# PROESSIONAL INFORMATION

**SCHEDULING STATUS:** **S4**

**PROPRIETARY NAME: ADCO LAMIVUDINE AND ZIDOVUDINE 150/300**

**(AND DOSAGE FORM) (FILM-COATED TABLET)**

**COMPOSITION:**

Each film-coated tablet contains:

| | |
|---|---|
| Zidovudine | 300 mg |
| Lamivudine | 150 mg |

Sugar free

**List of excipients:** Colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and colour Opadry white (Polyvinyl chloride, titanium dioxide, Macrogol/PEG 3350, talc).

**PHARMACOLOGICAL CLASSIFICATION:**

A: 20.2.8 Antiviral agents

**PHARMACOLOGICAL ACTION:**

**Pharmacodynamics:**

Lamivudine, a pyrimidine analogue and zidovudine, a thymidine analogue reverse transcriptase inhibitor are selective inhibitors of human immunodeficiency virus HIV-1 and HIV-2. Lamivudine has been shown to be synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Both medicines are metabolised, sequentially by intracellular kinases to the 5'-triphosphate (TP). Lamivudine-TP and zidovudine-TP are substrates for and competitive inhibitors of HIV reverse transcriptase. However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination.

*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*.

In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine

within 12 weeks. In some patients harbouring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy.

Dual resistance required the presence of multiple mutations, the most essential of which may be at codon 333 (Gly→Glu). The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine-resistant isolates of HIV-1 have been selected *in vitro* and have also been recovered from patients treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of the resistant isolates showed that the resistance was due to mutations in the HIV-1 reverse transcriptase gene at codon 184 from methionine to either isoleucine or valine.

HIV isolates with reduced susceptibility to zidovudine have been selected *in vitro* and were also recovered from patients treated with zidovudine.

Genotypic analyses of the isolates showed mutations which result in 5 amino acid substitutions (Met41→Leu, Asp67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) in the HIV-1 reverse transcriptase gene. In general, higher levels of resistance were associated with greater number of mutations.

Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination, isolates have emerged with a mutation at codon 184, which confers resistance to lamivudine. In the presence of the 184 mutation, cross-resistance to didanosine and zalcitabine has been seen in some patients. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple medicines, including lamivudine, have emerged.

HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for > 1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of genotypic resistant mutations with such combination therapies was different (Ala62→Val, Val75→Ile, Phe77→Leu, Phe116→Tyr, and Gln1→Met) from the pattern with zidovudine monotherapy, with the 151 mutation being most commonly associated with multidrug resistance. The mutation at codon 151 in combination with the

mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine.

Multiple-drug resistance has been observed in 5 % patients receiving zidovudine and didanosine combination therapy for 2 years.

Lamivudine in combination with zidovudine reduces HIV-1 viral load and increases CD4+ cell counts. Clinical end-point data indicate that lamivudine in combination with zidovudine, and lamivudine/zidovudine-containing treatment regimens result in a significant reduction in the risk of disease progression and mortality.

Individually, lamivudine and zidovudine therapy has resulted in HIV clinical isolates which show reduced sensitivity *in vitro* to the nucleoside analogue to which they have been exposed. Evidence from clinical studies shows that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior anti-retroviral therapy.

The relationship between *in vitro* susceptibility of HIV to lamivudine and/or zidovudine and the clinical response to therapy remain under investigation.

*In vitro* sensitivity testing has not been standardised and results may vary according to methodological factors.

**Pharmacokinetics:**

**Absorption:**

Lamivudine and zidovudine are well absorbed from the gastrointestinal tract. The bioavailability of oral lamivudine in adults is normally between 80 to 85 % and for zidovudine 60 to 70 %.

The $C_{max}$ values for lamivudine was found to be between 1,3 to 1,8 µg/ml and the $C_{max}$ value for zidovudine was found to be between 1,5 to 2,2 µg/ml.

