SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZIDOCOMB 150/300, 150 mg/300 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg lamivudine and 300 mg zidovudine.

Sugar free.

For the full list of excipients, see section 6.1.

WARNING:
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE SECTION 4.4) EARLY SYMPTOMS (SYMPTOMATIC HYPERLACTATAEMIA) INCLUDE BENIGN DIGESTIVE SYMPTOMS (NAUSEA, VOMITING AND ABDOMINAL PAIN), NON-SPECIFIC MALAISE, LOSS OF APPETITE, WEIGHT LOSS, RESPIRATORY SYMPTOMS (RAPID AND/OR DEEP BREATHING) OR NEUROLOGICAL SYMPTOMS (INCLUDING MOTOR WEAKNESS). LACTIC ACIDOSIS HAS A HIGH MORTALITY AND MAY BE ASSOCIATED WITH PANCREATITIS, LIVER FAILURE OR RENAL FAILURE. LACTIC ACIDOSIS GENERALLY OCCURRED AFTER A FEW OR SEVERAL MONTHS OF TREATMENT.
TREATMENT WITH ZIDOCOMB 150/300 SHOULD BE DISCONTINUED IN THE SETTING OF SYMPTOMATIC HYPERLACTATAEMIA AND METABOLIC/LACTIC ACIDOSIS, PROGRESSIVE HEPATOMEGALY, OR RAPIDLY ELEVATING AMINOTRANSFERASE LEVELS.
CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING ZIDOCOMB 150/300 TO ANY PATIENT (PARTICULARLY OBESE WOMEN) WITH HEPATOMEGALY, HEPATITIS OR OTHER KNOWN RISK FACTORS FOR LIVER DISEASE AND HEPATIC STEATOSIS (INCLUDING CERTAIN MEDICINES AND ALCOHOL). PATIENTS CO-INFECTED WITH HEPATITIS C AND TREATED WITH ALPHA-INTERFERON AND RIBAVIRIN MAY CONSTITUTE A SPECIAL RISK.
PATIENTS AT INCREASED RISK SHOULD BE FOLLOWED CLOSELY.
ZIDOCOMB 150/300 IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF ZIDOCOMB 150/300 HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED ZIDOCOMB 15/300. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ZIDOCOMB 150/300 AND ARE CO-INFECTED WITH HIV AND HBV.
IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

3. PHARMACEUTICAL FORM

Film-coated tablets.

ZIDOCOMB 150/300: White, scored on both tablet faces, film-coated, modified capsule-shaped tablets, debossed with "D 02" on both tablet faces.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZIDOCOMB 150/300 is indicated as part of anti-retroviral combination therapy for the treatment of HIV-infected adults and children over 12 years of age, with progressive immunodeficiency (CD4+ count ≤ 500 cells/mm3).

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).

ZIDOCOMB 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 of broken skin (abrasions, cuts, eczema etc);
- exposure of mucous membranes including the eye.

No randomised clinical studies on the use of ZIDOCOMB 150/300 following occupational exposure have been performed. It has been reported that a retrospective case-controlled study has concluded that the use of zidovudine for post exposure prophylaxis reduces the rate of infection. Reports have shown that the use of zidovudine and lamivudine in combination has demonstrated a greater reduction in viral load than either medicine used alone.

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 ZIDOCOMB 150/300, zidovudine and/or lamivudine.

4.2 Posology and method of administration

Zidovudine 150/300 therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Posology

Adults and children over the age of 12 years:

The recommended dose of ZIDOCOMB 150/300 is one tablet twice daily.

When ZIDOCOMB 150/300 is used in combination with another anti-retroviral medicine, the professional information of the particular medicine should be consulted for information.

For situations where discontinuation of therapy with one of the active constituents of ZIDOCOMB 150/300, or dose reduction, is necessary, separate preparations of lamivudine and zidovudine are available in tablets/capsules and oral solution.

Post exposure prophylaxis following exposure:

The course of medication should be begun as soon as possible (preferably within 1 - 2 hours) after the exposure has occurred and continue 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 guidelines are based on the recommendations of the CDC (Centres for Disease Control) in the USA:

Duration	ZIDOCOMB 150/300 **Dosage**
Days 1-3	1 ZIDOCOMB 150/300 tablet taken twice daily. This equates to a daily dose of 600 mg zidovudine and 300 mg lamivudine.
Days 4-28	1 ZIDOCOMB 150/300 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 section 4.1) the CDC 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.

