.

- Lactate 5 to 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 **ADCO-LAMIVUDINE 300 mg TABLETS** to patients with known risk factors for liver disease.

Treatment with **ADCO-LAMIVUDINE 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 **ADCO-LAMIVUDINE 300 mg TABLETS**. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **ADCO-LAMIVUDINE 300 mg TABLETS** until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of **ADCO-LAMIVUDINE 300 mg TABLETS** is increased due to decreased clearance. The dose of **ADCO-LAMIVUDINE 300 mg TABLETS** should therefore be adjusted (see section 4.2).

Liver disease

Use of **ADCO-LAMIVUDINE 300 mg TABLETS** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **ADCO-LAMIVUDINE 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 professional information for these medicines.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

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

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

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

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

Patients co-infected with HIV and HBV who discontinue **ADCO-LAMIVUDINE 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 **ADCO-LAMIVUDINE 300 mg TABLETS** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

4.5 Interaction with other medicines and other forms of interaction

Zidovudine plasma levels are not significantly altered when co-administered with **ADCO-LAMIVUDINE 300 mg TABLETS** (see section 5.2).

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine plasma concentrations at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment.

Administration of co-trimoxazole with the **ADCO-LAMIVUDINE 300 mg TABLETS**/zidovudine combination in patients with renal impairment should be carefully assessed.

ADCO-LAMIVUDINE 300 mg TABLETS may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Use of **ADCO-LAMIVUDINE 300 mg TABLETS** in combination with zalcitabine is therefore not recommended.

Due to similarities, **ADCO-LAMIVUDINE 300 mg TABLETS** should not be administered concomitantly with other cytidine analogues, such as emtricitabine.

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended.

Coadministration of sorbitol solution (3,2 g, 10,2 g, 13,4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14 %, 32 %, and 36 % in lamivudine exposure (AUC∞) and 28 %, 52 %, and 55 % in the C_{max} of lamivudine in adults. When possible, avoid chronic coadministration of **ADCO-LAMIVUDINE 300 mg TABLETS** with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account.

Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats.

Placental transfer of lamivudine has been shown to occur in humans.

More than 1000 reported outcomes from first trimester and more than reported 1000 outcomes from second and third trimester exposure in pregnant women indicate no malformative and foeto/neonatal effect. Lamivudine can be used during pregnancy if clinically needed. The malformative risk is unlikely in humans based on those data.

For patients co-infected with hepatitis who are being treated with lamivudine and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

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 infants exposed *in utero* and/or post-natally to nucleoside analogues (see section 4.4).

Breastfeeding

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum.

Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4 % of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed

infants reach 24 weeks of age. There are no data available on the safety of lamivudine when administered to babies less than three months old. It is recommended that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

Studies in animals showed that lamivudine had no effect on fertility.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

The following side effects have been reported during therapy of HIV disease with **ADCO-LAMIVUDINE 300 mg TABLETS** alone, and in combination with other anti-retrovirals.

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	*Less frequent*	Neutropenia, thrombocytopenia, anaemia, pure red cell aplasia.
Metabolism and nutrition disorders	*Less frequent*	Lactic acidosis.
Nervous system disorders	*Frequent*	Peripheral neuropathy, paraesthesia, headache, insomnia.
Respiratory, thoracic and mediastinal disorders	*Frequent*	Cough, nasal symptoms
Gastrointestinal disorders	*Frequent*	Upper abdominal pain or cramps, nausea, vomiting, diarrhoea, pancreatitis.

	Frequency unknown	Rises in serum amylase
Hepato-biliary disorders	*Less frequent*	Hepatitis.
	Frequency unknown	Transient rises in serum liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders	*Frequent*	Skin rash.
	Less frequent	Angioedema.
	Frequency unknown	Alopecia.
Musculoskeletal and connective tissue disorders	*Frequent*	Arthralgia and muscle disorders.
	Frequency unknown	Rhabdomyolysis.
General disorders and administration site conditions	*Frequent*	Malaise, fatigue and fever.

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

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 20.2.8 Antiviral agents

Nucleoside analogue, ATC Code: J05AF05

Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication in vitro, including zidovudine-resistant clinical isolates of the human immunodeficiency virus (HIV). Lamivudine is metabolised intracellularly to the active 5'-triphosphate, which inhibits the RNA- and DNA-dependant activities of HIV reverse transcriptase by termination of the viral DNA chain. Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content. In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells. In vitro, lamivudine therefore has a high therapeutic index. Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolated from patients who have received lamivudine therapy before. Lamivudine has been shown to act additively or synergistically with other anti-HIV agents, particularly zidovudine, inhibiting the replication of HIV in cell culture. in vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine-sensitive when they acquire resistance to lamivudine.

5.2 Pharmacokinetic properties

Pharmacokinetics in adults:

Following oral administration, lamivudine is well absorbed with bioavailability of approximately 80 %.

The mean lime (T_{max}) to maximum serum concentration (C_{max}) is about an hour. At therapeutic dose levels of 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1 to 1,5 ug/ml.

The mean volume of distribution from intravenous studies has been reported as 1,3 L/kg and the mean terminal half-life of elimination as 5 to 7 hours. The mean systemic clearance of

lamivudine is approximately 0,32 L/kg/h, with predominantly renal clearance of more than 70 % via active tubular secretion, but little hepatic metabolism, at less than 10 %. The intracellular half-life of the lamivudine triphosphate active metabolite is prolonged, averaging over 10 hours in peripheral blood lymphocytes.

A delay in T_{max} and reduction in C_{max} have been observed when co-administered with food, but no dose adjustment is needed, as lamivudine bioavailability is not altered. Lamivudine displays limited binding to albumin and exhibits linear pharmacokinetics over the therapeutic dose range. Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. No dosage adjustments are necessary, as this is not considered to be of significance to patient safety.

Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The true extent of penetration or relationship with any clinical efficacy is unknown.

Pharmacokinetics in children:

In general, lamivudine pharmacokinetics in paediatric patients is similar to adults. However, absolute bioavailability is reduced to approximately 65 % in paediatric patients, with an increased clearance of 0,52 L/kg/h.

There are limited pharmacokinetic data for patients < 3 months of age.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate

Film coating:

Hypromellose

Macrogol

Polysorbate 80

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep well closed, store in a dry place and at or below 25 °C in the original package.

Protect from moisture and light.

6.5 Nature and contents of the container

ADCO-LAMIVUDINE 300 mg TABLETS is packed in sizes of 28's, 30's and 600's in a white HDPE container with a white polypropylene cap or white child resistant plastic cap that has a pulp lining.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special precautions

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand, 1685

0860 ADCOCK (232625)

8. REGISTRATION NUMBER(S)

44/20.2.8/0294

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 July 2010

10. DATE OF REVISION OF TEXT

04 January 2022

Solely for use in South Africa and in the Sub-Saharan African countries stated below: Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Comoros, Congo, Coted' Ivoire, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Rwanda, Senegal, Seychelles, Sierra Leone, Somalia, Swaziland, Tanzania, Togo, Uganda, DR Congo (Zaire), Zambia, Zimbabwe.