The median (range) of lamivudine and zidovudine tmax values were 0,75 (0,50 to 2,00) hours and 0,50 (0,25 to 2,00) hours respectively.

The extent of lamivudine and zidovudine absorption following administration with food were similar when administered without food, although the rate of absorption was slowed. Based on the above, the combination of lamivudine and zidovudine may be administered with or without food.

**Distribution:**

The mean volume of distribution of lamivudine and zidovudine is 1,3 and 1,6 l/kg respectively. Lamivudine has a low plasma protein binding of less than 36 % and displays linear kinetics over the therapeutic dosage range.

Zidovudine plasma protein binding is between 34 to 38 %. Lamivudine and zidovudine penetrate the central nervous system and reaches the cerebrospinal fluid (CSF). The cerebrospinal fluid to plasma ratio of lamivudine is 0,12 and that of zidovudine is 0,6.

**Metabolism:**

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared by renal excretion of unchanged substance.

The 5'-glucuronide of zidovudine is the major metabolite of zidovudine in both plasma and urine, accounting for approximately 50 to 80 % of the administered dose, eliminated by renal excretion.

**Elimination:**

The majority of lamivudine is eliminated unchanged in the urine. The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is 0,32 l /h/kg with predominately renal clearance ( > 70 %) via the organic cationic transport system.

For renal function impaired patients having a creatinine clearance of ≤ 50 ml/min a reduction in dose is required (see '**DOSAGE AND DIRECTIONS FOR USE').**

The mean terminal plasma half-life of zidovudine is 1,1 hours and the mean systemic clearance was 1,6 l /h/kg. Renal clearance of zidovudine is estimated to be 0,34 l/h/kg, indicating glomerular filtration and active secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure. For patients that have impaired renal function with a creatinine clearance of less than 10 ml/min the $t_{1/2}$ for lamivudine is approximately 19,4 hours.

**Pharmacokinetics of the lamivudine and zidovudine combination when used in combination with other antiretroviral agents:**

**Zidovudine:**

Pharmacokinetic interaction studies indicate that there were no clinically significant alterations to zidovudine pharmacokinetics when given concomitantly with the following anti-retroviral agents:

*Nucleoside reverse transcriptase inhibitors (NRTI's):* zalcitabine, didanosine and abacavir; *non-nucleoside reverse transcriptase inhibitors*

(NNRTI's): nevirapine and efavirenz; *and protease inhibitors:* indinavir sulphate, saquinavir mesylate, ritonavir, amprenavir and nelfinavir.

There is a known interaction between zidovudine and stavudine (d4T) (see 'INTERACTIONS'). The concomitant use of these two agents should be avoided.

**Lamivudine:**

Pharmacokinetic interaction studies indicate that there were no clinically significant alterations to lamivudine pharmacokinetics when given concomitantly with the following antiretroviral agents:

*Non-nucleoside reverse transcriptase inhibitors* (NNRTI's): efavirenz; and *protease inhibitors*: indinavir sulphate, ritonavir and nelfinavir.

**Pharmacokinetics of lamivudine and zidovudine combination when used in combination with other tuberculostatic agents:**

**Zidovudine:**

Co-administration of zidovudine and rifampicin decreases the AUC of zidovudine by approximately 48 %; however, the clinical significance of this is unknown.

**Lamivudine:**

Metabolism of lamivudine is a minor route of elimination. Lamivudine is mainly cleared by renal excretion of unchanged lamivudine. The likelihood of metabolic medicine interactions e.g. rifampicin with lamivudine is low due to the small extent of hepatic metabolism (5 to 10 %) and low plasma protein binding.

**INDICATIONS:**

**ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** is indicated as part of antiretroviral combination therapy for the treatment of HIV infected adults and children over 12 years of age, with progressive immunodeficiency (CD4+ count ≤ 500 cells/$mm^3$).