Special populations

Renal impairment

Lamivudine and Zidovudine concentrations are increased in patients with renal impairment due to decreased clearance. Therefore, as dosage adjustment of these may be necessary. It is recommended that separate preparations of lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance ≤ 50 mL/min). The professional information for lamivudine and zidovudine must be consulted for full details of these dosage adjustments.

Hepatic impairment

The influence of hepatic impairment on lamivudine levels is under investigation. Lamivudine clearance is largely renal. Based on preliminary safety data no dosage adjustment is necessary. However 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 professional information for 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 section 4.3). 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 ZIDOCOMB 150/300 is not possible separate preparations of zidovudine and lamivudine should be used.

Elderly population

No specific data are available, however special care is advised in this age group due to age-associated changes such as the decrease in renal function and alteration of haematological parameters.

Paediatric population

ZIDOCOMB 150/300 is not indicated for children below the age of 12 years as appropriate dose reduction for the weight of the child cannot be made (see section 4.3).

Method of administration

For oral administration.

ZIDOCOMB 150/300 may be administered with or without food.

4.3 Contraindications

- The use of ZIDOCOMB 150/300 is contraindicated in patients with known hypersensitivity to lamivudine, zidovudine or to any of the excipients of ZIDOCOMB 150/300, listed in section 6.1.
- Zidovudine is contraindicated in patients with abnormally low neutrophil counts (< 0,75 x 109/ℓ), or abnormally low haemoglobin levels (< 7,5 g/dℓ or 4,65 mmol/ℓ). Therefore, ZIDOCOMB 150/300 is contraindicated in these patients.
- ZIDOCOMB 150/300 is not indicated for children below the age of 12 years as appropriate dose reduction for the weight of the child cannot be made.
- There is a known interaction between zidovudine and stavudine. The concomitant use of ZIDOCOMB 150/300 and stavudine should be avoided (see section 4.5).
- Concomitant use with zalcitabine.

4.4 Special warnings and precautions for use

Patients receiving ZIDOCOMB 150/300 or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection.

Therefore, patients should remain under close clinical observation by medical practitioners experienced in the treatment of HIV infection.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including ZIDOCOMB 150/300, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Lactic acidosis / hyperlactataemia

Use of ZIDOCOMB 150/300 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 medicines 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 ZIDOCOMB 150/300 to patients with known risk factors for liver disease.

Treatment with ZIDOCOMB 150/300 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 ZIDOCOMB 150/300.

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of ZIDOCOMB 150/300 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 ZIDOCOMB 150/300 is increased due to decreased clearance. The dose of ZIDOCOMB 150/300 should therefore be adjusted (see section 4.2).

Liver disease

Use of ZIDOCOMB 150/300 can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of ZIDOCOMB 150/300 has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant professional information for these medicines.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is

evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

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

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

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 ZIDOCOMB 150/300 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 ZIDOCOMB 150/300 therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Haematological adverse reactions:

Anaemia, neutropaenia and leucopaenia (usually secondary to neutropaenia) can be expected to occur in patients with advanced symptomatic HIV disease receiving zidovudine, therefore haematological parameters should be carefully monitored (see section 4.3 and 4.8) in patients receiving ZIDOCOMB 150/300. These haematological effects are not usually observed before four- to six-weeks therapy. For patients with advanced symptomatic HIV disease, it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy and at least monthly thereafter.

In patients with early HIV disease haematological adverse reactions are infrequent. Depending on the overall condition of the patient, blood tests may be performed less often, e.g. every one to three months. Decreases in the haemoglobin level of more than 25 % from baseline and falls in the neutrophil count of more than 50 % from baseline may require more frequent monitoring.

Additionally, dosage adjustment of zidovudine may be required if severe anaemia or myelosuppression occurs during treatment with ZIDOCOMB 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 10^9/L (see section 4.2). As dosage adjustment of ZIDOCOMB 150/300 is not possible; separate preparations of zidovudine and lamivudine should be used. Medical practitioners should refer to the individual professional information for these medicines.

Sero-conversion to HIV-positive status may still occur despite the prompt use of ZIDOCOMB 150/300. The recommended prophylactic dose must be strictly adhered to (see section 4.2).

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy, including ZIDOCOMB 150/300 has been associated with hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Redistribution/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 been observed either separately or together in some patients receiving combination antiretroviral therapy which includes ZIDOCOMB 150/300 (see section 4.8).

In addition, the lipodystrophy syndrome has a multi-factorial aetiology; with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

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, atypical mycobacterial infections, cytomegalovirus, retinitis, Pneumocystis jirovecii (carinii) pneumonia 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.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

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 ZIDOCOMB 150/300 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.

ZIDOCOMB 150/300 should not be taken with any other medicines containing lamivudine or medicines containing emtricitabine.

Use with Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine and zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co-administered with lamivudine or zidovudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and ZIDOCOMB 150/300 should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anaemia. Discontinuation of ZIDOCOMB 150/300 should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

Exacerbation of anaemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Co-administration of ribavirin and zidovudine is not advised (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

As ZIDOCOMB 150/300 contains lamivudine and zidovudine, any interactions that have been identified with these medicines individually may occur with ZIDOCOMB 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:

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

The possibility of interactions with other medicines administered concurrently with ZIDOCOMB 150/300 should be considered, 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 only in part by this mechanism and were shown not to interact with lamivudine. Please refer to the pharmacokinetics section for full details on the interaction of lamivudine with other anti-retroviral medicines.

Trimethoprim:

Administration of prophylactic doses of co-trimoxazole results in a 40 % increase in lamivudine exposure, because of trimethoprim component; the sulphamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine (see section 4.2).

When concomitant administration with co-trimoxazole is warranted patients should be monitored clinically. Co-administration of ZIDOCOMB 150/300 with high doses of co-trimoxazole for the treatment of *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis should be avoided. Lamivudine has no effect on the pharmacokinetics of co-trimoxazole at doses studied.

Zalcitabine:

Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. ZIDOCOMB 150/300 is therefore not recommended to be used in combination with zalcitabine (see section 4.3).

Miscellaneous:

Co-administration of lamivudine with intravenous ganciclovir or foscarnet is not recommended until further information is available.

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

Cladribine

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.

Medicines containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol).

Avoid chronic co-administration of ZIDOCOMB 150/300 with medicines containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol).

Interactions relevant to zidovudine:

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

Lamivudine:

A modest increase in C_{max} (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Clarithromycin:

Interaction studies have shown an interaction between zidovudine and clarithromycin and caused a decrease in zidovudine AUC by 12 %. ZIDOCOMB 150/300 should be separately administrated of clarithromycin by at least 2 hours.

Rifampicin:

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

Valproic acid:

The co-administration of zidovudine and valproic acid increases the AUC of zidovudine by 80 %. Monitor for signs of zidovudine toxicity.

Phenytoin:

Phenytoin blood levels have been reported to be low in some patients receiving zidovudine, while in one patient a high level was noted. These observations suggest that phenytoin concentrations should be carefully monitored in patients receiving ZIDOCOMB 150/300 and 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*. The concomitant use of ribavirin with ZIDOCOMB 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 ZIDOCOMB 150/300 (see section 4.3).

Paracetamol:

Paracetamol use during treatment with zidovudine in a placebo-controlled trial was associated with an increased incidence of neutropaenia 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.

Atovaquone:

The co-administration of zidovudine (750 mg twice daily with food / 200 mg three times per day) and atovaquone increases the AUC of zidovudine by 33 %.

Miscellaneous:

Other medicines, including but not limited to, aspirin, codeine, morphine, methadone, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and isoprinosine, may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibilities of medicines interaction before using such medicines particularly for chronic therapy, in combination with ZIDOCOMB 150/300.

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) may also increase the risk of adverse reactions to zidovudine. If concomitant therapy with ZIDOCOMB 150/300 and any of these medicines is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more medicines should be reduced.

Please refer to the Pharmacokinetics section for full details on the interaction of zidovudine with other anti-retroviral medicines.

Since some patients receiving ZIDOCOMB 150/300 may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Such prophylaxis has included co-trimoxazole, aerosolised pentamidine, pyrimethamine and acyclovir. Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with these medicines.