**Post exposure prophylaxis in adults following occupational exposure:**

The best prophylaxis against occupational exposure is adherence to universal precautions including, amongst others, careful disposal of sharp objects e.g. needles and scalpels and the use of protective barriers (e.g. gloves, eyeglasses, etc).

**ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** is indicated for initial prophylactic treatment (until results of serology tests are available) in HIV negative adults whenever there has been exposure to material known to be, or strongly suspected to be, infected with HIV. This includes:

- percutaneous injury (from needles, instruments, bone fragments, etc)
- exposure to broken skin (abrasions, cuts, eczema, etc)
- exposure of mucus membranes including the eye.

Randomised clinical studies on the use of **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** following occupational exposure have not been performed.

The addition of a protease inhibitor to the combination regimen is recommended in the following cases:

- when a large volume of inoculation has occurred;
- when the source material has a high viral titre; or
- when inoculation has occurred from a patient with HIV resistant to **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300**, zidovudine and/or lamivudine.

**CONTRAINDICATIONS:**

- Hypersensitivity to lamivudine, zidovudine or to any ingredient of the preparation.
- Patients with abnormally low neutrophil cell counts (< 0,75 x 109/l) or abnormally low haemoglobin levels (< 7,5 g/dl or 4,65 mmol/l).
- Children below the age of 12 years.
- The concomitant use of either zalcitabine or stavudine with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** should be avoided.

**WARNINGS:**

Opportunistic infections and other complications of HIV infection may continue to develop in patients receiving **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** or any other antiretroviral therapy. Patients should therefore remain under close clinical observation by physicians experienced in the treatment of HIV infection.

***ADCO LAMIVUDINE AND ZIDOVUDINE 150/300*** *or any other current antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be advised that appropriate precautions should continue to be employed.*

**Haematological:** Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients with advanced symptomatic HIV disease receiving zidovudine, therefore haematological parameters should be carefully monitored (see '**CONTRAINDICATIONS**' and '**SIDE EFFECTS AND SPECIAL PRECAUTIONS**') in patients receiving **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300**. These haematological effects are not usually observed before four to six weeks therapy. It is generally recommended that blood tests be performed for patients with advanced symptomatic HIV disease on at least every two weeks for the first three months of therapy, and thereafter at least monthly.

In patients with early HIV disease, haematological adverse reactions are infrequent. Blood tests may be performed less often, for example every one to three months, depending on the overall condition of the patient. If haemoglobin levels are decreased by more than 25 % from baseline and falls in the neutrophil count of more than 50 % from baseline occur, more frequent monitoring may be required.

If severe anaemia or myelosuppression occurs during treatment with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300**, or in patients with pre-existing bone marrow compromise e.g. haemoglobin < 9 g/dl (5,59 mmol/l) or neutrophil count < 1,0 x 109/l (see '**DOSAGE AND DIRECTIONS FOR USE'**), dosage adjustment of zidovudine may be required. As dosage adjustment of **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** is not possible, separate preparations of zidovudine and lamivudine should be used. Physicians should refer to the individual package inserts of these medicines for dosage specifications.

Sero-conversion to HIV-positive status may still occur despite the prompt use of **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300**. The recommended prophylactic dose must be strictly adhered to (see '**DOSAGE AND DIRECTIONS FOR USE'**).

**Pancreatitis:** Rare cases of pancreatitis have been reported for patients treated with lamivudine and zidovudine. A causal relationship between drug treatment or the underlying HIV disease could not be established. If clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur, treatment with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** should be stopped immediately.

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

either alone or in combination, including **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** in the treatment of HIV infection. A majority of these cases have been in women (see 'Special precautions').

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 **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** to any patient and in particular to those with known risk factors of liver disease. Treatment with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations) (see '**Special precautions').**

**Fat redistribution:** Fat redistribution or accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and blood glucose levels have occurred. In addition, the lipodystrophy syndrome has a multi-factorial aetiology, with e.g. HIV disease, older age and duration of antiretroviral treatment all playing vital, possibly synergistic roles.

**INTERACTIONS:**

Any interactions that have been identified with zidovudine and lamivudine individually may occur with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300.**

The interactions listed below should not be considered exhaustive but are representative of the classes of medicine where caution should be exercised.

Interactions relevant to lamivudine:

Due to limited metabolism and plasma protein binding, and almost complete renal clearance, the likelihood of metabolic interactions with lamivudine is low.

Possible interactions with other medicines administered concurrently with ADCO LAMIVUDINE AND ZIDOVUDINE 150/300 should be investigated, particularly when the main route of elimination is active renal secretion especially via the cationic transport system e.g. trimethoprim. The nucleoside analogues (e.g. zidovudine, didanosine and zalcitabine) and other medicines (e.g. ranitidine, cimetidine) are eliminated partly by this mechanism and were shown not to interact with lamivudine.

Please refer to the 'Pharmacokinetics' sections for details on the interaction of lamivudine with other antiretroviral agents.

**Trimethoprim:**

It has been reported that administration of prophylactic doses of co-trimoxazole resulted in a 40 % increase in lamivudine exposure and this can be attributed to the trimethoprim component. No dosage adjustment of lamivudine is necessary, unless the patient has renal impairment (see '**DOSAGE AND DIRECTIONS FOR USE')**.

Patients should be monitored clinically, when concomitant administration with co-trimoxazole is warranted.

High doses of co-trimoxazole in combination with ADCO LAMIVUDINE AND ZIDOVUDINE 150/300 for the treatment of *Pneumocystis*

*(carinii) jirovecii pneumonia* (PCP) and toxoplasmosis should be avoided. The doses studied showed that lamivudine has no effect on the pharmacokinetics of co-trimoxazole.

Zalcitabine: Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently.

Therefore, **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** is not recommended to be used concurrently with zalcitabine (see '**CONTRAINDICATIONS').**

**Miscellaneous:** Until further information is available, co-administration of lamivudine with intravenous ganciclovir or foscarnet is not recommended.

Lamivudine metabolism does not involve CYP3A, making interactions with medicines metabolised by this system (e.g. protease inhibitors) unlikely.

**Interactions relevant to zidovudine:**

Zidovudine has limited protein binding but is eliminated primarily by hepatic conjugation to an inactive of glucuronidated metabolite.

**Lamivudine:**

Zidovudine has no effect on the pharmacokinetics of lamivudine.

Slight increase in $C_{max}$ (28 %) was observed for zidovudine when administered with lamivudine; however, overall exposure (AUC) was not significantly changed.

**Rifampicin:**

The co-administration of zidovudine and rifampicin decreases the AUC of zidovudine by 48 % ± 34 %. However, the clinical significance of this is unknown.

**Phenytoin:**

In some patients receiving zidovudine, the phenytoin blood levels have been reported to be low, while in one patient a high level was noted.

These observations imply that phenytoin concentrations should be monitored carefully in patients receiving **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** in combination with phenytoin.

**Probenecid:**

Limited data suggest that probenecid increases the mean half-life and area under the plasma concentration curve of zidovudine by decreasing glucuronidation. Renal excretion of the glucuronide (and possibly zidovudine itself) is reduced in the presence of probenecid.

**Ribavirin:**

Zidovudine in combination with ribavirin is antagonistic *in vitro* and concomitant use with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** should be avoided.

**Stavudine:**

Zidovudine may inhibit the intracellular phosphorylation of stavudine when the two medicinal products are used concurrently. Stavudine is therefore not recommended to be used in combination with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** (see '**CONTRAINDICATIONS'**).

**Paracetamol:**

Paracetamol use during treatment with zidovudine in a placebo-controlled trial was associated with an increased incidence of neutropenia, especially following chronic therapy. However, the available pharmacokinetic data indicate that paracetamol at the doses studied does not increase plasma levels of zidovudine nor of its glucuronide metabolite.