4.6 Fertility, pregnancy and lactation

The safety and/or efficacy of ZIDOCOMB 150/300 during pregnancy and lactation has not been established. Therefore, the use of ZIDOCOMB 150/300 during pregnancy is not recommended.

The use of zidovudine in pregnant women, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal-foetal transmission of HIV. However, no such data are available for lamivudine.

There have been reports of mild and transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed *in utero* or *peri-partum* to nucleoside reverse transcriptase inhibitors (NRTIs), such as ZIDOCOMB 150/300. The clinical relevance of transient elevations in serum lactate is unknown. There have also been reports of developmental delay and seizures. However, a causal relationship between these events and NRTI exposure *in utero* or *peri-partum* has not been established.

Late onset of neurological disorders relating to mitochondrial dysfunction have been observed in children who have been exposed *in utero* and/or postnatally to nucleoside analogues as contained in ZIDOCOMB 150/300**.**

Both lamivudine and zidovudine are excreted into human milk at similar concentrations to those found in serum.

Since lamivudine, zidovudine and HIV pass into breast milk it is recommended that mothers taking ZIDOCOMB 150/300 do not breastfeed their infants.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

ZIDOCOMB 150/300 can cause dizziness, fatigue, loss of mental acuity and drowsiness.

Patients should be advised not to drive a vehicle or use machines until they know how they are affected.

4.8 Undesirable effects

Side effects have been reported during therapy for HIV disease with lamivudine and zidovudine separately or in combination. With many 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.

Side effects related to the combined use of lamivudine and zidovudine:

As ZIDOCOMB 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 added toxicity following concurrent administration of the two compounds.

Side effects related to lamivudine:

Blood and the lymphatic system disorders:

Less frequent: Neutropenia and anaemia (both occasionally severe), thrombocytopenia, pure red cell aplasia

Immune system disorders:

Frequent: Angioedema, immune reconstitution inflammatory syndrome

Metabolism and nutrition disorders:

Frequent: Hyperlactatemia

Less frequent: Lactic acidosis, lipodystrophy (redistribution/ accumulation of body fat (see section 4.4).

Nervous system disorders:

Frequent: Headache, insomnia

Less frequent: Paraesthesia. Peripheral neuropathy has been reported although a causal relationship to treatment is uncertain. Late-onset neurological disorders.

Respiratory, thoracic and mediastinal disorders:

Frequent: Cough, nasal symptoms

Gastrointestinal disorders:

Frequent: Nausea, vomiting, upper abdominal pain, diarrhoea

Less frequent: Pancreatitis

Hepato-biliary disorders:

Less frequent: Transient rises in liver enzymes (AST, ALT), hepatitis

Skin and subcutaneous tissue disorders:

Frequent: Rash, alopecia

Musculoskeletal, connective tissue and bone disorders:

Frequent: Arthralgia, muscle disorders including musculoskeletal pain

Less frequent: Rhabdomyolysis

General disorders and administrative site conditions:

Frequent: Fatigue, malaise, fever

Zidovudine:

Blood and the lymphatic system disorders:

Frequent: Anaemia (which may require transfusions), neutropenia and leukopenia.

These occur more frequently at higher dosages (1 200 – 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/mm^3. Dosage reduction or cessation of therapy may become necessary (see section 4.2). The incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin B_{12} levels were low at the start of zidovudine therapy, and in those patients taking paracetamol concurrently (see section 4.5).

Less frequent: Thrombocytopenia, and pancytopenia (with marrow hypoplasia), pure red cell aplasia, aplastic anaemia

Immune system disorders:

Frequent: Immune reconstitution inflammatory syndrome

Metabolism and nutrition disorders:

Frequent: *Hyperlactatemia*

Less frequent: *Lactic acidosis, anorexia, lipodystrophy (redistribution/ accumulation of body fat (see section 4.4)*

Psychiatric disorders:

Less frequent: Anxiety and depression

Nervous system disorders:

Frequent: Headache, dizziness

Less frequent: Insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions

Late-onset neurological disorders

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, dyspepsia and pancreatitis

Hepato-biliary 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 and sweating

Musculoskeletal, connective tissue and bone 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 administrative site conditions:

Frequent: Malaise

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

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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 drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no experience of overdosage with ZIDOCOMB 150/300. However, there are limited data available on the consequences of ingestion of acute overdoses of lamivudine and zidovudine in humans. No fatalities occurred, and all patients recovered. No specific signs or symptoms have been identified following such overdosage.