**Miscellaneous:**

The following medicines, including but not limited to, may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism: aspirin, codeine, morphine, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone, isoprinosine and methadone. The possibilities of drug interaction before using such medicines, particularly for chronic therapy, in combination with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300**, should be considered.

The risk of adverse reactions to zidovudine may also increase, with concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine,

vinblastine and doxorubicin). Extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced, if concomitant therapy with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** and any of these medicines is necessary.

Some patients receiving **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** may continue to experience opportunistic infections therefore the concomitant use of prophylactic antimicrobial therapy may have to be considered. This named prophylaxis has included pyrimethamine, co-trimoxazole, aerosolised pentamidine and acyclovir. The limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with these medicines.

**PREGNANCY AND LACTATION:**

The safety of lamivudine in human pregnancy has not been established, thus treatment during the first trimester of pregnancy is not advised.

The use of zidovudine in pregnant women, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternalfoetal transmission of HIV. This has, however, not been established for lamivudine. Consequently the administration of **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** during pregnancy should only be considered if expected benefits outweigh any possible risks.

To avoid the transmission of HIV to infants, HIV-infected mothers should not breastfeed. Both lamivudine and zidovudine are excreted into human milk, in similar concentrations to those found in serum. Since lamivudine, zidovudine and HIV pass into breast milk, it is recommended that mothers taking **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** do not breastfeed their infants.

**DOSAGE AND DIRECTIONS FOR USE:**

*Adults and children over the age of 12 years:*

The recommended dose: One tablet twice daily.

**ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** may be administered with or without food.

A medical practitioner experienced in the management of HIV infection should initiate therapy.

During combination therapy with other antiretroviral agents, the package insert of the particular agent should be consulted for information.

If a discontinuation of therapy with one of the active constituents of **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** or dose reduction is necessary, separate preparations of lamivudine and zidovudine are required.

**Post exposure prophylaxis following exposure:**

The course of medication should be started as soon as possible (preferably within 1 to 2 hours) after the exposure has occurred and continued until confirmation of HIV-status of source material. **In cases where the source material is confirmed to be infected with HIV, it is recommended that the prophylactic course be continued for a period of 4 weeks.**

The following dosing guideline should be followed: 1 tablet taken twice daily.

This equates to a daily dose of 600 mg zidovudine and 300 mg lamivudine.

If the use of a protease inhibitor is necessary (see **'INDICATIONS'),** the local Centres for Disease Control guidelines should be consulted for dosing requirements.

Treatment should be discontinued as soon as the source material is confirmed not to be infected with HIV.

**Renal impairment:**

Due to decreased clearance, the concentrations of lamivudine and zidovudine are elevated in patients with renal impairment. Therefore, as dosage adjustment of these may be required, it is advised that separate preparations of lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance < 50 ml/min). The package insert for separate preparations must be consulted for full details of these dosage adjustments.

**Hepatic impairment:**

The influence of hepatic impairment on lamivudine levels has not been fully elucidated. Lamivudine clearance is largely renal. Based on preliminary safety data, no dosage adjustment is necessary. Lamivudine should be used with caution in patients with hepatomegaly or other risk factors for hepatic disease. Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Therefore, as dosage adjustments for zidovudine may be necessary, it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with severe hepatic impairment. The package insert of zidovudine must be consulted for full details of the dosage adjustments.

Dosage adjustments in patients with haematological adverse reactions:

Dosage adjustment of zidovudine may be necessary if the haemoglobin level falls below 9 g/dl or 5,59 mmol/l, or the neutrophil count falls below 1,0 x 109/l (see **'CONTRAINDICATIONS'**). This is more likely in patients with poor bone marrow reserve prior to treatment, particularly in patients with advanced HIV disease. As dosage adjustment of zidovudine may be necessary, **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** cannot be used and separate preparations of zidovudine and lamivudine should be used. Medical practitioners should refer to individual package inserts for these medicines.

**Dosage in the elderly:**

Special care is advised in elderly patients due to age-associated changes such as the decrease in renal function and alteration of haematological parameters.

**SIDE EFFECTS AND SPECIAL PRECAUTIONS:**

**Side effects:**

During therapy for HIV disease with lamivudine and zidovudine separately or in combination, adverse events have been reported. With many of these events it is unclear whether they are related to lamivudine, zidovudine or to the wide range of medicines used in the management of HIV disease or are as a result of the underlying disease process.

As **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of synergistic toxicity following concomitant administration of the two compounds.

**Lamivudine:**

The adverse events that have been reported are:

**Blood and lymphatic system disorders:**

*Less frequent:* anaemia, neutropenia, pure red cell aplasia and thrombocytopenia

**Gastrointestinal disorders:**

*Frequent:* upper abdominal pain, nausea, vomiting and diarrhoea

*Less frequent:* pancreatitis (causal relationship not established) and rises in serum amylase

**General disorders and administration site conditions:**

*Frequent:* fatigue, malaise, fever

**Hepatobiliary disorders:**

*Less frequent:* transient rises in liver enzymes (AST, ALT)

**Musculoskeletal and connective tissue disorders:**

*Frequent:* muscle disorders including musculoskeletal pain, arthralgia

*Less frequent:* rhabdomyolysis

**Nervous system disorders:**

*Frequent:* headache

*Less frequent:* paraesthesia, peripheral neuropathy (no causal relationship to has been determined)

**Respiratory, thoracic and mediastinal disorders:**

*Frequent:* cough, nasal symptoms

**Skin and subcutaneous tissue disorder:**

*Frequent:* rash, alopecia

**Metabolism and nutrition disorders:**

*Frequent:* hyperlactacaemia

*Less frequent:* lactic acidosis, lipodystrophy (redistribution/accumulation of body fat) (see **'WARNINGS')**

**Zidovudine:**

**Blood and lymphatic system disorders:**

*Frequent:* anaemia (which may require transfusions), neutropenia and leucopenia have been reported as the most serious adverse reactions.

These adverse reactions occur more often at higher dosages (1 200 to 1 500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4+ cell counts < 100/mm3. A reduction in the dosage or cessation of therapy may become essential (see '**DOSAGE AND DIRECTIONS FOR USE').**

Incidence of neutropenia increases in patients whose neutrophil counts, haemoglobin levels and serum vitamin B12 levels were low at the start of zidovudine therapy, and in those patients who are concurrently taking paracetamol (see '**INTERACTIONS').**

**Metabolism and nutrition disorders:**

*Frequent:* hyperlactacaemia

*Less frequent:* lactic acidosis, anorexia, lipodystrophy (see 'WARNINGS')

**Psychiatric disorders:**

*Less frequent:* anxiety and depression

**Nervous system disorders:**

*Frequent:* headache, dizziness

*Less frequent*: insomnia, paraesthesia*,* somnolence, loss of mental acuity, convulsions

**Cardiac disorders:**

*Less frequent:* cardiomyopathy

**Respiratory, thoracic and mediastinal disorders:**

*Less frequent:* dyspnoea, cough

**Gastrointestinal disorders:**

*Frequent:* nausea, vomiting, abdominal pain and diarrhoea

*Less frequent:* flatulence, oral mucosa pigmentation, taste disturbance and dyspepsia, pancreatitis

**Hepatobiliary disorders:**

*Frequent*: raised blood levels of liver enzymes and bilirubin

*Less frequent:* liver disorders such as severe hepatomegaly with steatosis

**Skin and subcutaneous tissue disorders:**

*Less frequent:* rash, pruritus, nail and skin pigmentation, urticaria, sweating

**Musculoskeletal and connective tissue disorders:**

*Frequent:* myalgia

*Less frequent:* myopathy

**Renal and urinary disorders:**

*Less frequent:* urinary frequency

**Reproductive system and breast disorders:**

*Less frequent:* gynaecomastia

**General disorders and administration site conditions:**

*Frequent:* malaise

*Less frequent:* fever, generalised pain and asthenia, chills, chest pain and influenza-like syndrome