If overdosage occurs the patient should be monitored for evidence of toxicity (see section 4.8), 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 medical practitioners should refer to the individual package inserts for lamivudine and zidovudine.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 20.2.8 Antiviral agents

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC Code: J05AR01

5.1 Pharmacodynamic properties

Lamivudine and zidovudine are potent, selective inhibitors of HIV-1 and HIV-2. Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Both drugs era 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. Lamivudine and zidovudine triphosphates show significantly less affinity for host cell DNA polymerases.

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 harboring 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 of 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 mutations, cross-resistance to didanosine and zalcitbatine has been seen in some patients. In some patients treated with zidovudine plus didanosine or zalcibatine, isolates resistant to multiple medicines, including lamivudine, have emerged.

HIV isolates with multimedicine 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 Gln151→Met) from the pattern with zidovudine monotherapy, with the 151 mutations being most commonly associated with multimedicine 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-medicine 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.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Intravenous studies with lamivudine and zidovudine showed that the mean apparent volume of distribution is 1,3 and 1,6 L/kg respectively. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 36 % serum albumin in vitro). Zidovudine plasma protein binding is 34 % to 38 %.

Medicine interactions involving binding site displacement are not anticipated with lamivudine/zidovudine. Data show that lamivudine and zidovudine penetrate the central nervous system and reach the cerebrospinal fluid (CSF). The mean ratios of CSF/serum lamivudine and zidovudine concentrations 2 - 4 hours alter oral administration were approximately 0, 12 and 0,5 respectively. The true extent of penetration of lamivudine or relationship with any clinical efficacy is unknown.

Metabolism

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared by renal excretion of unchanged medicine. The likelihood of metabolic medicine interactions with lamivudine is low due to the small extent of hepatic metabolism (5 - 10 %) and low plasma binding. The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50 - 80 % of the administered dose eliminated by renal excretion. 3'-amino-3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

Elimination

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, with predominantly renal clearance (> 70 %) via the organic cationic transport system. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance ≤ 50 ml/min (see section 4.2). It

has been reported from studies with intravenous zidovudine, the mean terminal plasma half-life was 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 tubular secretion by the kidneys.

Zidovudine concentrations are increased in patients with advanced renal failure.

Pharmacokinetics of ZIDOCOMB 150/300 **when used in combination with other anti-retroviral medicines:**
Zidovudine:

Data from pharmacokinetic/medicine interaction studies indicate that there were no clinically significant alterations to zidovudine pharmacokinetics when given concomitantly with the following anti-retroviral medicines:

Nucleoside reverse transcriptase inhibitors (NRTIs): zalcitabine, didanosine and abacavir;

Non-nucleoside reverse transcriptase inhibitors (NNRTIs): 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 section 4.5). The concomitant use of these two medicines should be avoided.

Lamivudine:

Data from pharmacokinetic/medicine interaction studies indicate that there were no clinically significant alterations to lamivudine pharmacokinetics when given concomitantly with the following anti-retroviral medicines:

Non-nucleoside reverse transcriptase inhibitors (NNRTIs): efavirenz; and

Protease inhibitors: indinavir sulphate, ritonavir, amprenavir and nelfinavir.

Pharmacokinetics of ZIDOCOMB 150/300 **when used in combination with tuberculostatic medicines:**
Zidovudine:

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

Lamivudine:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Colloidal silicon dioxide (HDK®N20 Pharma)
Magnesium stearate
Microcrystalline cellulose (Avicel PH102)
Sodium starch glycolate.
Tablet coating:
Opadry White 13B58802 consisting of:
Hypromellose (HPMC2910)
Macrogol (PEG)
Polysorbate 80
Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 Years.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light and moisture.

Keep in bottle tightly closed when not in use.

6.5 Nature and contents of container

ZIDOCOMB 150/300 tablets are packed into 75 ml HDPE opaque white bottles with 38 mm child-resistant heat induction seal cap.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8. REGISTRATION NUMBER

53/20.2.8/0184

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 February 2021

10. DATE OF REVISION OF THE TEXT

28 May 2026

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