If the severity of the symptoms warrants it, a reduction or suspension of zidovudine therapy may assist in the assessment and management of these conditions. In this situation **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** should be discontinued and separate preparations of zidovudine and lamivudine should be administered (see **'Special precautions').**

**Special precautions:**

When administering ADCO LAMIVUDINE AND ZIDOVUDINE 150/300 to any patient, particularly obese women with hepatomegaly, hepatitis or other known risk factor for liver disease, caution should

be exercised. These patients should be monitored closely while on therapy with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300.**

**Lactic acidosis/severe hepatomegaly with steatosis:**

Long-term use of **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** can result in potentially fatal lactic acidosis. Symptomatic hyperlactacaemia and lactic acidosis are uncommon. Clinical features are non-specific and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/l), and respond as follows:

Lactate 2 to 5 mmol/l: monitor regularly, and be alert for clinical signs.

Lactate 5 to 10 mmol/l without symptoms: monitor closely.

Lactate 5 to 10 mmol/l with symptoms: STOP all therapy. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma) monitor regularly, and be alert for clinical signs.

Lactate > 10 mmol/l: STOP all therapy (80 % mortality in case studies).

In cases where dosage adjustment is necessary, it is recommended that separate preparations of lamivudine and zidovudine should be administered. In these special cases, the medical practitioner should refer to the individual package inserts for these medicines.

During treatment with **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300**, patients should be cautioned regarding the concomitant use of self-administered medications due to the possibility of interactions.

**ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** should be used with caution in patients with advanced cirrhotic liver disease due to chronic Hepatitis B infection, where there is a small risk of rebound hepatitis if lamivudine is discontinued.

In studies in male and female rats, neither zidovudine nor lamivudine have shown evidence of impairment of fertility. No data is available on the effect of the zidovudine-lamivudine combination on human fertility.

**Pancreatitis:**

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers.

Discontinue use of **ADCO LAMIVUDINE AND ZIDOVUDINE 150/300** until diagnosis of pancreatitis is excluded.

**Effects on the ability to drive and operate machinery:**

No studies to investigate the effect of lamivudine or zidovudine on driving performance or the ability to operate machinery have been performed. Nevertheless, the clinical status of the patient and the adverse event profile of lamivudine and zidovudine should be borne in mind, when considering the patient's ability to drive and operate machinery.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

There is no experience of overdosage with ADCO LAMIVUDINE AND ZIDOVUDINE 150/300. There are limited data available on the consequences of ingestion of acute overdose of lamivudine and zidovudine in humans. No specific signs or symptoms have been identified following overdosage. If overdosage occurs, the patient should be monitored for evidence of toxicity (see **'SIDE EFFECTS AND SPECIAL PRECAUTIONS'**), and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied. Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine, but enhance the elimination of the glucuronide metabolite. For more details, physicians should refer to the individual package inserts for lamivudine and zidovudine.

**IDENTIFICATION:**

A white, film-coated caplet, embossed with "ZLM" on one side.

**PRESENTATION:**

56 and 60's Tablets are packed into a white cylindrical HDPE container with a white ribbed HDPE closure. The closure contains an aluminium induction sealing wad. Purified cotton and a silica gel bag are placed in the container.

HDPE securitainers with polypropylene closure in packs of 56's and 60's.

**STORAGE INSTRUCTIONS:**

Store at or below 25 °C in tightly closed containers.

## PROESSIONAL INFORMATION

Protect from moisture and light. Keep in the original container.

KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBER:**

44/20.2.8/0106

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**

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